PROGRAM ABSTRACT

July 22nd & 23rd 2021

IRCND 2021 | Virtual
Baltimore, MD, USA

This is an inaugural conference for Global Association for the Study of Neurodegenerative Diseases (GASND).

Write to US: gasnd.association@gmail.com
Website: GASND.org/IRCND

Inaugural International Conference on Neurodegenerative Diseases

Virtual IRCND 2021, July 22-23, 2021

Baltimore, MD, USA

Virtual IRCND 2021 is an inaugural conference for Global Association for the Study of Neurodegenerative Diseases (**GASND**). IRCND2021 provides an outstanding forum for researchers in the neurodegenerative disease field to meet, exchange ideas related to their achievements, further facilitate the understanding of pathogenesis and develop new treatments for intervention.

Chair:
Wanli W. Smith, MD., Ph.D.
Johns Hopkins University
School of Medicine

Co-Chair:
Xinglong Wang, Ph.D.
College of Medicine, University Nebraska Medical Center, USA

2021 ORGANIZING COMMITTEE

Bobby Thomas, Ph.D., Professor
Medical University of South Carolina, USA

Xiongwei Zhu, Ph.D., Professor
Case Western Reserve University, USA

Mark R. Cookson, Ph.D. Senior Investigator
Laboratory of Neurogenetics, NIA/NIH, USA

Yidong Bai, Ph.D., Professor
University of Texas Health San Antonio, USA

Patrick Lewis, Ph.D. Professor
The Royal Veterinary College, UK

Elisa Greggio, Ph.D. Associate Professor
University of Padova, ITALY

Nicolas Arbez, Ph.D. Senior Investigator
Institut de Recherche Servier,
Neuropsychiatry Center for Therapeutic Innovation, Croissy sur Seine, France

Shaida A Andrabi, Ph.D.
The University of Alabama at Birmingham, USA

Marie-Ève Tremblay, Ph.D.
University of Victoria, Canada

Global Association for the Study of Neurodegenerative Diseases, INC. (GASND)

Website: GASND.org

President-2021: Wanli W. Smith MD, Ph.D.

Global Association for the Study of Neurodegenerative Diseases, INC. (GASND) is a 501(c)(3) non-profit organization committed to advancing scientific research on pathogenesis and therapeutics of neurodegenerative diseases and related disorders.

GASND provides a platform for the free exchange of ideas and information, and a resource to advance scientific research and education on topics related to the study of neurodegenerative diseases and related disorders. The mission of GASND is to improve our understanding of what causes neurodegenerative diseases, to identify biomarkers for disease process and treatment evaluation, to identify drug targets and to develop new approaches for treatment and prevention.

Neurodegenerative diseases are characterized by the loss of function and eventual death of nerve cells in the brain or peripheral nervous system. Millions of people suffer from neurodegenerative diseases which overwhelms health care support and creates a heavy financial burden for their families and society. Currently, the pathogenesis of neurodegenerative diseases is not fully understood. There is no curative therapy. GASND is committed to understanding causes of neurodegenerative diseases and to finding new drug targets, biomarkers and treatment. GASND welcomes scientists and supporters worldwide to join as members.

GASND office contact: Amber M. Smith
Email: Gasnd.association@gmail.com

MESSAGE FROM PRESIDENT

MAY 1, 2021

Global Association for Study of Neurodegenerative Diseases, INC. (GASND) provides a platform to advocate scientific research on pathogenesis and therapeutics of neurodegenerative diseases and related disorders. Millions of people suffer from neurodegenerative diseases which causes an overwhelmed health care support system and heavy financial burden for their families and society. Our mission is to understand the causes and to find new drug targets, biomarkers and treatment.

To fulfill its mission to combat neurodegenerative disease, GASND is committed to unite with scientists and supporters worldwide to expand intellectual collaboration, and to build an association that rejects any barriers to global-scale scientific cooperation. GASND promotes scientific exchange, and advocates education with a lifelong learning resource for scientific training and professional development for our members. We help young fellows and students to become the next generation of scientists and health care providers.

GASND members are dedicated to learning, finding and sharing new scientific discoveries for fighting neurodegenerative diseases. I thank all members and supporters for investing their effort and intellectual energy with GASND. I am very honored and humbled to have the opportunity to lead this newly formed global association of passionate and committed neuroscientists. We will push the field forward to help those who suffer from neurodegenerative diseases.

Wanli W. Smith MD, Ph.D.
President-2021
Contact: Tel: (1)443-956-0168
Email: admin@gasnd.org

VISION STATEMENT

GASND aims: to serve as the scientific organization for the study of Neurodegenerative Diseases and related disorders, to provide a source for scientific information exchange about research on Neurodegenerative Diseases and related disorders, to support the professional development of students and young researchers who focus upon Neurodegenerative Diseases and related disorders, to attract researchers from a range of multiple disciplines, modes of employment, and various career stages, to promote GASND conferences, and to build and maintain financial support for GASND activities.

MISSION STATEMENT

GASND is committed to scientific research on the pathogenesis and therapeutics of neurodegenerative diseases and related disorders. The GASND provides a multidisciplinary platform for the free exchange of information and ideas, and serves as a resource for scientific research and education on topics related to the study of Neurodegenerative Diseases and related disorders. The mission of GASND is to improve our understanding of neurodegenerative pathogenesis, to identify biomarkers for disease process and treatment evaluation, to identify drug targets and to develop new approaches for treatment and prevention.

IRCND2021 Program Overview

Neurodegenerative diseases are characterized by the loss of function and eventual death of nerve cells in the brain or peripheral nervous system. Millions of people suffer from neurodegenerative diseases which causes overwhelmed health care support and heavy financial burden for their families and society. Currently, the pathogenesis of neurodegenerative diseases is not fully understood. There is no curative therapy.

To highlight important findings and achievements in the field and to promote exchange of information across neurodegenerative diseases, the program committee has invited well-known keynote speakers to introduce exciting presentations to our participants. The program committee has planned several themes for the conference. We have received 71 talk abstracts which covers all four themes, with many exciting recent findings.

Program themes:

A. Organelle dynamics and trafficking: Accumulating genetic and biochemical evidence links impaired organelle dynamics to neurodegenerative diseases. Established and emerging pathways include mitophagy, inter-organelle contacts, lysosome biogenesis and repair, autophagy, endosomal sorting, Golgi trafficking and synaptic vesicle trafficking.

B. Glial and Neuroinflammation: For many years, neuroinflammation has been linked to neurodegenerative diseases. Recent genetic, pathological, clinical, and biochemical investigations have reinvigorated studies positing the central role of neuroinflammation and the contribution of microglia and astrocytes in the neurodegenerative process.

C.RNA binding proteins, RNA biology and neurodegeneration: Another common theme across neurodegenerative disorders is altered RNA metabolism. This includes loss of function of RNA binding proteins, impaired RNA splicing, transport and stability, alterations in microRNA and tRNA biogenesis, and changes in non-coding RNAs.

D. Protein synthesis, aggregation, biomarker and treatment: Despite the involvement of distinct proteins in different neurodegenerative disorders, the process of protein misfolding and aggregation is remarkably similar for different triggering proteins. To identify biomarkers for disease process and treatment evaluation, to identify drug targets and to develop new approaches for treatment and prevention are always in the frontier line of research in the field.

Program committee

Chair:
Mark. R. Cookson, Ph.D
National Institute on Aging, National Institutes of Health, USA

Co-Chair:
Xiongwei Zhu, Ph.D.
Case Western Reserve University, USA

Members: **Patrick Lewis, Ph.D.**
Marie-Ève Tremblay, Ph.D.
Wanli W. Smith, MD., Ph.D.
Elisa Greggio, Ph.D.
Xinglong Wang, Ph.D.

Keynote Speaker: Erika L. F. Holzbaur, Ph.D

Dr. Erika L. F. Holzbaur is a Professor, the Chair of Physiology, University of Pennsylvania Perelman. She received her Ph.D and postdoctoral fellow training in Pennsylvania State University. She joined University of Pennsylvania as an assistant professor in 1992, and prompted to full professor there in 2004. Her study focuses on the dynamics of organelle motility along the cellular cytoskeleton. She is interested in the mechanisms leading to coordinated motor activity, including motor recruitment and regulation by adaptors and scaffolding proteins. Her work was the first to clearly establish that opposing dynein and kinesin motors are simultaneously bound to organelles moving along the axon, where they are regulated in a cargo-specific manner by adaptors, activators, and scaffolding proteins. Further, she has identified distinct regulatory zones at synaptic sites and the axon terminal where the initiation or termination of cargo motility is modulated by microtubule dynamics, post-translational modifications of the microtubule cytoskeleton, and the localized recruitment of microtubule-associated proteins. She has also investigated the cellular mechanisms leading to neurodegeneration, including the first identification and characterization of a human mutation in the dynein/dynactin motor complex that causes late-onset motor neuron degeneration. These studies led directly to her work investigating the dynamics of autophagy in neurons, as autophagosomes are a major axonal cargo for the retrograde dynein motor. Her research defined the highly conserved pathway of axonal autophagy, a constitutive mechanism for the clearance of damaged organelles and aggregated proteins that is required to maintain neuronal homeostasis. Her work was the first to identify a key role for optineurin in the clearance of damaged mitochondria via mitophagy, downstream of PINK1 kinase and the E3 ubiquitin ligase parkin. As mutations in optineurin and the associated kinase TBK1 cause familial ALS, and mutations in PINK1 and parkin cause familial Parkinson's disease, this discovery demonstrates that the failure to clear damaged mitochondria is likely to contribute to the pathogenesis observed in multiple forms of neurodegeneration, a hypothesis currently under investigation in our lab. She has developed a significant record of contributions to neuronal cell biology, focusing on the cellular and biophysical analysis of molecular motors, the mechanistic analysis of organelle trafficking, the elucidation of pathways for autophagy and mitophagy in neurons, and an improved understanding of pathogenic mechanisms leading to neurodegenerative disease. She is a great mentor. She has trained 27 predoctoral and 21 postdoctoral trainees, many of whom have gone on to tenure-track positions at institutions (eg. Yale, NIH, etc). She has constant received NIH grants for many years (ef. R35, RO1, PO grants). She served various grant review panels (eg. HIN study section chair) and as a editorial board for several journals (eg. Cell). She also served as co-organizer or Chair to organize many internal conferences. She is a President-elect for American Society for Cell Biology, for the 2023 term.

Keynote Speaker: Michela Deleidi, MD., Ph.D.

Michela Deleidi, MD., Ph.D.
Helmholtz Young Investigator Group Leader-
"Mitochondria and Inflammation in Neurodegenerative Diseases"

German Center for Neurodegenerative Diseases (DZNE) Tübingen

Assistant Professor, Department of Neurodegenerative Diseases, University of Tübingen

Otfried-Müller. Str 23
72076 Tübingen-Germany
https://www.deleidilab.org

Michela Deleidi. MD., Ph.D. studied medicine at Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy. She completed her residency in neurology followed by a research fellowship at the Neuroregeneration Institute at Harvard Medical School, Boston, USA. During this time, she focused on pluripotent stem cell technology for Parkinson's disease (PD) modeling and regenerative medicine applications. She was awarded an Alexander von Humboldt Fellowship and she relocated to Germany to pursue her PhD studies at the German Center for Neurodegenerative Diseases (DZNE) in Tübingen. By combining cellular reprogramming with genome editing, her work led to one of the first stem cell-based models of PD, clearly showing a mechanistic link with lysosomal storage diseases. Since 2016, Michela Deleidi is a Helmholtz Young Investigator at DZNE and an assistant professor of Neurology at the University of Tübingen. Her research mostly focuses on the role of the immune system as an early trigger of neurodegenerative diseases.

NIH Session: Success on grant application and review

Carol Hamelink, Ph.D.

Scientific Review Officer
Neural Oxidative Metabolism, Mitochondria and cell Death (NOMD)
Molecular, Cellular and Developmental Neurosciences IRG
Center for Scientific Review,
National Institutes of Health

Rockledge II,Room 4183 6701
Rockledge Drive, MSC 7850 Bethesda,
MD 20892-7850, USA

Dr. Hamelink will talk about policy and new changes in NIH grant applications and the review process for all current and future NIH grantees. NIH promotes young investigators with a new type of grant, the R01 Katz application, which requires a new scientific direction for an early stage investigator as applied toward critical questions with high significance and impact in the biomedical field, but does not allow any preliminary data. This section will greatly benefit young investigators who are just starting in their career or moving in a new research direction.

Dr. Carol Hamelink's Biography: She received her Ph.D. in nutrition from the University of Maryland College Park. Her research there focused on the neurodegenerative effects of alcohol consumption on the hippocampus acting through the HPA axis. Subsequently, she was a postdoctoral research fellow at the National Institute of Mental Health, where she worked in the Laboratory of Cellular and Molecular Regulation studying the protective effects of pituitary adenylate cyclase activating polypeptide (PACAP) in pathophysiological stress. She joined CSR in 2005 and serves as the Scientific Review Officer for CSR's Neural Oxidative Metabolism, Mitochondria and Cell Death (NOMD) study section. With her amiable personality and excellent leadership, for many years she has led successful and fair grant review processes, which push the frontiers of research in neurodegenerative diseases.

Award Program

Young Investigator Awards are available for postdoctoral fellows and students based on scientific merit, and the quality of their abstract and presentation, as assessed by the IRCND awards committee. Applications for this award must be made online at the time of abstract submission in the IRCND conference. Award-recipients will present their work during the IRCND meeting with a 10 minute talk. Award winners will be recognized in the conference program with the award certificate.

Total 23 abstracts have been submitted for award competition. There will be 11 recipients for this award in 2021.

Research & Education Lifetime Achievement Award (R&E award).
The GASND and IRCND start a tradition in the inaugural conference with the aim to appreciate the senior mentors in neurodegeneration (ND) field for their contribution as a great mentor and as a well-known leader in scientific research to advance our understanding of ND pathogenesis and to develop new treatment for combat ND.

The GASND and IRCND aim to promote and faster the young investigators. We also like to appreciate the senior mentors for their lifetime effort on training and mentoring. Everyone in the GASND has been received various advice and guidance from one's mentors or professors. The great sprite and friendship between mentors and trainee not only push forward the scientific discovery but also highlight the power of family-like united strength in our scientific community.

Drs. Christopher A. Ross and Ted M. Dawson are two recipients for this award in IRCND2021.

Christopher A. Ross, MD., Ph.D.

Ted M. Dawson, MD. Ph.D

Award Committee

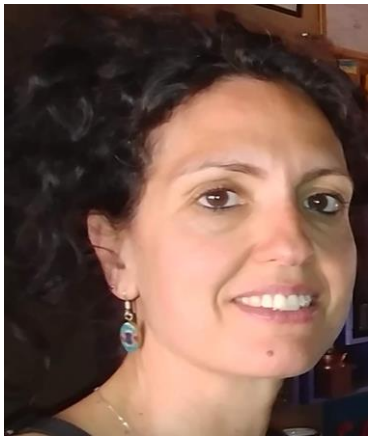
Chair: Yidong Bai, Ph.D.

Co-Chair: Bobby Thomas, Ph.D.

Reviewers and Judges

Elisa Greggio, Ph.D.
Wolfdieter Springer, Ph.D
Mark Cookson, Ph.D.
Mariana Pehar, Ph.D.
Xiongwei Zhu, Ph.D.
Bobby Thomas, Ph.D.
Patrick Lewis, Ph.D.
Bindu D Paul, Ph.D.
Haining Zhu, Ph.D.
Shaida Andrabi, Ph.D.
Yidong Bai, Ph.D.

Long Range Planning Committee



Chair: Elisa Greggio, Ph.D.
Co-chair: Nicolas Arbez, Ph.D.

Membership Committee

Chair: Shaida Andrabi, Ph.D.

Young Investigator Awards are based on scientific merit, and the quality of abstract and presentation, as assessed by the IRCND awards committee.

• Charlotte Brzozowski	*University of Minnesota, USA*
• Susanna Cogo,	*University of Reading, UK*
• Federica De Lazzari,	*University of Padova, Italy*
• Cenxiao Fang,	*University of Minnesota, USA*
• Ju Gao,	*University of Nebraska Medical Center, USA*
• Nolwazi Gcwensa,	*University of Alabama at Birmingham, USA*
• Victor Z. Lau,	*University of Victoria, Victoria, BC, Canada*
• Li Li,	*Stanford University, USA*
• Casey Mahoney-Crane,	*University of Alabama at Birmingham, USA*
• Anna Masato,	*University of Padova, Italy*
• Nicoletta Plotegher,	*University of Padova, Italy*
• Jasjot Singh,	*University of Bonn, Germany*
• Bing Wen,	*Shandong University, China*

EXCELLENT SERVICE AWARD

Recognize IT service and support teams that deliver the highest levels of excellence and support

Johns Hopkins University, USA

Zhipeng Hou
Pan Li
Bo Ning
Rashi Sultania
Mali Jiang
Jing Jin
Srividhya Subramanian

University of Nebraska Medical Center, USA

Ariele Peters
Justin Dunn

GASDN office, Baltimore, MD, USA

Amber M. Smith

IRCND2021

Support teams

IT support team 1

Mali Jiang
Bo Ning
Rashi Sultania
Wanli W. Smith

IT support team 2

Pan Li
Zhipeng Hou
Jing Jin
Srividhya Subramanian

Logistical support team

Xinglong Wang
Ariele Peters
Justin Dunn
Amber M Smith

Neurobiology Division,
Department of Psychiatry,
Johns Hopkins University
School of Medicine

IRCND2021 program at a glance

	22-Jul	Track1 (blue)	Track 2 (green)
8:15-9:45	15 mintalk	Chairs: Shaida Andrabi and Andrew Pieper	chairs: Xinglong Wang and Mali Jiang
1	8:15-8:30	Elena Ziviani	Tomoki Kuwahara
2	8:30-8:45	Eugenio Barone, Professor	Yinxia Chao
3	8:45-9	YiDeng Liang	Zhaohui Liu
4	9-9:15	Andrew Pieper	Ian Martin
5	9:15-9:30	Mohammed Iqbal Hossain	Md. Razaul Karim
		Common sessions (yellow)	
9:30-9:40		Break	
9:40-9:45		Open remark: Wanli smith	
9:45-10:15		Keynote: Erika L. F. Holzbaur	
10:20-12:40			
	20 min talk	Chairs: Rita Cowell and Qian Cai	Chairs: Mark Cookson and Marie-Ève Tremblay
1		Dominic Winter	Long-Jun Wu
2		Patrick Lewis	Robert A. Clark
3		Qian Cai	Mark R Cookson
4		Rita M. Cowell	Atsushi Kamiya
5		Wenzhang Wang	Marie-Ève Tremblay
6		Wolfdieter Springer	Mariana Pehar
7		Yulan Xiong	Zhenyu Yue
12:40-12:50		Break	
12:50-3:00	10 min talk	Young Invstigator 1	
		Chairs: Yidong Bai and Haining Zhu	
		Cenxiao Fang	
		Ju Gao	
		Victor Z. Lau	
		Casey Mahoney-Crane	
		LI LI	
		Scott C. Vermilyea	
		Ms. Charlotte Brzozowski	
		Chloe McKee	
		Ms. Preethy Sridharan	
		Bing Wen	
		Arun Upadhyay	
		Nolwazi Gcwensa	
		Luwen Wang	

	23-Jul	Track1 (blue)	Track 2(green)
		Track 1 C1 (20 min talk)	Young Invstigator 2 (10 min talk)
8:15-9:45	20 min talk	Chairs: Zhong Pei, Wanli Smith	Bobby Thomas and Partick Lewis
1	8:15-8:35	Zhong Pei	Anna Masato
2	8:35-8:55	Rahul Bharadwaj	Xiaobo Wang
3	8:55-9:15	Wanli Smith	Nicoletta Plotegher
4	9:15-9:35	Bindu D. Paul	Mr. Jasjot Singh
5	9:35-9:55	Jun Hua	Susanna Cogo
			Ludovica Iovine
			Francesco Agostini
			Lucia Iannotta
			Federica De Lazzari
			Giulia Tombesi
		Common sessions (yellow)	
9:55-10:05		Break	
10:05-10:25		NIH: Carol Hamelink	
10:25-10:55		Keynote: Michela Deleid	
10:55-11:25		R &E award: Christopher A. Ross	
11:25-11:35		Break	
11:35-1:5	20 min talk	chairs: Xiongwei Zhu and Zixu Mao	chairs: Elisa Greggio and Darren Moore
1		Zixu, Mao	Elisa Greggio
2		Xiongwei Zhu	Huaibin Cai
3		Pan Li	Tong Li
4		Haining Zhu	Michael K. Lee
5		Udai Pandey	Mali Jiang
6		Xinglong Wang	Darren Moore
7		Shaida A Andrabi	Jie Shen
2:00-2:30		R& E award: Ted Dawson	
2:30-2:45		Xinglong Wang: awardand conclusions	
		2022 confernece plan	

IRCND 2021 | Virtual

Inaugural International Research Conference on Neurodegenerative Disease

July 22nd – 23rd, 2021

Day 1	Thursday July 22, 2021	EST time
8:15 – 9:45	**Track 1-A1**	**A. Organelle dynamics and trafficking** 15 min talk (11min talk and 4min question) **Session chairs: Drs. Shaida Andrabi and Andrew Pieper** https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
8:15 – 8:30	**Elena Ziviani, PhD** University of Padua, Italy	Mitochondrial quality control in neurodegeneration
8:30 – 8:45	**Eugenio Barone, Ph.D.** Sapienza University of Rome, Italy	Oxidative stress links brain insulin resistance and mitochondrial defects in Down syndrome brain early in life: implication for neurodegeneration
8:45 – 9:00	**Yideng Liang, MD, PhD** U.S. Food & Drug Administration, USA	Nuclear localization enhances the dentatorubral and pallidoluysian atrophy (DRLPA)-like in mice
9:00 – 9:15	**Andrew Pieper, Ph.D.** Case Western Reserve University, USA	Discovery of a Neuroprotective Molecule
9:15 – 9:30	**Mohammed Iqbal Hossain, Ph.D.** University of Alabama at Birmingham, USA	Restoration of Cathepsin D and Lysosomal Function in Stroke is Neuroprotective
9:30 – 9:40	**Break**	
9:40 – 9:45	**Wanli Smith, MD, PhD** **Conference Chair** Johns Hopkins University School of Medicine, USA	Opening Remarks https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
9:45 – 10:15	Wanli W. Smith introduces Keynote Speaker: **Erika L. F. Holzbaur, PhD, Professor** University of Pennsylvania Perelman School of Medicine	Dynamics of autophagy in neuronal homeostasis and neurodegeneration

10:20 – 12:40	**Track 1-A2**	**A. Organelledynamics and trafficking** 20 min talk (11min talk and 4min question) **Session chairs: Drs. Rita Cowell and Qian Cai** https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
10:20 – 10:40	**Dominic Winter, Ph.D.** University of Bonn, Germany	Lysosomal Proteomics Reveals Cell- and Tissue-Specific Organelle Compositions
10:40 – 11:00	**Patrick Lewis, PhD.** Royal Veterinary College, University of London, UK	Understanding LRRK2 in Parkinson's – mapping protein families to function and disease
11:00 – 11:20	**Qian Cai, PhD** Rutgers University, USA	Mitophagy regulation of energy metabolism in neurons
11:20 – 11:40	**Rita M. Cowell, PhD** University of Alabama at Birmingham, USA	Parkinson Disease through the lens of cellular identity: From prioritization of risk variants to the identification of novel transcriptional programs for mitochondrial and synaptic function
11:40 – 12:00	**Wenzhang Wang, PhD** Case Western Reserve University, USA	The β-Amyloid Induces Abnormal Mitochondrial Proteostasis in Alzheimer's Disease
12:00 – 12:20	**Wolfdieter Springer, PhD** Mayo Clinic Jacksonville, FL, USA	Selective mitochondrial autophagy in health, aging, and neurodegeneration
12:20 – 12:40	**Yulan Xiong, PhD** University of Connecticut School of Medicine, USA	Dysregulation of the phosphorylation cycle of AP2M1 by LRRK2 impairs endocytosis and leads to dopamine neurodegeneration
8:15 – 9:45	**Track 2-B1 and D1**	**B. Glia and Neuroinflammation** **D. Protein synthesis, aggregation, biomarker and treatment** 15 min talk (11min talk and 4min question) **Session chairs: Drs. Xinglong Wang and Mali Jiang** https://zoom.us/j/97786172841?pwd=bDRZY1dCeGlWK1VZMFdIT3FWRmczQT09
8:15 – 8:30	**Tomoki Kuwahara, Ph.D.** The University of Tokyo, Japan	Regulation of stressed lysosomes by LRRK2 in macrophage lineage cells
8:30 – 8:45	**Yinxia Chao, Ph.D.** National Neuroscience Institute, Singapore	Autoimmune biomarker screening and functional validation in Parkinson's disease
8:45 – 9:00	**Zhaohui Liu, MD, PhD** Medical School of Soochow University, China	Activation of Nrf2 in astrocytes suppressed PD-like phenotypes via antioxidant and autophagy pathways in rat and Drosophila models
9:00 – 9:15	**Ian Martin, PhD** Oregon Health & Science University, USA	Unraveling LRRK2-Induced Neurodegeneration in Parkinson's Disease Models
9:15 – 9:30	**Md. Razaul Karim, Ph.D.** University of Minnesota, USA	Differential metabolism of a-Syn pre-formed fibril (PFFs) neuronal and non-neuronal cells
9:30 – 9:40	**Break**	

10:20 – 12:40	**Track 2-B2**	**B. Glia and Neuroinflammation** 20 min talk(16min talk and 4min question) **Session chairs: Drs. Mark Cookson and Marie-Ève Tremblay** https://zoom.us/j/97786172841?pwd=bDRZY1dCeGlWK1VZMFdIT3FWRmczQT09
10:20 – 10:40	**Long-Jun Wu, PhD** Mayo Clinic, MN, USA	TREM2 mediates microglial neuroprotection against TDP-43-related neurodegeneration
10:40 – 11:00	**Robert A. Clark, MD, PhD** University of Texas Health, USA	Harnessing the Potential of Hematopoietic Stem Cells for Targeted Delivery of Therapeutic Genes for Neurodegenerative Diseases
11:00 – 11:20	**Mark R Cookson, PhD** National Institute on Aging, National Institute of Health, USA	Parkinson's disease associated alleles at the LRRK2 locus influence disease risk via microglia
11:20 – 11:40	**Atsushi Kamiya, PhD** Johns Hopkins University School of Medicine, USA	Glial pathology induced by adolescent cannabis exposure and genetic insults impacting brain maturation and cognitive behaviors
11:40 – 12:00	**Marie-Ève Tremblay, PhD** University of Victoria, Canada	Microglial ultrastructural diversity in health and neurodegeneration
12:00 – 12:20	**Mariana Pehar, PhD** University of Wisconsin at Madison, USA	Upregulation of FABP7 induces a proinflammatory phenotype in astrocytes that is detrimental for neuronal survival
12:20 – 12:40	**Zhenyu Yue, PhD** Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, USA	Microglial Autophagy: A Neuroprotective Mechanism in Parkinson's and Alzheimer's disease
12:40 – 12:50	**Break**	
12:50 – 3:00	**Young Investigators Session 1**	10 min talk(8min talk and 2min question) **Session chairs: Drs. Yidong Bai and Haining Zhu** https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
12:50-1:00	**Bing Wen** Shandong University, China	Bilateral basal ganglia hemorrhage due to tentorial dural arteriovenous fistula and systematic literature review
1:00-1:10	**Ju Gao, MD** University of Nebraska Medical Center, USA	Regulation of brain function by TDP-43 phase separation
1:10-1:20	**Victor Z. Lau** University of Victoria, Victoria, BC, Canada	Senescent Glia Drive and Underlie Alzheimer's Disease
1:20-1:30	**Casey Mahoney-Crane** University of Alabama at Birmingham, USA	The Role of the GBA1 L444P heterozygous mutation in fibril-induced a-synuclein inclusions
1:30-1:40	**Li Li** Stanford University, USA	A Mitochondrial Membrane-Bridging Machinery Mediates Signal Transduction of Intramitochondrial Oxidation

1:40-1:50	**Scott C. Vermilyea, Ph.D.** University of Minnesota, USA	Loss of tau expression attenuates neurodegeneration associated a-synuclein pathology in vivo
1:50-2:00	**Charlotte Brzozowski** University of Alabama at Birmingham, USA	Inhibition of LRRK2 kinase activity promotes anterograde axonal transport and presynaptic targeting of a-synuclein
2:00-2:10	**Chloe McKee** University of Victoria, Canada	Microglial ultrastructural diversity in male and female aged wild-type and fractalkine receptor deficient mice
2:10-2:20	**Preethy Sridharan** Case Western Reserve University, USA	Role of mitochondrial fission in progressive neurodegeneration and memory deficit after traumatic brain injury
2:20-2:30	**Cenxiao Fang, PhD** University of Minnesota, USA	Integrated Stress Response in alpha-synucleinopathy
2:30-2:40	**Arun Upadhyay, Ph.D.** Northwestern University, USA	Isolation and proteomic profiling of amyloid fibril core with ultra-high purity from AD mouse brains
2:40-2:50	**Nolwazi Gcwensa, Ph.D** University of Alabama at Birmingham, USA	Alpha-synuclein aggregation in the Amygdala
2;50-3:00	**Luwen Wang, PhD** University of Nebraska Medical Center, USA	Neuronal Mfn2 alleviates tau pathology–induced neurodegeneration and cognitive decline

Day 2	Friday July 23, 2021 EST time	
8:15 – 9:55	**Track 1- C1 and D2**	**C. RNA binding proteins, RNA biology and neurodegeneration** **D. Protein synthesis, aggregation, biomarkers and treatment** 20 min talk (16 min talk and 4min question) **Session chairs: Drs. Zhong Pei and Wanli W. Smith** https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
8:15 – 8:35	**Zhong Pei, MD, PhD** Sun Yat-Sen University, China	Systemic exosomal siRNA-mediated inhibition of huntingtin expression in transgenic mice of Huntington's disease
8:35 – 8:55	**Rahul Bharadwaj, Ph.D.** Department of Neuropathology, Lieber Institute for Brain Development, Johns Hopkins University School of Medicine, USA	Age-associated changes in the human midbrain dopamine cell transcriptome and proteome
8:55 – 9:15	**Wanli W Smith, MD, PhD** Johns Hopkins University School of Medicine, USA	Inhibition of LRRK2 GTP binding activity reduces neuroinflammation
9:15 – 9:35	**Bindu D. Paul, PhD** Dept. of Pharmacology & Molecular Sciences, Johns Hopkins University School of Medicine, USA	Neuroprotective roles of the gaseous signaling molecule, hydrogen sulfide, in Alzheimer's disease
9:35 – 9:55	**Jun Hua, PhD** Hugo W. Moser Research Institute at Kennedy Krieger, Johns Hopkins University, School of Medicine, USA	Imaging neurovascular abnormalities in neurodegenerative diseases
8:15 – 9:55	**Track 2: Young Investigators Session 2**	10 min talk(8min talk and 2min question) **Session chairs: Drs. Partick Lewis and Bobby Thomas** https://zoom.us/j/97786172841?pwd=bDRZY1dCeGlWK1VZMFdIT3FWRmczQT09
8:15-8:25	**Anna Masato, PhD** University of Padova, Italy	DOPAL initiates aSynuclein-mediated proteinopathy leading to enhanced vulnerability in Parkinson's disease
8:25-8:35	**Xiaobo Wang** Johns Hopkins University School of Medicine, USA	Mutant TMEM230 induced neurodegeneration and impaired axonal mitochondrial transport
8:35-8:45	**Nicoletta Plotegher** University of Padova, Italy	The activities of LRRK2 and GCase are positively correlated in clinical biospecimens and experimental models of Parkinson's disease
8:45-8:55	**Mr. Jasjot Singh** University of Bonn, Germany	Characterization of Lysosomal Protein Interactions and Structures by Cross Linking Mass Spectrometry
8:55-9:05	**Ludovica Iovine, PhD** University of Padova, Italy	Trafficking of the glutamate transporter is impaired by pathogenic LRRK2
9:05-9:15	**Susanna Cogo, PhD** University of Reading, UK	Understanding the importance of LRRK2 GTP-binding in macrophages
9:15-9:25	**Francesco Agostini** University of Padova, Italy	PAK6 enhances neuronal autophagy via TFEB

9:25-9:35	**Lucia Iannotta** University of Padova, Italy	Unravelling the involvement of the PAK6-LRRK2 axis in modulating ciliogenesis in the brain
9:35-9:45	**Federica De Lazzari, PhD** University of Padova, Italy	Unraveling the role of DJ-1 in the bioenergic homeostasis
9:45-9:55	**Giulia Tombesi** University of Padova, Italy	The Parkinson's disease kinase LRRK2 orchestrates dendritic spine dynamics via BDNF signaling pathway
9:55 – 10:05	**Break**	
10:05 – 10:25	**Carol Hamelink, PhD**	**NIH Session - Grant application and review** https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
10:25 – 10:55 10:55 – 11:25	Elisa Greggio introduces Keynote Speaker: **Michela Deleidi, MD, PhD** Wanli Smith introduces R &E Award Speaker: **Christopher A Ross, MD, PhD**	1.Dissecting the role of the immune system in human brain disease: from 2D to 3D iPSC organoids-"Mitochondria and Inflammation in Neurodegenerative Diseases" 2. Huntington disease Pathogenesis: Towards preventive precision medicine for neurodegeneration
11:25-11:35	**Break**	
11:35 – 1:55	**Track 1-C2**	**C. RNA binding proteins, RNA biology and neurodegeneration** 20 min talk (11min talk and 4min question) **Session chairs: Drs. Xiongwei Zhu and Zixu Mao** https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
11:35 – 11:55	**Mao Zixu, Ph.D.** Emory University School of Medicine, USA	Loss of Drosha and miRNA Biogenic Machinery in the Pathogenesis of Alzheimer's Disease
11:55 – 12:15	**Xiongwei Zhu, Ph.D.** Case Western Reserve University, USA	METTL3-dependent RNA m^{6}A dysregulation in Alzheimer's disease
12:15 – 12:35	**Pan Li, Ph.D.** Johns Hopkins University School of Medicine, USA	RNA toxicity and perturbation of rRNA processing in spinocerebellar ataxia type 2
12:35 – 12:55	**Haining Zhu, PhD** University of Arizona, USA	RNA Binding Protein FUS and Amyotrophic Lateral Sclerosis
12:55 – 1:15	**Udai Pandey, Ph.D.** University of Pittsburgh Medical Center, USA	Mutations in GEMIN5 lead to neurodevelopmental disorder with cerebellar atrophy, ataxia and motor dysfunction
1:15 – 1:35	**Xinglong Wang, Ph.D.** University of Nebraska Medical Center, USA	TDP-43 and Mitochondrial Dysfunction in Alzheimer's disease
1:35 – 1:55	**Shaida A Andrabi, Ph.D.** University of Alabama at Birmingham, USA	Cathepsin D/Granulin interaction is vital for lysosomal function and neuronal survival in stroke

11:35 – 1:55	Track 2-D3	**D. Protein synthesis, aggregation, biomarker and treatment** 20 min talk(16min talk and 4min question) **Session chairs: Drs. Elisa Greggio and Darren Moore** https://zoom.us/j/97786172841?pwd=bDRZY1dCeGlWK1VZMFdIT3FWRmczQT09
11:35 – 11:55	**Elisa Greggio, PhD** University of Padova, Italy	14-3-3 proteins in neurodegeneration: highly versatile roles and novel regulation mechanisms
11:55 – 12:15	**Huaibin Cai, PhD** National Institute of Health	Function and regulation of ALDH1A1-positive nigrostriatal dopaminergic neurons in motor control and Parkinson's disease
12:15 – 12:35	**Tong Li, PhD** Johns Hopkins University School of Medicine, USA	Amyloid-β and tau pathologies are both necessary for stimulating pathological progression of Alzheimer's disease
12:35 – 12:55	**Michael K. Lee, PhD** University of Minnesota, USA	Role of Tau in progressive synaptic and memory deficits in a transgenic mouse model of a-synucleinopathy
12:55 – 1:15	**Mali Jiang, MD, PhD** Johns Hopkins University School of Medicine, USA	Immortalized Striatal Precursor Neurons Generated from Huntington's disease (HD) patient iPSCs for drug screening
1:15 – 1:35	**Darren Moore, PhD** Van Andel Institute, USA	Pathophysiological Mechanisms of VPS35 in Parkinson's Disease
1:35 – 1:55	**Jie Shen, Ph.D.** Harvard Medical School, USA	LRRK2 and Parkinson's Disease
2:00-2:45	**Conclusion Session**	https://jhjhm.zoom.us/j/91496084794?pwd=UGJuNTQrY2l3QXQxSHNRVWNLMGQ5Zz09
2:00 – 2:30	Shaida A Andrabi Introduces R & E award Speaker: **Ted Dawson, MD, PhD** Johns Hopkins University School of Medicine, USA	PARIS (ZNF746) controls the survival of dopamine neurons in Parkinson's Disease
2:30 – 2:45	**Xinglong Wang, PhD** **Incoming IRCND 2022 Conference Chair** University of Nebraska Medical Center, USA	Awards, conclusion, upcoming year meeting plan

Track 1 and common sessions

IT Support team 1
Mali Jiang (leader)
Bo Ning (problem shooting)
Rashi Sultania

Track 2 sessions

IT Support team 2
Pan Li (leader)
Zhipeng Hou (problem shooting)
Jing Jin
Srividhya Subramanian

Logistical Support team
Xinglong Wang
Ariele Peters
Justin Dunn
Amber M. Smith

Keynote Speaker 1:

Dynamics of autophagy in neuronal homeostasis and neurodegeneration

Erika L. F. Holzbaur, Ph.D

University of Pennsylvania Perelman School of Medicine

Neurons rely on autophagy, a critical homeostatic mechanism, to maintain cellular health over the decades of human life. Deficits in autophagy cause the accumulation of undegraded cargos including protein aggregates and dysfunctional mitochondria, and are characteristic of major neurodegenerative diseases including Parkinson's disease (PD). We have identified a constitutive pathway for axonal autophagy, in which autophagosomes are generated preferentially at synaptic sites and at the axon terminal, and are then rapidly transported to the soma. This transport is driven by the molecular motors cytoplasmic dynein and kinesin, interacting with the microtubule cytoskeleton, and is carefully regulated by associated scaffolding proteins including Huntingtin and HAP1. Transport inhibition leads to a failure of autophagosome maturation and cargo degradation. To more closely examine the contributions of axonal autophagy to neuronal homeostasis and neurodegeneration, we examined autophagosome dynamics in neurons expressing the most common PD-causing mutation in *LRRK2*: the G2019S mutation induces hyperactive LRRK2 kinase activity leading to increased phosphorylation of the Rab GTPases that regulate intracellular trafficking. We found that expression of the G2019S mutation in LRRK2 significantly reduced the processivity of autophagosome transport. Altered transport was correlated with impaired organelle maturation; both deficits were reversed by pharmacological inhibition of LRRK2 kinase activity. Together, our findings demonstrate that increased LRRK2 kinase activity is sufficient to induce defects in autophagosome transport and maturation, which can be reversed pharmacologically, and further implicate defective autophagy in the pathogenesis of neurodegenerative disease.

Keynote Speaker 2:

Dissecting the role of the immune system in human brain disease: from 2D to 3D iPSC organoids- “Mitochondria and Inflammation in Neurodegenerative Diseases"

Michela Deleidi

German Center for Neurodegenerative Diseases (DZNE) Tübingen

Parkinson's disease (PD) is an ageing-related disorder that is conventionally considered as a condition that arises and exclusively affects the central nervous system. However, mounting evidence suggests that complex interactions between the brain and the periphery contribute to disease. Several studies suggest a relevant role of inflammation on both disease onset and progression. Supporting this hypothesis is the observation that many PD genes are highly expressed in immune cells and regulate their functions. Among these, the leucine-rich repeat kinase 2 (LRRK2) gene is particularly notable. Genetic polymorphisms in LRRK2 have been associated with susceptibility to leprosy as well as inflammatory bowel diseases. Functionally, LRRK2 modulates innate immune responses against intracellular bacteria with pleiotropic effects on bacterial control and inflammation depending on the pathogen. In this talk, I will summarize recent data from our group highlighting the role of LRRK2 in the brain and the peripheral immune system. Furthermore, I will summarize recent efforts from our laboratory and the research community aimed at implementing induced pluripotent stem cell models for the study of the role of neurodegenerative-disease associated genes in early immunological pathways. A particular attention will be paid to the discussion of current advantages and limitations of organoid-based modeling of human neurodegenerative diseases. The development of highly controlled human in vitro models will aid the analysis of tissue- and cell-specific immune pathways involved in brain diseases.

R & E award Speaker 1

Huntington disease Pathogenesis: Towards preventive precision medicine for neurodegeneration.

Christopher A. Ross MD PhD

Director, Division of Neurobiology, Director, Baltimore Huntington's Disease Center
Johns Hopkins University School of Medicine, Baltimore, MD 21287

HD is an autosomal dominant neurodegenerative disorder with a well-defined etiology: A CAG repeat expansion in the Huntingtin (HTT) gene, coding for an expanded CAG repeat in its mRNA and a polyglutamine repeat in the Huntingtin protein (Htt). Above the threshold of around 36-40, the age of onset can be estimated based on the CAG expansion length for those who undergo predictive genetic testing. Despite widespread expression of the HD gene throughout the lifespan, there is selective neuronal degeneration in specific brain regions. Extensive natural history studies have identified several biomarkers, including progression of regional brain atrophy, beginning long before clinical signs and symptoms. These features make HD a model for studying other neurodegenerative diseases with complex genetics, such as Alzheimer's disease, Fronto-Temporal Dementia, and Parkinson's disease. This review will emphasize pathogenesis of HD with potential relevance for therapeutics, especially mechanisms most directly related to the Huntingtin message and protein product. Three Htt-lowering trials have had to be terminated for lack of efficacy or deleterious effects, but others, with different agents and strategies are continuing or planned. Additional promising potential therapeutic targets include somatic CAG expansion, Htt biochemistry, cell transdifferentiation in situ, and selected cellular pathogenic pathways, especially those approachable by small molecules. Different therapeutic strategies, or combinations, might be optimal at different points in the disease course.

Christopher A. Ross M.D. Ph.D.
Professor of Psychiatry, Neurology, Pharmacology and Neuroscience
Director, Division of Neurobiology
Director, Baltimore Huntington's Disease Center
Johns Hopkins University School of Medicine
Co-Chair Scientific Affairs Committee,
Huntington Study Group

CMSC 8-121
600 North Wolfe Street
Baltimore, MD 21287

Phone 410-614-0011
Fax 410-614-0013
Email caross@jhu.edu

R & E award Speaker 2

PARIS (ZNF746) controls the survival of dopamine neurons in Parkinson's Disease

Ted M. Dawson, M.D., Ph.D.

Institute for Cell Engineering, Departments of Neurology, Neuroscience and Pharmacology & Molecular Sciences Johns Hopkins University School of Medicine

Parkinson's disease (PD) is due, in part, to the progressive loss of dopamine neurons in the substantia nigra pars compacta, which leads to bradykinesia, rigidity, rest tremor and postural instability. Degeneration of other neuronal populations and/or neuronal dysfunction due to the accumulation and aggregation of a-synuclein, the major protein constituent of Lewy Bodies and Lewy Neurites leads other clinical features including autonomic dysfunction, anxiety, depression, abnormalities of sleep, cognitive impairment, among others. Fresh insights into the pathogenesis of PD have come from understanding the genetic underpinnings of PD. Mutations in the cytosolic ubiquitin E3 ligase, parkin and the protein kinase PINK1 cause autosomal recessive PD. Defects in mitochondrial quality control contribute substantially to the demise of DA neurons due to parkin and PINK1 inactivation. PARIS (ZNF746), a PINK1 and parkin substrate, is a cytosolic protein that shuttles between the cytosol and nucleus, where it acts a co-repressor to control the levels of PGC-1a, a master co-regulator of mitochondrial biogenesis and mitochondrial anti-oxidant defenses. Knockout of PARIS dramatically prevents the loss of DA neurons due parkin and PINK1 inactivation as well as accumulation and aggregation of a-synuclein through preventing the down regulation of PGC-1a thereby maintaining mitochondrial biogenesis and mitochondrial anti-oxidant defenses. Strategies aimed at inhibiting or reducing PARIS levels in PD hold exciting promise as disease modifying therapies for the major causes of autosomal recessive PD and sporadic PD.

Ted M. Dawson, M.D., Ph.D.
Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases
Director, Institute for Cell Engineering
Professor, Departments of Neurology, Neuroscience and Pharmacology & Molecular Sciences
Johns Hopkins University School of Medicine
733 North Broadway, MRB 731
Baltimore, MD 21205

Phone: 1-410-614-3359
Fax: 1-410-614-9568
Email: tdawson@jhmi.edu
hopkinsmedicine.org/cell-engineering

Track 1-A1, 7/22, 8:15-9:30am

Mitochondrial quality control in neurodegeneration

Elena Ziviani
Biology Department, Padua University

Mitochondrial dysfunction and quality control has become a central theme in neurodegenerative diseases. Ubiquitination of mitochondrial membrane proteins is a critical step preceding Autophagy-dependent degradation of mitochondria (also know as Mitophagy). Mitophagy is generally driven by ubiquitin ligases, like the E3 Ubiquitin ligase Parkin that is recruited to mitochondria to ubiquitinate mitochondrial proteins. Since a single Parkin substrate that is required for mitochondrial clearance has not been identified, mitophagy appears to be driven by accumulation of ubiquitinated targets on mitochondria, induced by ubiquitin ligases other than Parkin. These ligases are effectively antagonized by specific Deubiquitinating enzymes (DUBs); therefore specific DUBs inhibitors are beneficial in this context, presumably by up-regulating Parkin-independent mitophagy. Our work aims at identifying novel DUBs that affect mitophagy. We recently discovered that mitophagy can be enhanced *in vivo* in flies and in disease models of Parkinson's Disease by reducing either the levels or activity of the proteasome-associated deubiquitinating enzyme USP14 (Chakraborty et al., EMBO Mol Med, Sept 2018) or the endosome-associated deubiquitinating enzyme USP8 (von Stockum S. et al., Life Science Alliance, April 2019). We knocked down USP14 or USP8 in two established fly models of impaired mitophagy, and this restored mitochondria function and ultrastructure, and brain dopamine levels. Remarkably, at the systemic level, it extended the flies' lifespan and rescued climbing behavior. Further studies will clarify whether specific DUBs inhibition is protective in mammalian models of impaired mitophagy, and may bring DUBs targets forward as candidate therapeutic avenues.

Name:
Elena Ziviani

Company:
Biology Department, University of Padova

Email:
elena.ziviani@gmail.com

Phone:
+393429521781

Oxidative stress links brain insulin resistance and mitochondrial defects in Down syndrome brain early in life: implication for neurodegeneration.

Chiara Lanzillotta1 , Antonella Tramutola1 , Fabio Di Domenico1, Marzia Perluigi1 and Eugenio Barone1

1 Department of Biochemical Sciences "A. Rossi-Fanelli", Sapienza University of Rome, Rome, Italy;

Dysregulation of brain insulin signaling and of mitochondrial activity with reduced downstream neuronal survival and plasticity mechanisms are fundamental abnormalities observed in Alzheimer's disease (AD). This phenomenon, known as brain insulin resistance, is associated with poor cognitive performance and is driven by the inhibition of IRS1 protein. Since Down syndrome (DS) and AD neuropathology share many common features, we investigated metabolic aspects of neurodegeneration in DS and whether they contribute to early onset AD in DS. We evaluated levels and activation of proteins involved in the insulin signaling pathway (IR, IRS1, BVR-A, MAPK, PTEN, Akt, GSK3β, PKCζ, AS160, GLUT4) in in post-mortem brain samples collected from people with DS before and after the development of AD pathology (DSAD) compared with their age-matched controls. Furthermore, we analyzed whether changes of brain insulin signaling were associated with alterations of: (i) proteins regulating brain energy metabolism (mitochondrial complexes, hexokinase-II, Sirt1); (ii) oxidative stress (HNE and 3- NT); (iii) APP cleavage; and (iv) proteins mediating synaptic plasticity mechanisms (PSD95, syntaxin and BDNF). Similar analyses were performed in Ts65dn (DS model) and euploid mice (n=6/group) at different ages (1, 3, 9 and 18 months) to draw the trajectory of the neuropathological alterations with age. DS cases were characterized by key markers of brain insulin resistance (reduced IR and increased IRS1 inhibition) early in life. Furthermore, downstream from IRS1, an overall uncoupling among the proteins of insulin signaling was observed. Dysregulated brain insulin signaling was associated with reduced hexokinase II (HKII) levels, reduced mitochondrial complexes levels, increased indices of oxidative stress. Loss of syntaxin-1 and PSD95 was also evident. These alterations precede the development of AD neuropathology and clinical presentations in DS. We propose that a close link exists among brain insulin resistance, mitochondrial defects and oxidative stress that drives the impairment of energy metabolism early in life in DS, thus contributing to early onset AD in DS.

Title: Prof.

Name: Eugenio Barone
Company:
Sapienza University of Rome
Email: eugenio.barone@uniroma1.it

Phone:+390649910935

Nuclear localization enhances the dentatorubral and pallidoluysian atrophy (DRLPA)-like in mice.

Yideng Liang[1&2], Bo Ning[1], Xiaobo Wang[1], Xiaofang Wang[1], Frederick C. Nucifora[1], Russ L Margolis[1], Christopher A. Ross[1] and Wanli W Smith[1]

[1]Division of Neurobiology, Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA 21287
[2]Current address: Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA 20993

ABSTRACT

Dentatorubral and pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder, caused by a CAG expansion in the atrophin-1 gene. The clinical features include chorea, ataxia, incoordination, emotional changes, and dementia, progressing to early mortality. The atrophin-1 protein sequence contains a putative N terminal nuclear localization signal (NLS) and a putative C-terminal nuclear export signal (NES). To investigate if nuclear localization of atrophin-1 plays a role in the pathogenesis of DRPLA, we have designed alterations of the NLS and NES by site-directed mutagenesis. We generated transgenic mice expressing mutant full length atrophin-1 (repeat length = 65) with alteration of either the nuclear export signal (At65QmNES, predicted to have more atrophin-1 in nuclei than cytosol compared to control), and the nuclear localization signal (At65QmNLS, predicated to keep atrophin-1 more cytosolic), respectively. At the equivalent expression of atrophilin-1, At65QmNES mice displayed more nuclear accumulation of atrophin-1 and its fragments than At65QmNLS or control mice expressing endogenous normal Atrophin-1. Moreover, At65QmNES mice had shorter life span, and more severe locomotor defects compared with At65QmNLS (and non-transgenic control) mice. We further found that At65QmNES caused more neurodegeneration and astrogliosis in mouse brains compared with At65QmNLS mice. These data provide evidence that nuclear localization enhances the phenotype of mutant atrophin-1-linked neurodegeneration. In addition, our data indicate that the AT65QmNES transgenic mouse will be a valuable tool for future pathogenesis and therapeutic studies of DRPLA.

Name:Yideng Liang

Company:Johns Hopkins University School of Medicine

Email: yideng.liang@fda.hhs.gov

Phone:
4438416776

Discovery of a Neuroprotective Molecule

Andrew Pieper
Case Western Reserve University

Acquired and genetic neurodegenerative conditions currently afflict upwards of 50 million people worldwide. With our rapidly aging population, this number is expected to triple over the next 30 years. However, despite the magnitude of the problem, there are still no medicines for patients capable of stopping neurodegeneration. To address this problem, we undertook a nonbiased *in vivo* screen in living mice of small drug-like molecules to identify pharmacologic agents capable of enhancing the net magnitude of hippocampal neurogenesis, which is the product of proliferation and survival of young hippocampal neurons. This screen yielded an aminopropyl carbazole agent that was named P7C3, and was shown to promote survival of young newborn hippocampal neurons without affecting the proliferation rate of neural precursor cells. Mechanistically, P7C3 and its derivative compounds foster neuronal survival by enhancing levels of nicotinamide adenine dinucleotide (NAD^+) under conditions of otherwise NAD^+-depleting toxic stress leading to cell death. This enables P7C3 compounds to also enhance survival of mature neurons in the central and peripheral nervous system, with protective efficacy now having been demonstrated in broad preclinical rodent models of neurodegeneration, including traumatic brain injury, Alzheimer's disease, Parkinson's disease, and stress-associated depression. Neuroprotective efficacy of the P7C3 family of compounds has also been demonstrated in the hippocampus of nonhuman primates. In addition to optimizing its chemical properties and implementing other key steps in drug development, P7C3 compounds in the laboratory have provided a tool for discovering new biology of neuroprotection.

Title:

Name:
Andrew Pieper

Company:
Case Western Reserve University

Email:
AndrewAPieper@gmail.com

Phone:
9727681935

Restoration of Cathepsin D and Lysosomal Function in Stroke is Neuroprotective

M. Iqbal Hossain, Joshua M.Marcus, Jun Hee Lee, Patrick L. Garcia, Charles N. Falany and Shaida A. Andrabi

Department of Pharmacology and Toxicology, and Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama

Stroke is a leading cause of death and disability. The pathology of stroke is very complex and not fully understood. Lysosomes play as important role in the maintenance of cellular homeostasis. In neurons, Cathepsin D (CTSD) is an essential protease involved in the regulation of proteolytic activity of lysosomes. The role of CTSD and lysosomal function is not clearly defined in cerebral ischemia. Here, we used oxygen-glucose deprivation (OGD) in mouse cortical neurons and the middle cerebral artery occlusion (MCAO) model of stroke to assess the role of CTSD in stroke. Our results show a time-dependent decrease in CTSD protein levels and activity in mouse brain after stroke and in neurons following OGD, with concurrent defects in lysosomal function. We found that shRNA-mediated knockdown of CTSD in neurons is sufficient to cause lysosomal dysfunction. Restoration of CTSD protein levels via lentiviral transduction increases CTSD activity in neurons and thus renders resistance to OGD-mediated defects in lysosomal function and cell death. This study indicates that CTSD-dependent lysosomal function is critical for maintaining neuronal survival in cerebral ischemia. Therefore, strategies focused on maintaining CTSD function in neurons are potentially novel therapeutic approaches to prevent neuronal death in stroke

Name:
Mohammed Iqbal Hossain

Company:
University of Alabama at Birmingham

Email:
iqbal7@uab.edu

Phone:
2052537969

Track2- B1 and D1, 7/22, 8:15-9:30Am

Regulation of stressed lysosomes by LRRK2 in macrophage lineage cells

Tomoki Kuwahara

The University of Tokyo

Leucine-rich repeat kinase 2 (LRRK2), a Rab kinase associated with Parkinson's disease (PD), has been implicated in the regulation of lysosomes. We have investigated the cellular role of endogenous LRRK2 under lysosomal stress conditions. We found that, in RAW264.7 macrophage cell line and primary macrophages, treatment with lysosomotropic agents such as chloroquine induced the recruitment of LRRK2 onto enlarged lysosomes and enhanced LRRK2 activity to phosphorylate its substrate Rab GTPases. The phosphorylation of Rab8 on lysosomes worked to suppress lysosomal enlargement, whereas that of Rab10 induced the exocytic release of lysosomal contents. This release mechanism regulated by LRRK2/Rab was different from so-called lysosomal exocytosis and selectively observed in macrophage lineage cells. On lysosomes loaded with chloroquine, LC3 was colocalized with LRRK2, but this was likely different from lysophagy that accompanies the formation of double-membrane autophagosomes. Together, we have identified a novel mechanisms of lysosome regulation by LRRK2 under lysosomal stress conditions, which may also be relevant to the pathomechanism of PD.

Name:
Tomoki Kuwahara

Company:
The University of Tokyo

Email:
kuwahara@m.u-tokyo.ac.jp

Phone:
+81358413533

Autoimmune biomarker screening and functional validation in Parkinson's disease

Yin Xia CHAO[1,2,3], Jolene Tan[3], Bernett Lee[4], Olaf RÖTZSCHKE[4], Eng-King Tan[1,2,3]
Departments of Neurology (1) Singapore General Hospital, National Neuroscience Institute (2), Duke NUS Medical School (3)
Singapore Immunology Network, Agency for Science, Technology and Research (4)

Involvement of the immune system in the pathogenesis of Parkinson's disease (PD) has been proposed. However, there is a lack of an integrated platform for large scale immune profile screening and functional validation of shortlisted immune targets specifically for PD. Using NFS (neurotrophic factor S) as an example, I illustrate how my group has built an integrated system to screen and validate the immune markers in PD patients. Using two antibody screening platforms, we have identified a group of autoantibodies in PD patients, including NFS-autoantibody. We used a peptide library to characterize the NFS autoantibody epitopes. NFS specific T and B cells were also identified in a subset of PD patients. We will further characterize these T and B cells using clonal expansion, and ultimately produce PD specific NFS- autoantibodies and T cells in vitro for further functional study.

Email: chao.yinxia@singhealth.com.sg

Activation of Nrf2 in astrocytes suppressed PD-like phenotypes via antioxidant and autophagy pathways in rat and Drosophila models

Qing Guo , Bing Wang , Xiaobo Wang, Zhaohui Liu*

Department of Human Anatomy and Cytoneurobiology, Medical School of Soochow University, Suzhou, Jiangsu 215123, China

Abstract:
The oxidative-stress-induced impairment of autophagy plays a critical role in the pathogenesis of Parkinson's disease (PD). In this study, we investigated whether the alteration of Nrf2 in astrocytes protected against 6-OHDA- and rotenone-induced PD-like phenotypes using 6-OHDA-induced rat PD and rotenone-induced Drosophila PD models. In the PD rat model, we found that Nrf2 expression was significantly higher in astrocytes than in neurons. CDDO-Me (an Nrf2 inducer) administration attenuated PD-like neurodegeneration mainly through Nrf2 activation in astrocytes by activating the antioxidant signaling pathway and enhancing autophagy in the substantia nigra and striatum. In the PD Drosophila model, the overexpression of Nrf2 in glial cells displayed more protective effects than such overexpression in neurons. Increased Nrf2 expression in glial cells significantly reduced oxidative stress and enhanced autophagy in the brain tissue. The administration of the Nrf2 inhibitor ML385 reduced the neuroprotective effect of Nrf2 through the inhibition of the antioxidant signaling pathway and autophagy pathway. The autophagy inhibitor 3-MA partially reduced the neuroprotective effect of Nrf2 through the inhibition of the autophagy pathway but not the antioxidant signaling pathway. Moreover, Nrf2 knockdown caused neurodegeneration in flies. Treatment with CDDO-Me attenuated the Nrf2-knockdown-induced degeneration in the flies through the activation of the antioxidant signaling pathway and increased autophagy. An autophagy inducer, rapamycin, partially rescued the neurodegeneration in Nrf2-knockdown Drosophila by enhancing autophagy. Our results indicate that the activation of the Nrf2-linked signaling pathways in glial cells plays an important neuroprotective role in PD models. Our findings not only provide a novel insight into the mechanisms of Nrf2–antioxidant–autophagy signaling but also provide potential targets for PD interventions.

Keywords: Parkinson's disease; Nrf2; neurodegeneration; oxidative stress; autophagy

Email: zhliu@suda.edu.cn

Unraveling LRRK2-Induced Neurodegeneration in Parkinson's Disease Models-

Vinita G. Chittoor-Vinod,[1,2] Hanna Roshak,[1,2] Kelsey Shea,[1,2] Steffany Villalobos-Cantor,[1,2] Leire Abalde-Atristain,[3] and **Ian Martin**[1,2]

[1]Department of Neurology, Jungers Center for Neurosciences Research, Oregon Health and Science University, Portland, Oregon 97239, [2]Parkinson Center of Oregon, Portland, Oregon 97239, and [3]The Vollum Institute, Oregon Health and Science University, Portland, Oregon 97239

A major role for leucine-rich repeat kinase 2 (LRRK2) mutations in familial and idiopathic PD has emerged. The common LRRK2 G2019S mutation results in age-related dopamine neuron loss and locomotor dysfunction in Drosophila melanogaster through a mechanism involving elevated bulk neuronal protein synthesis. Under nonpathologic conditions, protein synthesis is tightly controlled by metabolic regulation. Whether nutritional and metabolic influences on protein synthesis can modulate the pathogenic effect of LRRK2 on protein synthesis and thereby impact neuronal loss is a key unresolved question. Here, we show that dietary amino acids are important determinants of neurodegeneration in a Drosophila model of LRRK2 PD. Restricting all amino acids effectively suppresses protein synthesis and the dopaminergic neuron loss and locomotor deficits caused by mutant. Similarly, amino acid restriction blocks neurite loss and cell death in rat primary neurons expressing LRRK2 G2019S. Moderately high amino acids similarly attenuate these PD-related phenotypes through a sestrin stress-responsive induction of 5'-AMP-activated protein kinase (AMPK) and autophagy. At the highest amino acid diet of the range tested, PD-related neurodegeneration occurs in an age-related manner, but is also observed in control strains, suggesting that it is independent of mutant LRRK2 expression. These studies suggest that diet plays an important role in the development of PD-related phenotypes linked to LRRK2.

Name:
Ian Martin

Company:
OHSU
Email:
martiia@ohsu.edu

Phone:
5034949140

Differential metabolism of α-Syn pre-formed fibril (PFFs) neuronal and nonneuronal cells

Md. Razaul Karim, Emilie Gasparini, Hector Martell Martinez, Md. Abdur Rashid, Balvindar Singh, and Michael K. Lee

Department of Neuroscience, University of Minnesota, Minneapolis, MN 55414, USA
Institute for Translational Neuroscience, University of Minnesota, Minneapolis, MN 55414, USA

Parkinson's disease (PD) and other α-synucleinopathies are characterized by the accumulation of α-synuclein (αS) aggregates. Studies indicate that αS pathology can spread via the cell-to-cell transmission of αS pathology. To better understand how various brain cells contribute to the spreading of αS pathology, we examined the metabolism of αS pre-formed fibril (PFFs) by neurons and glial cells (microglia, astrocytes, and oligodendrocytes). Our results show that microglia and astrocytes rapidly metabolize αS PFF where the half live of αS PFF in these glial cells are ~5 hours. In neurons, while the full-length αS rapidly disappears following αS PFF uptake, truncated αS accumulates with the half-life of over 48 hours. Epitope mapping and fractionation studies indicate that in αS PFF is truncated at C-terminal region and remains insoluble/aggregated. The differential processing of αS can be recapitulated in cell lines as differentiated CLU neuronal cell lines show stable accumulation of truncated αS while undifferentiated cells rapidly metabolize αS. Immunolocalization and subcellular fractionation studies show that αS PFF is initially localized to endosomes followed by lysosomes. Inhibition of lysosomal function leads to stabilization of full-length and truncated αS in all cell types. Our data show that lysosomal degradation system is involved in the metabolism of extracellular αS aggregates taken up by various cell types. Further, our studies indicate that glial cells protect neurons αS aggregates by rapid clearance of αS aggregates while αS aggregates taken up by neurons are metabolized to aggregation prone C-terminally truncated αS.
Supported by NIH grants NS012093 and NS086074

Name:
Md. Razaul Karim

Company:
University of Minnesota

Email:
karimr@umn.edu

Phone:
6128896301

Track 1- A2. 7/22, 10:20Am-12:40Pm

Lysosomal Proteomics Reveals Cell- and Tissue-Specific Organelle Compositions

Peter Mosen, Fatema Akter, Anne Sanner, Srigayatri Ponnaiyan, and Dominic Winter

Institute for Biochemistry and Molecular Biology, University of Bonn, Germany

Lysosomes are the central lytic organelles of eukaryotic cells. Their main function is the degradation of cellular macromolecules and the recycling of their building blocks. Furthermore, it is becoming wellestablished that lysosomes are involved in a large number of other processes and act as metabolic signaling center of the cell. The lysosome's crucial role is exemplified in case of its malfunction, which results in a group of ~70 rare inherited diseases, so-called lysosomal storage disorders, as well as more common conditions such as neurodegenerative diseases. Better knowledge of the lysosomal proteome holds the promise for a better understanding of such disorders as well as general cellular mechanisms. We utilized lysosome enrichment and mass spectrometry-based proteomics to investigate the lysosomal proteome from six different widely-used cell lines. Comparison of lysosomal composition revealed, for the first time on a large scale, unique lysosomal properties of each cell line. To facilitate the reproducible and sensitive analysis of the lysosomal proteome in complex samples without enrichment, we further developed targeted assays covering the currently known lysosomal proteome, which outperform unbiased approaches for the analysis of whole tissue samples. Finally, we generated stable isotope-labeled standards for a selection of 143 lysosomal core proteins, enabling the absolute quantification of the lysosomal proteome from cells and tissues. Utilizing this strategy, analysis of enriched lysosomes, cell lines, and nine different mouse tissues, resulted in a first draft of lysosomal protein stoichiometry and revealed differences in absolute lysosomal protein abundances for different types of cells and tissues

Name:
Dominic Winter

Company:
University of Bonn, Gernany

Email:
dwin@uni-bonn.de

Phone:
+49228737081

Understanding LRRK2 in Parkinson's – mapping protein families to function and disease

Patrick Lewis, Ph.D.
Royal Veterinary College,
University of London, UK

Email: plewis@rvc.ac.uk

Abstract:

Mutations in leucine rich repeat kinase 2 are the most common genetic cause of Parkinson's, but despite well over a decade of research our understanding of the cellular functions of LRRK2 and its role in disease aetiology remain incomplete. LRRK2 belongs to two distinct protein families: the ROCO proteins (based upon the presence of a ROC/COR domain) and the Receptor Interacting Protein (RIP) kinases. To gain insights into LRRK2 function, we have previously examined the interactomes of the ROCO proteins and are now extending this to the RIP kinases – comparing and contrasting the pathways held in common and divergent with LRRK2.

Talk title: Mitophagy regulation of energy metabolism in neurons

Abstract:

Mitochondria are the main cellular energy powerhouses and supply most of the energy in the form of ATP to fuel essential neuronal functions through oxidative phosphorylation (OXPHOS). In Alzheimer disease (AD), metabolic and mitochondrial disruptions are an early feature preceding any histopathological and clinical manifestations. Mitochondrial malfunction is also linked to synaptic defects in early AD. Mitophagy serves as a key cellular quality control mechanism involving sequestration of damaged mitochondria within autophagosomes and their subsequent degradation in lysosomes. However, it remains largely unknown whether mitophagy is involved in the regulation of energy metabolism in neurons, and if so, whether metabolic deficiency in AD is attributed to mitophagy dysfunction. Here we reveal that mitophagy is broadly activated in metabolically enhanced neurons upon OXPHOS stimulation, which sustains high energetic activity by increasing mitochondrial turnover and hence facilitating mitochondrial maintenance. Unexpectedly, in AD-related mutant HsAPP Tg mouse brains, early stimulation of OXPHOS activity fails to correct energy deficits but exacerbates synapse loss as a consequence of mitophagy failure. Excitingly, lysosomal enhancement in AD neurons restores impaired metabolic function by promoting elimination of damaged mitochondria, protecting against synaptic damage in AD mouse brains. Taken together, we propose a new mechanism by which mitophagy controls bioenergetic status in neurons, furthering our understanding of the direct impact of mitophagy defects on AD-linked metabolic deficits and shedding light on the development of novel therapeutic strategies to treat AD by the early stimulation of mitochondrial metabolism combined with elevation of lysosomal proteolytic activity.

Name:
Qian Cai

Company:
Rutgers University

Email:
cai@biology.rutgers.edu
Phone:
848-445-1633

Parkinson Disease through the lens of cellular identity: From prioritization of risk variants to the identification of novel transcriptional programs for mitochondrial and synaptic function

Rita M. Cowell, Ph.D.

Chair of Neuroscience/Adjunct Associate Professor

Southern Research/University of Alabama at Birmingham

Here, I will present an approach my lab is using to prioritize PD GWAS-implicated genes for biological studies, using cell-type-specific transcriptional profiles as a guide. I will outline the process we used for gene selection, reporting the most common neuroanatomical enrichment patterns for PD-linked genes and demonstrating how a subset of genes influence synuclein-mediated toxicity in model systems. I will follow this analysis with a demonstration of how a similar approach can be used to guide functional studies of genes implicated in inherited forms of PD, to identify subsets of dopaminergic neurons vulnerable in synuclein models, and to reveal convergent molecules for drug targeting. Then, I will present functional studies regarding the identification of a transcriptional regulator capable of modulating the progression of dopaminergic dysfunction and loss in a mouse model of synucleinopathy. Altogether, this presentation will highlight the importance of considering cellular transcriptional identity in the design of PD-related studies and discuss novel pathways and putative genes for informing PD etiology and drug discovery.

Dr. Rita M. Cowell
Southern Research and the University of Alabama at Birmingham
rcowell@southernresearch.org
205-581-2216

The β-Amyloid Induces Abnormal Mitochondrial Proteostasis in Alzheimer's Disease

Wenzhang Wang
Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA

Impaired mitochondrial homeostasis is one of the prominent features of Alzheimer's disease (AD) but underlying mechanism is poorly understood. Mitochondrial quality control mechanisms stringently protect protein homeostasis (proteostasis), in which mitochondrial proteases and chaperones guard mitochondrial proteins by refolding and degradation of misfolded or damaged proteins. In this regard, we investigated the mitochondrial proteostasis in human AD brains and in AD models *in vitro* and *in vivo*. Our study demonstrated impaired mitochondrial proteostasis characterized as enormous mitochondrial misfolded proteins in human brains and in genetic models of AD. Importantly, the neurotoxic species of amyloid β, Aβ1-42, might trigger the mitochondrial unfolded protein response and deteriorate mitochondrial protease LONP1 in matrix that contributed the disturbed mitochondrial proteostasis in AD. These findings suggested a novel mechanism underlying featured mitochondrial dysfunction in AD and will benefit the future studies for therapeutic efforts to the disease.

Name:
Wenzhang Wang

Company:
Case Western Reserve University

Email:
wxw157@case.edu

Phone:
12163944466

Wolfdieter Springer, Ph.D. Associate Professor of Neuroscience Mayo Clinic Jacksonville, Florida, USA Email: springer.wolfdieter@mayo.edu

Title: Selective mitochondrial autophagy in health, aging, and neurodegeneration.

Abstract: The ubiquitin (Ub) kinase PINK1 and the E3 Ub ligase PRKN selectively recognize, label, and target damaged mitochondria to the autophagy-lysosome system for elimination (mitophagy). Loss of function mutations in either gene invariably lead to recessive early-onset Parkinson's disease (PD) and it is thought that the failure to identify and clear damaged mitochondria eventually results in neuronal death. In line with broad neuroprotective functions, reduced enzymatic activities or altered mitophagy flux may also contribute to risk, onset, and progression of later onset PD as well as other age-related, neurodegenerative conditions including Alzheimer's disease. These mitophagy dysfunctions can occur at different steps of a dynamic process and may be mitochondrial, autophagic, and/or lysosomal in nature, and thus are difficult to track. Phosphorylated Ub (pS65-Ub) is the joint product of PINK1 and PRKN, and due to an enzymatic feedforward mechanism can be used to determine both Ub kinase and ligase activities. Besides its functions as an allosteric activator and receptor for PRKN, pS65-Ub also serves as the 'mitophagy tag', and, while transient, can be used as specific and quantitative marker of mitochondrial damage. We have recently developed means to assess and follow pS65- Ub in cells and tissues as well as in blood samples from animal models and patients. This has further underscored the importance of mitophagy under endogenous conditions and its relevance to health, aging, and neurodegenerative disease. Additional efforts are underway to determine the suitability of pS65-Ub as a potential disease or pharmacodynamics marker

Dysregulation of the phosphorylation cycle of AP2M1 by LRRK2 impairs endocytosis and leads to dopamine neurodegeneration

Qinfang Liu1, 3, Judith Bautista-Gomez4, Daniel A. Higgins4, Jianzhong Yu2, 3*, **Yulan Xiong1**,3 *

1 Department of Neuroscience, University of Connecticut School of Medicine, Farmington, CT 06030, USA 2 Department of Physiology & Neurobiology, University of Connecticut, Storrs, CT 06269 USA 3 Department of Anatomy & Physiology, Kansas State University College of Veterinary Medicine, Manhattan, KS 66506, USA 4 Department of Chemistry, Kansas State University, Manhattan, KS 66506, USA

Abstract

Recent genetic evidence has revealed endocytic pathway plays a major role in Parkinson's disease (PD). However, the molecular mechanism is poorly understood. Here we report that LRRK2, the most genetic cause of PD, binds to and phosphorylates the µ1 subunit of the adaptor protein AP2 (AP2M1), the core component of endocytosis recently implicated in PD risk. Both knockout and overexpression of LRRK2 cause abnormal AP2M1 phosphorylation cycle and in turn endocytic defects. Mechanistically, LRRK2 knockout decreases AP2M1 phosphorylation required for the initial clathrin coated vesicle (CCV) formation while LRRK2 overexpression inhibits AP2M1 uncoating for entering into a new cycle of CCV formation. Dysregulated phosphorylation of AP1M1 from the brain but not thyroid tissues of LRRK2 knockout and G2019S-knockin mice suggests a previously unknown tissue-specific regulatory mechanism of endocytosis. Furthermore, we found LRRK2- dependent phosphorylation of AP2M1 mediates LRRK2-induced dopaminergic neurodegeneration in a Drosophila model of PD. Together, our study provides a direct mechanistic link between LRRK2, AP2 and endocytosis in PD pathogenesis

Name: Yulan Xiong

Company: University of Connecticut School of Medicine

Email:yxiong@uchc.edu

Phone:8606794116

Track 2-B2, 7/22, 10:20Am-12:40Pm

TREM2 mediates microglial neuroprotection against TDP-43-related neurodegeneration

Long-Jun Wu

Department of Neurology, Mayo Clinic, Rochester, MN, USA.

Abstract
Triggering receptor expressed on myeloid cell 2 (TREM2) is a surface receptor that, in the central nervous system, is exclusively expressed on microglia. TREM2 variants have been linked to increased risk for neurodegenerative diseases, but the functional effects of microglial TREM2 remain largely unknown. Here we investigated TAR-DNA binding protein 43 kDa (TDP-43)-related neurodegenerative disease via viral-mediated expression of human TDP-43 protein (hTDP-43) in mice or inducible expression of hTDP43 with defective nuclear localization signals in transgenic mice. We found that TREM2 deficiency impaired microglia phagocytic clearance of pathological TDP-43, and enhanced neuronal damage and motor function impairments. Mass cytometry analysis revealed that hTDP-43 induced a TREM2-dependent subpopulation of microglia with high CD11c expression and higher phagocytic ability. Using mass spectrometry and surface plasmon resonance, we further demonstrated an interaction between TDP-43 and TREM2, *in vitro* and *in vivo,* in hTDP-43-expressing transgenic mouse brains. We computationally identified the region within hTDP-43 that interacts with TREM2 and observed the potential interaction in ALS patient tissues. Our data reveal the novel interaction between TREM2 and TDP-43, highlighting that TDP-43 is a potential ligand for microglial TREM2 and the interaction mediates neuroprotection of microglial TREM2 in TDP-43-related neurodegeneration.

Title:
Professor
Name:
Long-Jun Wu
Company:
Mayo Clinic
Email: wu.longjun@mayo.edu
Phone: 5074225135

Harnessing the Potential of Hematopoietic Stem Cells for Targeted Delivery of Therapeutic Genes for Neurodegenerative Diseases

Robert A. Clark, Senlin Li –

University of Texas Health San Antonio

Hematopoietic stem cell transplantation (HSCT), a well-established approach in the oncology field, is increasingly in development for other indications, including neurodegenerative diseases. However, the toxicities of bone marrow pre-conditioning regimens, as well as challenges in the targeting of therapeutic genes, have delayed progress. Glial cell line-derived neurotrophic factor (GDNF) is a potent neuroprotective agent in vitro, as well as in animal models of Parkinson's disease (PD). Unfortunately, central nervous system delivery of GDNF in clinical trials has generally failed due to poor diffusion within brain tissue and the large size of the target region in human brain. To overcome this GDNF delivery conundrum, syngeneic bone marrow hematopoietic stem cells (HSCs) were transduced with a lentiviral vector expressing macrophage-specific promoter-driven GDNF and transplanted into MitoPark mice exhibiting PD-like impairments. Following novel non-toxic mobilization-enabled HSCT, transgene-expressing macrophages infiltrated and delivered GDNF to degenerating midbrain regions. Macrophage-mediated GDNF delivery not only ameliorated motor and non-motor deficits, but also mitigated loss of midbrain dopaminergic neurons and restored their axonal terminals in the striatum, thus resulting in recovery of striatal dopamine levels. In parallel studies, we demonstrated similar efficacy in a toxin (MPTP) model of PD, suggesting a central neuroprotective mechanism, independent of the specific pathway of injury. Our data support further development of mobilization-enabled HSCT-based macrophage-mediated GDNF gene delivery as a potential disease-modifying therapy for PD.

Name:
Robert A Clark
Company:
UT Health San Antonio

Email:Clarkra@uthscsa.edu

Phone:
2105670866

Parkinson's disease associated alleles at the LRRK2 locus influence disease risk via microglia

Mark R Cookson, PhD
Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda MD, USA

An important concept for understanding genetic risk in complex diseases is the pleomorphic risk locus. In this framework, we can link sporadic and inherited diseases through single genes, even when specific alleles have variable effects on gene function. A concrete example is the LRRK2 locus where coding variation is associated with dominantly inherited Parkinson's disease (PD), albeit with incomplete age-dependent penetrance, and non-coding variants also change risk of sporadic PD. I will discuss my laboratory's efforts to experimentally dissect risk variants at LRRK2 using both human brain and patient-derived induced pluripotent stem cells (IPSC). Our work revealed that genetic variation associated with PD risk is found in regions of open chromatin that are specifically active in microglia. These observations have prompted us to revisit the role of endogenous LRRK2 in microglia using a number of model systems including in vivo approaches.

Name:
Mark Cookson

Company:
National Institute on Aging

Email:
cookson@mail.nih.gov

Phone:
+13014513870

Glial pathology induced by adolescent cannabis exposure and genetic insults impacting brain maturation and cognitive behaviors

Atsushi Kamiya, Ph.D.

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

The deleterious effects of cannabis use during adolescence, a critical period for brain maturation, have gained greater attention as an environmental factor conferring the risk for psychiatric disorders. To date the vast majority of research investigating the molecular and cellular consequences of cannabis use on the brain has focused on cannabis-induced alterations in neuronal function. However, recent evidence suggests that glial cells contribute to the detrimental effects of cannabis exposure associated with psychopathology of psychiatric disorders. As most cannabis users do not develop neuropsychiatric symptoms, one can envision that cannabis exposure may be an environmental risk factor in individuals genetically predisposed to psychiatric disorders or cognitive abnormalities. In this talk, I will discuss the synergistic impact of adolescent cannabis exposure and genetic insults on brain maturation and function, with a focus on microglia and astrocytes pathophysiology.

Atsushi Kamiya, Ph.D.

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
akamiya1@jhmi.edu

Microglial ultrastructural diversity in health and neurodegeneration

Marie-Ève Tremblay

Microglia are the resident innate immune cells of the central nervous system that play key physiological and immunological roles throughout life. In the past few years, novel approaches such as single-cell RNA sequencing revealed that microglia are not a homogenous cellular population, and several transcriptomic subsets were identified. Therefore, understanding how microglial heterogeneity contributes to varied physiological and immune functions in health and disease is now required to design cellular interventions that specifically target (modulate, inhibit, or stimulate) contextually-relevant microglial functions.

In my presentation, I will discuss our characterization of ‘dark microglia’, an ultrastructurally-distinct microglial subset predominantly associated with adult pathological states, using a combination of immunocytochemical transmission electron microscopy, chip mapping, and focused-ion beam scanning electron microscopy with 3D reconstruction. These dark microglia are rare in young adult mice, but become highly prevalent upon maternal immune activation, chronic psychological stress, normal aging, and neurodegenerative disease (e.g., Alzheimer, Huntington, multiple sclerosis) pathology, where they represent up to two-thirds of the normal microglial population.

Dark microglia (i) display unique markers of cellular stress and metabolic alteration (e.g., electron dense cytoplasm/nucleoplasm giving them a dark appearance in electron microscopy, dilation of the Golgi and endoplasmic reticulum, accumulation of glycogen granules), (ii) have hyper-ramified processes that ensheath the vasculature, and (iii) extensively wrap around and engulf pre-synaptic and post-synaptic elements, as well as excitatory synapses. These features suggest a unique metabolic activity and support putative active roles of dark microglia in vascular and synaptic remodeling, across stress-induced plasticity, aging, and neurodegenerative disease pathology.

Title:
Prof.

Name:
Marie-Eve Tremblay

Company:
University of Victoria

Email:
evetremblay@uvic.ca

Phone:
2507218739

Upregulation of FABP7 induces a proinflammatory phenotype in astrocytes that is detrimental for neuronal survival.

Noah Kinscherf 1 ; Marcelo Vargas 2 , Mariana Pehar 1,3.

1Division of Geriatrics and Gerontology, Department of Medicine, University of WisconsinMadison, Madison, WI, USA. 2Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA. 3Geriatric Research Education Clinical Center, Veterans Affairs Medical Center, Madison, WI, USA.

Astrocytes are key regulators of central nervous system homeostasis and in pathological conditions, through loss of normal function or acquired new characteristics, influence the progression of neurodegenerative processes. We recently identified FABP7 (fatty acid binding protein 7) as a key regulator of astrocyte-neuron interaction. The expression of FABP7 is specifically upregulated by astrocytes in neurodegenerative diseases, including Alzheimer's disease (AD). In primary hippocampal astrocytes, the overexpression of FABP7 promotes a proinflammatory phenotype linked to NF-kB signaling activation. Importantly, we observed that the conditioned media from astrocytes overexpressing FABP7 induces the death of hippocampal neurons in culture. We also observed a decrease in the expression of specific enzymes involved in Ab clearance, suggesting that the upregulation of FABP7 expression by astrocytes in AD could have a negative impact on amyloid pathology. These effects are dependent on ligand binding, since they were not observed after overexpression of a mutant FABP7 protein with impaired ability to bind ligands. Our results suggest that FABP7 signaling in astrocytes could be a potential therapeutic target to ameliorate astrocyte-mediated inflammation and neuronal toxicity in AD

Title:
Assistant Professor

Name:Mariana Pehar

Company:
University of Wisconsin-Madison

Email:
mapehar@medicine.wisc.edu

Phone:
6082658140

Microglial Autophagy: A Neuroprotective Mechanism in Parkinson's and Alzheimer's disease

Zhenyu Yue PhD

Departments of Neurology and Neuroscience, Friedman Brain Institute, Icahn School of Medicine, New York, NY 10029
zhenyu.yue@mssm.edu
https://labs.icahn.mssm.edu/yuelab/

Microglia maintain brain homeostasis by removing neuron-derived components such as myelin, cell debris and synapse. The evidence linking microglia to neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD) is growing, however, the precise mechanisms remain poorly understood. A common pathological hallmark of AD, PD and other age-related neurodegenerative diseases is the accumulation of protein aggregates as a result of disruption of proteostasis in aged brains. Autophagy, as a major cellular bulk degradation pathway, is known to protect neurons through cell autonomous clearance of protein and membrane associated cargo in neuron. Whether or not autophagy plays a significant role in neuroprotective function of microglia, however, remains elusive. Our aim is to dissect pathophysiological function of microglial autophagy in the molecular mechanism underlying Parkinson's and Alzheimer's disease. We have recently investigated physiology of microglial autophagy in CNS and uncovered the mechanism for how neuron produced alpha-synuclein and A-beta activate and mobilize microglial autophagy in protection through digestion. Our study provides insight into how a conserved lysosome degradation mechanism controls disease protein aggregate formation, spreading and clearance, therefore identifying a novel therapeutic target of PD and AD.

Track 1-C1, 7/23, 8:15-9:55 Am

Systemic exosomal siRNA-mediated inhibition of huntingtin expression in transgenic mice of Huntington's disease.

Tengteng Wu1 , Mengchao Yu2, Li Zhang2, Xi Chen2, Smith Wanli3, Zhong Pei1

1. Department of Neurology, the First Affiliated Hospital, Sun Yat-Sen University
2. State Key Laboratory of Pharmaceutical Biotechnology, NJU Advanced Institute of Life Sciences,Jiangsu Engineering Research Center for MicroRNA Biology and Biotechnology, School of Life Sciences, Nanjing University
3. Department of Psychiatry, Division of Neurobiology, Johns Hopkins University School of Medicine

Abstract

Cell-derived exosomes have been demonstrated to be efficient carriers of small RNAs into brain tissue. However, the therapeutic potential of exosome-mediated siRNA has not been tested in Huntington's disease. The present study examined the potential of exosome-mediated siRNA delivery in N171-82Q and YAC128 mice. siRNA targeting human huntingtin exon 1 (HuHtt) transcript was loaded with modified exosomes expressing the neuron-specific rabies viral glycoprotein (RVG) peptide. RVG modified-exosomes with GFP-siRNA was administrated to GFP transgenic mice to evaluate the penetration of exosomal-siRNA into the brain tissue. In the pilot study, HuHtt-siRNA RVG-exosomes was intravenously injected into N171-82Q mice at 10mg/kg every two days for 2 weeks. HuHtt-siRNA VG-exosomes was them intravenously injected into YAC128 mice at 10mg/kg twice a week for 8 weeks. Rotarod test and Western blot were used to examine motor function. and HTT expression, respectively. RVG modified-exosomes efficiently and specifically delivered siRNA into the mouse brain. In N171-82Q mice, siRNA-loaded RVG exosomes improved the motor function and reduced HuHtt protein. Similarly, In YAC128 mice, siRNA-loaded RVG exosomes treatment started at 6 week age postponed the onset of motor deficit and significantly reduced HuHtt protein. The present results demonstrate that RVG exosomes can efficiently transfer siRNA to the central nervous system. HuHtt-siRNA RVG-exosomes significantly reduce huntingtin expression and alleviate motor phenotype. The present study indicates a therapeutic potential of HuHtt-siRNA RVG-exosomes in Huntington's disease.

Zhong Pei, MD., Ph.D.

Department of Neurology, the First Affiliated Hospital, Sun Yat-Sen University, China

Email: peizhong@mail.sysu.edu.cn

Age-associated changes in the human midbrain dopamine cell transcriptome and proteome:

Rahul Bharadwaj

The human dopamine (DA) system is unique in that DA neurons, especially in the substantia nigra pars compacta (SNpc), undergo neurodegeneration as part of normal aging. However, the topographically distinct midbrain - ventral tegmental area (VTA) DA neurons are comparatively preserved over age. The underlying molecular bases for this age-associated selective DA degeneration is largely unknown. Now, with the availability of well-characterized control and diseased postmortem brain subjects, and the development of DA whole cell enrichment techniques, we are investigating age-associated molecular differences between the midbrain SNpc and VTA DA cell populations. We will perform laser capture microdissection (LCM) - RNA-sequencing and proteomics in whole DA neurons. Besides deriving DA cell-type mechanistic risk associations (transcriptome and proteome) for schizophrenia and Parkinson's disease genetic loci, we will identify protein networks underlying age-associated degenerative disorders such as late-onset Parkinson's disease (PD) and Lewy body disease (LBD). RNA-sequencing will allow for quantification of multiple gene features (genes/transcripts/exons/exon junctions) with corresponding quantitative mass spectrometry proteomics resolving transcript isoform expression for several DA cell-type expressed genes. Pilot study results from control subjects have identified some preliminary protein expression differences in oxidative stress related pathways. *Our study additionally seeks to generate age-associated expression and isoform characterization of known PD targets in midbrain DA neurons – a translational dataset for the development of drug targets aimed at the causal, and not purely symptomatic mechanisms of PD.*

Name:
Rahul Bharadwaj

Company:
Lieber Institute for Brain Development

Email:
rbharad2@jh.edu

Phone:
6179590965

Inhibition of LRRK2 GTP binding activity reduces neuroinflammation.

Wanli W Smith, MD., Ph.D.

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA 21287

Abstract

Mutations in the leucine-rich repeat kinase-2 (*LRRK2*) gene cause autosomal-dominant Parkinson's disease (PD) and contribute to sporadic PD. My presentation covers the research findings from our group on LRRK2 neurobiology, mutant-LRRK2-linked PD pathogenesis and anti-inflammatory effects of novel LRRK2 GTP binding inhibitors. Previously we identified that LRRK2 kinase and GTP binding activities play critical roles in neurodegeneration and protein inclusion formation. Recently we have identified a series of LRRK2 GTP binding inhibitors which can inhibit LRRK2 kinase activity, and provide a useful tool for further studying LRRK2 functions and for developing potential therapeutics for LRRK2-linked PD intervention. We found that LRRK2 GTP binding inhibitors not only protected against PD-linked mutant LRRK2-induced neuronal degeneration, but also displayed anti-inflammatory effects by reducing LPS-induced brain microgliosis and TNF-alpha release in B-type lymphoblast. Our findings not only provide insight into molecular mechanisms underlying PD pathogenesis but also identify lead-compounds for further drug discovery.

Wanli Smith, MD., Ph.D.

Associate Professor

Director of Cellular Neurobiology Laboratory

Neurobiology Division, Department of Psychiatry,

Johns Hopkins University School of Medicine,

CMSC 8-121, 600 North Wolfe Street; Baltimore, MD 21287

Phone: 410-6146268; Fax: 410-614-0013; Email: wsmith60@jhmi.edu

Neuroprotective roles of the gaseous signaling molecule, hydrogen sulfide, in Alzheimer's disease

Bindu D. Paul

Alzheimer's disease (AD) is a relentless, progressive neurodegenerative disease leading to cognitive and memory deficits as well as impaired executive function. Neuropathologic hallmarks of AD include deposition of amyloid plaques, neurofibrillary tangles (NFTs) and paired helical filaments in the brain. Mutations in the microtubule-associated protein Tau, a major component of the NFTs, result in its hyperphosphorylation in AD. We show that signaling by the gaseous molecule hydrogen sulfide (H2S) is dysregulated in AD. H2S signals via a posttranslational modification termed sulfhydration/persulfidation, which occurs on reactive cysteine residues, wherein the –SH group is converted to an –SSH group. Sulfhydration is a substantially prevalent modification and participates in diverse physiological processes. We show that sulfhydration is diminished in 3xTg-AD mice as well as in human AD brains. Furthermore, H2S prevents hyperphosphorylation of Tau by sulfhydrating its kinase, glycogen synthase kinase 3β (GSK3β). Finally, we demonstrate that sulfhydration is diminished in AD, while administering the H2S donor sodium GYY4137 (NaGYY) to 3xTg-AD mice ameliorates motor and cognitive deficits in AD. Thus, stimulating the transsulfuration pathway responsible for H2S production may have therapeutic benefits in not only AD, but other diseases involving dysregulated H2S metabolism.

References: Giovinazzo D, Bursac B, Sbodio JI, Nalluru S, Vignane T, Snowman AM, Albacarys LM, Sedlak TW, Torregrossa R, Whiteman M, Filipovic MR, Snyder SH, Paul BD. Proc Natl Acad Sci U S A. 2021;118(4). doi: 10.1073/pnas.2017225118.

Paul BD. Front Aging Neurosci. 2021;13:659402. doi: 10.3389/fnagi.2021.659402.

Bindu D. Paul, PhD
Department of Pharmacology and Molecular Sciences
Johns Hopkins University School of Medicine
725 N Wolfe St, Hunterian Rm 307
Baltimore, MD 21205
Email:
bpaul8@jhmi.edu

Imaging neurovascular abnormalities in neurodegenerative diseases

Jun Hua, JHMI, KKI

Neurovascular abnormalities have been associated with many neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Advanced MRI approaches have been developed to probe functional, microvascular, metabolic and lymphatic changes in the human brain. In this presentation, we will discuss the application of these techniques in neurodegenerative diseases.

Jun Hua

Company:
JHMI, KKI

Email:
jhua1@jhu.edu

Phone:
4439233848

Track 1-C2, 7/23, 11:35Am-1:55Pm

Loss of Drosha and miRNA Biogenic Machinery in the Pathogenesis of Alzheimer's Disease

Zixu Mao,
Emory University School of Medicine, Atlanta, GA, USA

MicroRNAs (miRNAs) are small noncoding RNAs. They are ubiquitously expressed, regulate gene expression at the post-transcriptional level, and affect every important cellular process. The basic steps and essential components required for the canonical miRNA biogenesis are well understood. The RNase III enzyme Drosha in complex with protein DGCR8 initiates the maturation process of miRNAs in the nucleus by converting primary miRNAs to their precursor forms. Every type of brain cell expresses miRNAs. Strong evidence indicates that dysregulation of individual miRNAs occurs in and even underlies many neurological disorders including Alzheimer's disease (AD). Despite many examples of dys-homeostasis of individual miRNAs in AD, it remains largely unknown if dysfunction of the miRNA biogenesis machinery itself may be involved in the disease processes. This presentation will summary some of the current findings on how Drosha may be regulated, underline its potential as a stress sensor in cells, and offer new immunohistochemical and biochemical evidence supporting Drosha being significantly dysregulated by stress conditions or models associated with AD and in the postmortem brain of human AD patients. Together, they highlight the significance of decline in miRNA biogenic function as a key molecular change in the pathogenesis of AD.

Name:
Zixu Mao

Company:
Emory University

Email:
zmao@emory.edu

Phone:
404-712-8581

METTL3-dependent RNA m^{6}A dysregulation in Alzheimer's disease

Fanpeng Zhao[1], Ying Xu[2], Shichao Gao[2], Wenzhang Wang[1], **Xiongwei Zhu[1]**
[1]Department of Pathology, Case Western Reserve University, Cleveland, Ohio, USA
[2] Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, the State University of New York, Buffalo, NY 14214, USA

Background: N6-methyladenosine (m^{6}A) modification of RNA influences fundamental aspects of RNA metabolism and m^{6}A dysregulation is implicated in various human diseases. In this study, we explored the potential role of RNA m^{6}A modification in the pathogenesis of Alzheimer disease (AD). **Methods:** We investigated the m^{6}A modification and the expression of m^{6}A regulators in the brain tissues of AD patients and determined the impact and underlying mechanism of manipulated expression of m^{6}A levels on AD-related deficits both *in vitro* and *in vivo*. **Results:** We found decreased neuronal m^{6}A levels along with significantly reduced expression of m^{6}A methyltransferase like 3 (METTL3) in AD brains. Interestingly, reduced neuronal m^{6}A modification in the hippocampus caused by METTL3 knockdown led to significant memory deficits, accompanied by extensive synaptic loss and neuronal death *in vivo*. Restored m^{6}A modification by inhibiting its demethylation *in vitro* rescued neuronal deficits and death induced by METTL3 knockdown. Soluble Aβ oligomers caused reduced METTL3 expression and METTL3 knockdown exacerbated while METTL3 overexpression rescued Aβ-induced synaptic PSD95 loss in vitro. Importantly, METTL3 overexpression rescued Aβ-induced synaptic damage and cognitive impairment *in vivo*. **Conclusions:** Collectively, these data suggested that METTL3 reduction-mediated m^{6}A dysregulation likely contributes to neurodegeneration in AD.

Title:
Professor

Name:
Xiongwei Zhu

Company:
Case Western Reserve University

Email:
xiongwei.zhu@case.edu

Title: *RNA toxicity and perturbation of* rRNA processing in spinocerebellar ataxia type 2

Pan P. Li, Ph.D.[1]*, Roumita Moulick, Ph.D.[2], Hongxuan Feng, Ph.D.[1], Xin Sun, Ph.D.[1], Nicolas Arbez, Ph.D.[1], Jing Jin, M.D., Ph.D.[1], Leonard O. Marque, B.S.[1], Erin Hedglen, M.A.[1], H.Y. Edwin Chan, Ph.D.[3], Christopher A. Ross, M.D., Ph.D.[1,4,5], Stefan M. Pulst, M.D.[6], Russell L. Margolis, M.D.[1,4] , Sarah Woodson, Ph.D.[2], Dobrila D. Rudnicki, Ph.D.[1]

[1]Department of Psychiatry and Behavioral Sciences, Division of Neurobiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]T.C. Jenkins Department of Biophysics, Johns Hopkins University, Baltimore, Maryland, USA; [3]Biochemistry Program, School of Life Sciences, The Chinese University of Hong Kong, Hong Kong; [4]Department of Neurology, and [5]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [6]Department of Neurology, University of Utah, Salt Lake City, Utah, USA; *Corresponding Author

Abstract

BACKGROUND: Spinocerebellar ataxia type 2 (SCA2) is a neurodegenerative disease caused by expansion of a CAG repeat in *Ataxin-2* (*ATXN2*) gene. The mutant ATXN2 protein with a polyglutamine tract is known to be toxic and contributes to the SCA2 pathogenesis.

OBJECTIVE: Here we tested the hypothesis that the mutant *ATXN2* transcript with an expanded CAG repeat (*expATXN2*) is also toxic and contributes to SCA2 pathogenesis.

METHODS: The toxic effect of *expATXN2* transcripts on SK-N-MC neuroblastoma cells and primary mouse cortical neurons was evaluated by caspase 3/7 activity and nuclear condensation assay, respectively. RNA immunoprecipitation assay was performed to identify RNA binding proteins (RBPs) that bind to *expATXN2* RNA. Quantitative PCR was used to examine if rRNA processing is disrupted in SCA2 and Huntington disease (HD) human brain tissue.

RESULTS: *expATXN2* RNA induces neuronal cell death, and aberrantly interacts with RBPs involved in RNA metabolism. One of the RBPs, transducin β-like protein 3 (TBL3), involved in rRNA processing, binds to both *expATXN2* and expanded *huntingtin* (*expHTT*) RNA *in vitro*. rRNA processing is disrupted in both SCA2 and HD human brain tissue.

CONCLUSION: These findings provide the first evidence of a contributory role of *expATXN2* transcripts in SCA2 pathogenesis, and further support the role *expHTT* transcripts in HD pathogenesis. The disruption of rRNA processing, mediated by aberrant interaction of RBPs with *expATXN2* and *expHTT* transcripts, suggest a point of convergence in the pathogeneses of repeat expansion diseases with potential therapeutic implications.

Title:Assistant Professor
Name:Pan Li
Company:Johns Hopkins University
Email:ple5@jhmi.edu
Phone:4438385160

RNA Binding Protein FUS and Amyotrophic Lateral Sclerosis

Haining Zhu
Department of Pharmacology and Toxicology
College of Pharmacy
University of Arizona

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with no effective treatment. Fused in Sarcoma (FUS) is a DNA/RNA binding protein and mutations in FUS cause a subset of familial ALS. Most ALS mutations are clustered in the C-terminal nuclear localization sequence of FUS and consequently lead to the accumulation of protein inclusions in the cytoplasm. The physiological function of FUS remains to be better understood. It is also unclear how mutations in FUS cause motor neuron degeneration and ALS. Our laboratory has characterized the wild-type and disease-causing mutants of FUS using a variety of approaches including proteomics, biochemistry, cell biology and genetic models. Our recent studies show that the ALS mutations of FUS suppress protein translation and dysregulate mRNA decay. We will also discuss the pos-translational modifications, particularly acetylation, of FUS that regulate its subcellular localization, RNA binding, and formation of protein-RNA condensates.

Zhu, Haining <haining@uky.edu>

Mutations in GEMIN5 lead to neurodevelopmental disorder with cerebellar atrophy, ataxia and motor dysfunction

Udai Pandey, PhD, Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA

GEMIN5 is an RNA-binding protein known to regulate the survival motor neuron (SMN) protein complex assembly and the formation of small nuclear ribonucleoproteins (snRNPs). We identified over 35 affected individuals from 28 unrelated families presenting with developmental delay, hypotonia, and cerebellar ataxia harboring biallelic variants in the GEMIN5 gene. Mutations in GEMIN5 perturb the subcellular distribution, stability, and expression of GEMIN5 protein and its interacting partners in patient iPSC-derived neurons, suggesting a potential loss-of-function mechanism. GEMIN5 mutations result in disruption of snRNP complex assembly formation in patient iPSC neurons. Furthermore, knock down of rigor mortis, the fly homolog of human GEMIN5, leads to developmental defects, motor dysfunction, and a reduced lifespan. Interestingly, we observed that GEMIN5 variants disrupt a distinct set of transcripts and pathways as compared to SMA patient neurons, suggesting different molecular pathomechanisms. These findings suggest that loss-of-function of GEMIN5 perturb physiological functions and result in a neurodevelopmental syndrome.

Name:
Udai Pandey

Company:
University of Pittsburgh Medical Center

Email:
udai@pitt.edu

Phone:
412-692-3192

TDP-43 and Mitochondrial Dysfunction in Alzheimer's disease

Xinglong Wang, Ph.D.

Abstract

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, characterized clinically by progressive decline in cognitive function and neuropathologically by the presence of senile plaques and neuronal loss in the brain. While current drugs for AD are always employed as symptomatic therapies with variable benefits, there is no treatment to delay its progression or halt neurodegeneration. TAR DNA-binding protein 43 (TDP-43) proteinopathy has increasingly been implicated as a prominent histopathological feature crucial for cognitive impairment in AD. We have found that accumulated cytoplasmic TDP-43 in degenerating neurons of patients with AD mainly resides inside of mitochondria. Within mitochondria, TDP-43 preferentially binds mitochondria-transcribed messenger RNAs (mRNAs) encoding respiratory complex I subunit ND3 and ND6, impair their expression and specifically cause complex I disassembly. Based on identified motifs critical for TDP-43 mitochondrial localization, we have synthesized a competitive inhibitory peptide that can prevent the accumulation of TDP-43 in mitochondria and abolish TDP-43-induced mitochondrial dysfunction and neuronal loss. Excitingly, suppression of TDP-43 mitochondrial localization by this synthetic inhibitory is sufficient to greatly alleviate TDP-43 proteinopathy, mitochondrial abnormalities, microgliosis and even neuronal loss without significant effect on amyloid plaque load in 12-month-old 5XFAD mice well after the onset of symptoms. Additionally, PM1 drastically improves the cognitive and motor function in 12-month-old 5XFAD mice and completely prevents the onset of mild cognitive impairment in 5-month-old 5XFAD mice. Our study suggests mitochondrial TDP-43 as a promising novel therapeutic target for AD and other TDP-43-linked neurodegenerative diseases.

Xinglong Wang, Ph.D
Lazar and Harriet Singer Professor of Neuroscience
Department of Pharmacology and Experimental Neuroscience | UNMC College of Medicine
E-mail: xinwang@unmc.edu, Phone: 402-559-7758

Cathepsin D/Granulin interaction is vital for lysosomal function and neuronal survival in stroke

Shaida A Andrabi[1,2] and Mohammed I. Hossain[1],

Departments of [1]Pharmacology and Toxicology, [2]Neurology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA (sandrabi@uab.edu)

Stroke is a leading cause of death and long-term disability. One prominent feature in the complex pathophysiology of stroke is the aggregation of damaged proteins, which is mainly attributed to lysosomal dysfunction. Our studies show that Cathepsin D (CTSD) loss is a critical pathological process leading to lysosomal dysfunction in stroke. Restoring CTSD could be a pivotal process to recover lysosomal function in stroke. Neuronal lysosomes lacking CTSD are proteolytically inactive, suggesting CTSD is an essential cathepsin required for neural lysosomal function. Severe phenotype, including progressive neurodegeneration and neuronal defects in different brain regions in CTSD knockout mice, further support the importance of CTSD in the brain. Our data show that loss of the activities of other lysosomal cathepsins in stroke is recovered by replenishing CTSD, demonstrating that in neurons, CTSD is critical for the function of lysosomes and cell survival. We analyzed the protein network of CTSD using LC-MS/MS on CTSD immunoprecipitated samples from neural cells and identified that Progranulin (PRGN) as the most interesting protein. Previous studies have indicated that PRGN interacts with CTSD to stabilize its function. PRGN is an essential cellular protein implicated in neurodegenerative diseases like ALS and FTD. A compelling body of evidence suggests that the lysosomal function of PRGN is due to its interactions with CTSD via its C-terminus, called Granulin E, which is endogenously generated by proteolytic cleavage from PRGN. Our data show that PRGN is significantly decreased in the neurons following OGD leading to loss of CTSD and lysosomal function. Our data also show that overexpressed Granulin E is neuroprotective by increasing the CTSD in neurons exposed to oxygen-glucose deprivation (OGD). These data provide evidence that Granulin E can be therapeutically very important as it can stabilize the CTSD levels/activity and preserve lysosomal function in stroke. The results indicate that drugs targeted to mimic Granulin E/CTSD interaction could be developed for limiting brain damage in stroke.

Track 2-D3, 7/23, 11:35Am-1:55Pm

14-3-3 proteins in neurodegeneration: highly versatile roles and novel regulation mechanisms

Susanna Cogo1,2, Francesco Agostini1, Elena Giusto3, Giulia Tombesi1, Lucia Iannotta1, Patrick Lewis4, Nicoletta Plotegher1, Marco Bisaglia1, Laura Civiero1,3, **Elisa Greggio1**

1 Department of Biology, University of Padova, Italy 2 School of Biological Sciences, University of Reading, UK 3 IRCSS, San Camillo Hospital, Venice, Italy 4 Royal Veterinary College, London, UK

14-3-3s represent a family of evolutionary conserved proteinsthat bind specific phosphorylated motifs on client partners to regulate their activity, localization, folding, degradation and protein-protein interactions. Accumulating data point to a key role of these chaperons in neurodegenerative disorders (NDs). In this talk, I will discuss how a subset of 14-3-3s can regulate the localization and function of two proteins mutated in familiar forms of NDs, namely the Parkinson's disease associated kinase LRRK2 and SPG11/spatacsin whose mutations cause Hereditary Spastic Paraplegia with parkinsonism. I will then provide evidence that phosphorylation of 14-3-3s by the kinase PAK6 constitute a novel mechanism to regulate the binding affinity of 14-3-3s toward their partners, including LRRK2 and TFEB, the master regulator of lysosomal biogenesis and autophagy

Elisa Greggio, PhD Department of Biology, University of Padova, Italy

elisa.greggio@unipd.it

Invited

Function and regulation of ALDH1A1-positive nigrostriatal dopaminergic neurons in motor control and Parkinson's disease

Kathleen Carmichael1,2, Rebekah Evans3,4, Elena Lopez1, Lixin Sun1, Mantosh Kumar1, Jinhui Ding3, Zayd Khaliq4, and Huaibin Cai1,*

1Transgenic Section, 3Computational Biology Group, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, U.S.A.
2The Graduate Partnership Program of NIH and Brown University, National Institutes of Health, Bethesda, MD 20892, U.S.A.
3Department of Neuroscience, Georgetown University Medical Center, Washington DC, 20057 USA.
4Cellular Neurophysiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health Bethesda, MD 20892

Abstract

Dopamine is an important chemical messenger in the brain, which modulates movement, reward, motivation, and memory. Different populations of neurons can produce and release dopamine in the brain and regulate different behaviors. Here we focus our discussion on a small but distinct group of dopamine-producing neurons, which display the most profound loss in the ventral substantia nigra pas compacta of patients with Parkinson's disease. This group of dopaminergic neurons can be readily identified by a selective expression of aldehyde dehydrogenase 1A1 (ALDH1A1) and accounts for 70% of total nigrostriatal dopaminergic neurons in both human and mouse brains. Recently, we presented the first whole-brain circuit map of these ALDH1A1-positive dopaminergic neurons and reveal an essential physiological function of these neurons in regulating the acquisition of motor skills. In this review, we first summarize previous findings of ALDH1A1-positive nigrostriatal dopaminergic neurons and their connectivity and functionality, and then provide perspectives on how the activity of ALDH1A1-positive nigrostriatal dopaminergic neurons is regulated through integrating diverse presynaptic inputs and its implications for potential Parkinson's disease treatment.

*Corresponding author: Dr. Huaibin Cai, Transgenics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Building 35, Room 1A112, MSC 3707, 35 Convent Drive, Bethesda, MD 20892–3707, USA. Tel: +1 3014028087; Fax: +1 3014802830; Email: caih@mail.nih.gov.

Title: Amyloid-β and tau pathologies are both necessary for stimulating pathological progression of Alzheimer's disease

Tong Li

Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract:

Alzheimer's disease (AD) is characterized pathologically by the accumulation of Amyloid-β plaques and neurofibrillary tangles (NFT). Understanding the relationship between these hallmark AD pathologies and disease progression have been the focus for AD research. The early genetic studies would support the "Amyloid cascade hypothesis", which support the notion that abnormal accumulation of Amyloid-β in the brain would trigger the aggregation of tau leading to neurodegeneration and dementia. However, it is not known why both pathological is required for development of AD and whether the Amyloid-β plaques plaque is necessary and sufficient to drive the pathological conversion of wild-type tau. To address these critical questions, we developed mouse models in which wild-type tau is converted into tau aggregates and NFT. Using these novel mouse models, we demonstrated that neuritic plaque is required but not sufficient for the pathological conversion of wild-type tau. In addition to the neuritic plaque, a second determinant is required to drive the conversion of wild-type tau. The combination of Amyloid-β and tau pathologies further induce pathological progress of AD, such as neuroinflammation. Use a single-cell RNA-sequencing strategy, we profile microglia subtypes in mouse models: 1) harboring Aβ plaques; 2) exhibiting tau tangles; and 3) bearing both Aβ and tau pathologies. We reveal novel microglia subtypes induced by both Aβ and tau pathologies, but not by either alone. Our findings imply that both Aβ and tau pathologies are required to mediate the disease stage-specific induction of microglia, and identify new therapeutic targets for the treatment of AD.

Tong Li

Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Email: tli1@jhmi.edu

Role of Tau in progressive synaptic and memory deficits in a transgenic mouse model of α-synucleinopathy

Michael K. Lee
Department of Neuroscience, University of Minnesota

Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are clinically and neuropathologically highly related α-synucleinopathies that collectively constitute the second leading cause of neurodegenerative dementias. Genetic and neuropathological studies directly implicate α-synuclein (αS) abnormalities in PDD and DLB pathogenesis. While αS is thought to cause presynaptic dysfunction, we show that human mutant A53T αS causes aberrant localization of the microtubule-associated protein tau to postsynaptic spines in neurons, leading to postsynaptic deficits. We tested the in vivo role of tau in mutant αS dependent synaptic and memory deficit a mouse model of α-synucleinopathy (TgA53T). TgA53T mice exhibit progressive memory deficits associated with postsynaptic deficits in the absence of obvious neuropathological and neurodegenerative changes in the hippocampus. Removal of mouse tau expression in TgA53T mice (TgA53T/mTau$^{-/-}$) completely ameliorates cognitive dysfunction and concurrent synaptic deficits without affecting αS expression or accumulation of selected toxic αS oligomers. Among the known tau-dependent effects, memory deficits in TgA53T mice were associated with hippocampal circuit remodeling linked to chronic network hyperexcitability. This remodeling was absent in TgA53T/mTau$^{-/-}$ mice. Further chronic EEG analysis indicate that loss of tau completely suppresses progressive epileptic activity in TgA53T mice. Our studies also indicate that postsynaptic deficits, aberrant network hyperactivity, and memory deficits are mechanistically linked. Our results directly implicate tau as a mediator of specific human mutant A53T αS-mediated abnormalities related to deficits in hippocampal neurotransmission and suggest a mechanism for memory impairment that occurs as a consequence of synaptic dysfunction rather than synaptic or neuronal loss.
Michael K Lee

Company:
University of Minnesota

Email:
mklee@umn.edu

Phone:
612-625-8472

Immortalized Striatal Precursor Neurons Generated from Huntington's disease (HD) patient iPSCs for drug screening

Mali Jiang[1], Ronald Wang[1], Rashi Sultania[1], Emma Whelan[1], Anthony Tang[1], Sergey Akimov[1], Wanli Smith[1], Christopher A. Ross[1,2]

[1]Division of Neurobiology, Department of Psychiatry and Behavioral Sciences, [2]Departments of Neuroscience, Neurology and Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disease with a combination of motor, cognitive and behavioral impairments caused by an expanded CAG trinucleotide repeat (of variable length) in the huntingtin gene. To develop a more facile cell model, HD patient iPSCs were immortalized and differentiated into highly homogeneous medium-spiny-neuron like cultures. These immortalized striatal precursor neurons (ISPNs) recapitulated HD-like phenotypes of the parental iPSCs including MAP2/DARPP32 positive immune staining. Moreover, HD-ISPNs (180-CAG repeats) displayed greater mitochondrial depolarization and fragmentation than those of control ISPNs (33-CAG repeats). To develop a drug screening cellular platform, HD-ISPNs were placed in a 96-well plate format using CellTiter-Glo luminescent cell viability assay to measure ATP levels after BDNF withdrawal. There were significantly higher levels of toxicity in HD-ISPN lines compared with normal control lines after BDNF withdrawal. Replacement of BDNF (40-50 ng/ml) attenuated mutant HD-induced toxicity in both HD precursor and mature ISPNs. We are currently performing screening tests using libraries of kinase inhibitors and diverse chemical compounds. Our results indicate that ISPNs derived from HD iPSCs can be a useful cellular model platform for drug screening to combat HD.

Name:
Mali Jiang

Company:
JHU

Email:
mjiang5@jhmi.edu

Phone:
4105024232

Title: **Pathophysiological Mechanisms of VPS35 in Parkinson's Disease**

Darren Moore, Ph.D.

Affiliation: **Professor and Chair, Department of Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan**

Abstract:

Parkinson's disease (PD) is a chronic neurodegenerative movement disorder of unknown etiology. Mutations in at least 15 genes are known to cause familial forms of PD whereas genome-wide association studies implicate certain familial genes as risk factors for sporadic PD. Despite the preponderance of genetic evidence in explaining many cases of PD, the mechanism(s) by which mutations in each of these gene products precipitates selective neurodegeneration remains largely enigmatic. In most cases, the physiological function of these PD-linked proteins and the molecular basis of familial mutations remain obscure, whereas the anticipated interplay amongst these proteins in common pathological pathways leading to PD is poorly defined. In this talk, we describe our recent efforts in dissecting the molecular and cellular basis of mutations in the dominant PD-linked gene product, VPS35. We will discuss the development of novel cellular and rodent models for exploring the pathogenic effects of VPS35 mutations and how we are beginning to utilize such models for the identification of key molecular targets and cellular pathways that are important for VPS35-dependent neuronal damage. In particular, we will describe our efforts exploring potential functional interactions of VPS35 with LRRK2, alpha-synuclein and tau proteins. Our studies are important for the identification and validation of novel molecular targets and pathways that can be exploited for the development of new therapeutic agents to treat PD.

Darren Moore, Ph.D.

Affiliation: **Professor and Chair, Department of Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan**

Email: Darren.Moore@vai.org

LRRK2 and Parkinson's Disease

Jie Shen
Professor of Neurology
Harvard Medical School
Brigham and Women's Hospital

Abstract

LRRK2 mutations are the most common genetic cause of Parkinson's disease. Our analysis of *LRRK2*-deficient mice revealed an important role of LRRK2 in the regulation of protein degradation pathways and homeostasis of α-synuclein. Our further development of *LRRK1/2* double knockout (*LRRK* DKO) mice showed that *LRRK* DKO mice develop selective, age-dependent loss of dopaminergic (DA) neurons, accompanied with increases in apoptosis and α-synuclein as well as impaired autophagy-lysosomal pathway. Interestingly, *LRRK* DKO mice exhibit impaired motor coordination and reduced spontaneous activity at 10 months of age, before the onset of DA neuron death. Moreover, we found age-dependent, progressive loss of dopaminergic terminals in the striatum of *LRRK* DKO mice beginning at 12 months of age. Evoked dopamine release measured by fast-scan cyclic voltammetry in the dorsal striatum is also reduced in the absence of LRRK. Thus, *LRRK* DKO mice are a valuable PD genetic animal model that recapitulates key features of Parkinson's disease. These results demonstrate that LRRK plays an essential role in the regulation of the autophagy-lysosomal pathway and the maintenance of the dopaminergic function and survival in the aging brain.

Jie Shen, Ph.D.

Email: JSHEN@BWH.HARVARD.EDU

Young Investigator Session 1-7/22, 12:50-3:00Pm

Integrated Stress Response in alpha-synucleinopathy

Cenxiao Fang[1], Deepak Jangir[1], Percy Griffin[1], Md. Razaul Karim[1], Joyce Meints[1], Swati More[2], Michael K. Lee[1,3]

[1]Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA
[2]Center for Drug Design, University of Minnesota, Minneapolis, MN, USA
[3]Institute for Translational Neuroscience; University of Minnesota , Minneapolis, MN, USA

ABSTRACT

Abnormalities in α-synuclein (αS) is directly linked to the pathogenesis of Parkinson's disease (PD) and related disorders called α-synucleinopathies. We showed that α-synucleinopathy in a αS transgenic model (TgA53T) and humans causes chronic endoplasmic reticulum stress (ERS)/unfolded protein response (UPR)/Integrated Stress Response (ISR). Treatment of TgA53T with salubrinal, a compound that inhibits dephosphorylation of eIF2α and attenuates ERS induced toxicity, can significantly delay onset of αS pathology and motor deficits. To further establish ERS/UPR/ISR as an important pathogenic factor in α-synucleinopathy, we examined if reducing phosphorylation of eIFα by the Protein kinase R-like ER Kinase (PERK), exacerbates α-synucleinopathy. We show that conditional deletion of PERK in neurons of TgA53T mice leads to significantly earlier onset of α-synucleinopathy, showing the pathologic importance of PERK-eIF2α pathway. While salubrinal inhibits both the protein phosphatase 1 regulatory subunit 15A (PPP1R15A, Gadd34) and PPP1R15B (CReP), studies show that inhibition of Gadd34 could be neuroprotective. Significantly, neither the pharmacological inhibition of Gadd34 or genetic loss Gadd34 function attenuated α-synucleinopathy in TgA53T model. Significantly, treatment of TgA5t model with an CReP inhibitor delays disease onset and attenuates pathology in TgA53T model. Our data suggest ISR components, particularly inhibition of CReP, is a therapeutic target for α-synucleinopathy.

Funding: supported by grants from NIH to MKL (NS038065, NS086074, NS092093, NS108686).

Title: Ph.D Name:Cenxiao Fang

Company: University of Minnesota

Email: cenxiao@umn.edu

Phone: 8135076117
Category: YoungAward

Regulation of brain function by TDP-43 phase separation

Ju Gao[1], Luwen Wang[1], Xiaojia Ren[1], Justin R Dunn[1], Ariele Peters[1], Masaru Miyagi[2], Hisashi Fujioka[3], Fangli Zhao[4], Candice Askwith[4], Jingjing Liang[5], and Xinglong Wang[1]

[1]Department of Pharmacology and Experimental Neurosciences, University of Nebraska Medical Center, Omaha, NE, USA.
[2]Department of Pharmacology, Case Western Reserve University, Cleveland, OH, USA.
[3]Electron Microscopy Core Facility, Case Western Reserve University, Cleveland, OH, USA.
[4]Department of Neuroscience, The Ohio State University, Columbus, OH, USA.
[5]Departments of Pathology, Case Western Reserve University, Cleveland, OH, USA.

Abstract
Mutations in TARDBP, the gene encoding TDP-43, cause amyotrophic lateral sclerosis (ALS), and TDP-43 proteinopathy is closely associated with a wide range of neurological disorders, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD). Extensive evidence has shown that TDP-43 undergoes liquid-liquid phase separation (LLPS) in vitro and in cultured cells. However, the *in vivo* physiological function of TDP-43 LLPS remains elusive. Here, we generated mice expressing endogenous LLPS-deficient murine TDP-43. LLPS-deficient TDP-43 mice demonstrate impaired neuronal function and behavioral abnormalities specifically related to the brain function. Without showing TDP-43 proteinophathy or neurodegeneration, LLPS-deficient mice display greatly enhanced global protein translation rate. Mechanistically, TDP-43 LLPS ablation increased its association with PABPC4, RPS6, RPL7, and other translational factors. Our findings show a specific physiological role for TDP-43 LLPS in the regulation of brain function and uncover a novel molecular mechanism of translational control by LLPS.

Title:
Postdoc

Name:
Ju Gao

Company:
University of Nebraska Medical Center

Email:
jugao@unmc.edu

Phone:
2162628896

Message:

Category:
YoungAward

Member:
agree

Title: **Senescent Glia Drive and Underlie Alzheimer's Disease.**

Victor Z. Lau[1,2], Marie-Ève Tremblay[2], Leanne M. Ramer[1]

[1]Simon Fraser University, Burnaby, BC, Canada.
[2]University of Victoria, Victoria, BC, Canada

Alzheimer's Disease (AD) predominantly occurs as a late-onset form (LOAD), involving neurodegeneration and cognitive decline with progressive memory loss. Risk factors and aging promote accumulation of well-known AD hallmarks in oxidative stress, amyloid-beta and tau protein pathology, and neuroinflammation. Homeostatic glial cells regulate and suppress these AD hallmarks; however, these pathological hallmarks also recruit other maladaptive glia, subsequently leading to increased pro-inflammatory cytokine release and further hallmark accumulation. Different stresses can additionally induce cellular senescence, or an irreversible differentiation process involving decreased supportive functions and increased, pro-inflammatory cytokine release. While these pathophysiological underpinnings all contribute to LOAD, they are not well integrated temporally and mechanistically. We propose that traditional AD hallmarks induce glial senescence in LOAD, where sufficient senescent glia exacerbate ongoing AD pathology and primarily drive LOAD into clinical, cognitive decline. We first explore literature relating aging and increases in pro-inflammatory glial activity, and then discuss emerging evidence linking oxidative stress, neurons containing tau pathology, and amyloid-beta to senescence in microglia, oligodendrocyte progenitor cells, and astrocytes. Our evidence-based framework predicts that plaque-associated microglia and disease- or neurodegeneration-associated microglia are senescent, and that senescent microglia cluster and create neuritic plaques corresponding to LOAD progression. This would explain why medications used to treat LOAD fail, because they do not reduce senescent glial burden. This novel framework is also coherent with the predominant hypotheses surrounding LOAD involving glia, neuroinflammation, the amyloid cascade, and tau, creates testable hypotheses about LOAD, and increases rationale in testing senolytic treatments for LOAD arrest and reversal.

Authors: (information of affiliated institutions is incomplete).

Contact Information:

vzplau@gmail.com

evetremblay@uvic.ca

lramer@sfu.ca

Title: The Role of the GBA1 L444P heterozygous mutation in fibril-induced α-synuclein inclusions.

Abstract 2021

The University of Alabama at Birmingham

Casey Mahoney

Parkinson's disease (PD) is characterized by α-synuclein (α-syn) inclusions formed by the corruption of presynaptic α-syn to form phosphorylated, insoluble aggregates (p-syn). The most common genetic risk factor of PD is mutations in the glucocerebrosidase1 (GBA1) gene which encodes for the lysosomal enzyme, glucocerebrosidase 1 (GCase). When GBA1 is mutated, GCase enzymatic activity is reduced which increases the prevalence of α-syn inclusions and sphingolipids. Importantly, PD patients heterozygous for the GBA1 L444P mutation ($GBA^{+/-}$) have a 5-fold increased risk of developing dementia, suggesting the significance of GCase activity in inclusion formation and cognitive deficits. Thus, we propose that the **GBA1 L444P heterozygous mutation leads to reduced GCase activity leading to enhanced accumulation of α-syn aggregates and cognitive deficits**. To test this, we utilized the preformed fibril (PFF) model to induce inclusion formation in $GBA1^{+/-}$ knock-in mice of both sexes. We show that there is reduced GCase activity in various brain regions, increased pathology in the hippocampus, increased accumulation of glucosylsphingosine as it pertains to age and mutation, and behavioral deficits trends regarding the mutation. Ultimately, these findings suggest there is hippocampal dysfunction in this model.

Casey Mahoney-Crane
Graduate Student Trainee
Volpicelli-Daley Lab | Department of Neurology
Graduate Biomedical Sciences | Neuroscience Theme
UAB | The University of Alabama at Birmingham
Email: mahoneyc@uab.edu

A Mitochondrial Membrane-Bridging Machinery Mediates Signal Transduction of Intramitochondrial Oxidation

LI LI

ABSTRACT

Mitochondria are the main site for generating reactive oxygen species, which are key players in diverse biological processes. However, the molecular pathways of redox signal transduction from the matrix to the cytosol are poorly defined. Here we report an inside-out redox signal of mitochondria. Cysteine oxidation of MIC60, an inner mitochondrial membrane protein, triggers the formation of disulfide bonds and the physical association of MIC60 with Miro, an outer mitochondrial membrane protein. The oxidative structural change of this membrane-crossing complex ultimately elicits cellular responses that delay mitophagy, impair cellular respiration, and cause oxidative stress. Blocking the MIC60-Miro interaction or reducing either protein, genetically or pharmacologically, extends lifespan and health-span of healthy fruit flies, and benefits multiple models of Parkinson's disease and Friedreich's Ataxia. Our discovery provides a molecular basis for common treatment strategies against oxidative stress.

Title:
postdoc

Name:
LI LI

Company:
stanford

Email:
LI.LI.FU3@GMAIL.COM

Phone:
6692039797

Message:

Category:
YoungAward

Loss of tau expression attenuates neurodegeneration associated α-synuclein pathology in vivo

Scott C. Vermilyea[1], Annie Christensen[1], Balvindar Singh[1], Md. Razaul Karim[1], Joyce Meints[1], Michael K. Lee[1,2]

[1]Department of Neuroscience, University of Minnesota – Twin Cities, Minneapolis, MN, USA
[2]Institute for Translational Neuroscience; University of Minnesota – Twin Cities, Minneapolis, MN, USA

Neuronal dysfunction and degeneration linked to α-synuclein (αS) pathology is thought to be responsible for the neurodegeneration in Parkinson's Disease (PD) and related Lewy Body Dementia (LBD). Studies indicate bidirectional pathological relationships between αS pathology and tau abnormalities. For example, we showed that A53T mutant human αS (HuαS) can cause tau dependent post-synaptic and cognitive deficits. Therefore, we examined whether tau is involved in the onset and progression of overt α-synucleinopathy. We induced α-synucleinopathy by intramuscular (IM) injections of HuαS preformed fibrils (PFF) in the A53T mutant transgenic mice (TgA53T), in mTau$^{-/-}$ or wildtype background. IM inoculation of TgA53T mice leads to motor dysfunction onset by ~70 days post inoculation (dpi) and end-stage paralysis by ~100 dpi. Significantly, TgA53T/mTau$^{-/-}$ mice exhibit reduced motor deficits at 70 dpi and delayed onset of paralysis. Analysis of neuropathology shows that end-stage TgA53T mice and TgA53T/mTau$^{-/-}$ mice show comparable pathology. However, at 70 dpi, TgA53T/mTau$^{-/-}$ mice had modest yet significant reductions of α-synucleinopathy, including the loss of ventral motor neurons. Similarly, *in vitro* application of PFF to primary hippocampal neurons demonstrated no change of PFF induced pS129αS aggregation as a function of tau expression, but neurotoxic indicators including morphology and postsynaptic density deficits were prevented with tau removal. We conclude that while tau expression does not impact onset and progression of αS aggregation, loss of tau expression protects neurons from downstream toxic effects of αS aggregation. Therefore, tau reduction and the pathways activated may represent novel therapeutic targets for α-synucleinopathy.

NIH Grants to MKL: NS108686 and NS112540

Title: Dr. Name: Scott C. Vermilyea

Company: University of Minnesota

Email: svermily@umn.edu

Phone: 6086040266

Category: YoungAward

Inhibition of LRRK2 kinase activity promotes anterograde axonal transport and presynaptic targeting of α-synuclein

Charlotte F. Brzozowski1,2, Baraa A. Hijaz1 , Vijay Singh1 , Nolwazi Gcwensa1 , Kaela Kelly3 , Edward S. Boyden4 , Andrew B. West3 , Deblina Sarkar4 , Laura A. Volpicelli-Daley1

1 Department of Neurology, Center for Neurodegeneration and Experimental Therapeutics, University of Alabama at Birmingham, Birmingham, AL 35294 USA 2 Interfaculty Institute for Biochemistry, University of Tübingen, 72076 Tübingen, Germany 3 Duke Center for Neurodegeneration Research, Department of Pharmacology and Cancer Biology, Duke University, Durham, North Carolina, USA 4 MIT Media Lab and McGovern Institute, Departments of Brain and Cognitive Science and Biological Engineering, United States.

Pathologic inclusions composed of α-synuclein called Lewy pathology are hallmarks of Parkinson's Disease (PD). Dominant inherited mutations in leucine rich repeat kinase 2 (LRRK2) are the most common genetic cause of PD. The presence of Lewy pathology is frequent particularly in G2019S-LRRK2 PD cases, where it is associated with more frequent nonmotor symptoms than cases without Lewy pathology. In PD model systems, neuronal expression of G2019S-LRRK2 increases α-synuclein aggregate formation. αSynuclein and LRRK2 both localize to and associate with membranes at the presynaptic terminal. G2019SLRRK2 expression in neurons increases the cytosolic fraction of α-synuclein, suggesting a mechanism whereby LRRK2 kinase activity can influence α-synuclein aggregation. To determine if LRRK2 kinase activity influences α-synuclein localization to the presynaptic terminal, we used the selective LRRK2 kinase inhibitor, MLi-2. Expansion microscopy was used to more precisely resolve localization of α-synuclein with respect to presynaptic markers. The findings show that reduced LRRK2 kinase activity increases αsynuclein overlap with presynaptic markers. Using live imaging of axonal transport of α-synuclein-GFP demonstrated that inhibition of LRRK2 kinase activity also increases anterograde axonal transport of αsynuclein. Mice fed chow containing the selective LRRK2 kinase inhibitor, PF360, showed increased αsynuclein overlap with glutamatergic, presynaptic cortico-striatal terminals and dopaminergic nigrostriatal presynaptic terminals, compared to mice fed control chow. These data suggest that LRRK2 kinase activity plays a role in the neuronal trafficking and subcellular localization of α-synuclein.

Title:
Ms

Name:Charlotte Brzozowski

Company: UAB

Email: cfbrzozo@uab.edu

Phone:
6462504397
Category:
YoungAward

Microglial ultrastructural diversity in male and female aged wild-type and fractalkine receptor deficient mice

Chloe Grace McKee[1, 2], Marie-Kim St-Pierre[4, 5], Raad Nashmi[1, 2, 3], Marie-Ève Tremblay[1, 4, 5, 6, 7]

[1] Division of Medical Sciences, University of Victoria, Victoria, BC, Canada
[2] Department of Biology, University of Victoria, Victoria, BC, Canada
[3] Center for Biomedical Research, University of Victoria, Victoria, BC, Canada
[4] Axe Neurosciences, Centre de Recherche du CHU de Québec-Université Laval, Québec, QC, Canada
[5] Département de Médecine Moléculaire, Faculté de Médecine, Université Laval, Québec, QC, Canada
[6] Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada
[7] Department of Biochemistry and Molecular Biology, The University of British Columbia, Vancouver, BC, Canada

Abstract:

Microglia, the resident immune cells of the central nervous system, diversify phenotypically in old age, losing their ability to respond efficiently to inflammatory challenges. Dark microglia, a subset defined by their ultrastructural features associated with cellular stress and aging become more numerous in mice exposed to chronic psychological stress, aging, Alzheimer's disease pathology, and fractalkine receptor deficiency (CX_3CR1 knockout), where fractalkine signaling between neurons and microglia is prevented. Sex is an important variable in microglial diversity, notably during aging, yet sex-specific differences in microglial ultrastructure and dark microglia remain elusive and will be the focus of my upcoming honors thesis. By performing electron microscopy, I will quantify sex differences in microglial ultrastructure in aged (18-month-old) wild-type and CX_3CR1 knockout mice within the hippocampus CA1 region, important for learning and memory. I will quantify ultrastructural features associated with microglial cellular stress and aging to provide insights into the emergence of different microglial subsets with aging, including dark microglia, but also gitter, senescent, or dystrophic microglia. Features that I will investigate include microglial loss of heterochromatin pattern, mitochondrial elongation, endoplasmic reticulum dilation, lysosomes, lipofuscin granules, lipidic inclusions, phagocytic inclusions, and contacts with synapses. I will provide in my presentation preliminary observations from this imaging. As aged female microglia are thought to be less effective at responding to challenges, I predict that aged female mice will have increased microglial ultrastructural diversity (i.e. subsets such as dark microglia) compared to aged males, which will be exacerbated in CX_3CR1 knockout compared to wild-type mice.

Name: Chloe McKee

Institution: University of Victoria

E-mail: chloemckee@uvic.ca

Phone: 780-974-9561

Category: Young investigator award

Role of mitochondrial fission in progressive neurodegeneration and memory deficit after traumatic brain injury

Preethy S. Sridharan[1], Emiko Miller[1], Yeojung Koh[2], Edwin Vásquez-Rosa[3], Min-Kyoo Shin[3], Kathryn Z. Franke[5], Xin Qi[4], Andrew A. Pieper[1,3,4,5]

[1]Department of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, OH
[2]Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, OH
[3]Department of Psychiatry, University Hospitals, Cleveland, OH
[4]Department of Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH
[5]Harrington Discovery Institute, University Hospitals, Cleveland, OH

Traumatic brain injury (TBI) is linked with a 2-4-fold increased risk of developing dementia later in life. Since aberrant mitochondrial fission has been identified as a critical component of other neurodegenerative disorders, we hypothesized that such alterations would be involved in TBI as well. Given the chronic nature of TBI, we were interested in whether acute modulation of mitochondrial fission could prevent chronic disease. We subjected C57/bl6 mice to either TBI or sham injury, and subsequently treated them with either a specific peptide inhibitor of mitochondrial fission mediator Drp1, known as P110, or with vehicle control by daily intraperitoneal injection for two weeks. Following treatment, mice were subjected to a battery of neurobehavioral tests, including novel object recognition (NOR), open field test, and balance beam. Brain tissues were then processed for western blot analysis and staining.

Injured mice showed elevated Drp1 in the hippocampus 24hrs after injury, which returned to normal 2 weeks later, suggesting an acute, time-dependent increase in mitochondrial fission after injury. There were also acute changes in phosphorylation of Drp1 at the S616 and S637 sites, indicating altered Drp1-mediated fission activity. Two weeks following TBI, mice showed a memory deficit in NOR, which returned to control levels in mice that had been treated with P110. The same mice, when retested in NOR 6 months post-injury, showed sustained memory protection from early P110 treatment. Our data indicate that early inhibition of mitochondrial fission after TBI protects mice from cognitive impairment at both acute and chronic stages of injury.

Title:
Ms

Name:
Preethy Sridharan

Company:
Case Western Reserve University

Email:
pss46@case.edu

Phone:
9787932744

Message:
MD/PhD Candidate
Department of Neurosciences

Category:
YoungAward

Bilateral basal ganglia hemorrhage due to tentorial dural arteriovenous fistula and systematic literature review

Bing Wen Qinzhou Wang
Department of Neurology, Qilu Hospital, Shandong University, Jinan 250012;

Email：wendy-bing@hotmail.com

【Abstract】 **Objective**: The most common cause of basal ganglia hemorrhage is hypertension, especially in patients with a history of hypertension or whose blood pressure is significantly higher than normal after onset. However, a small number of patients with cerebrovascular malformations can also manifest as basal ganglia hemorrhage, which is easy to be misdiagnosed. The purpose of this study was to investigate the clinical characteristics of cerebral hemorrhage caused by tentorial dural arteriovenous fistula（TDAVF）. **Methods：** We reported an unusual TDAVF case complicated with hypertension with successive bilateral basal ganglia hemorrhage in short term. The characteristics of cerebral hemorrhage caused by TDAVF reported in the literature were summarized and analyzed. **Results:** The digital subtraction angiography (DSA) revealed that there was arteriovenous fistula in the tentorial foramen area of this patient, and the TDAVF was fed by the right meningohypophyseal trunk, bilateral middle meningeal artery and posterior cerebral artery. A shunted pouch was present in the tentorial foramen area, and retrograde reflux drainage was seen in the deep venous system, from the meningeal vein to superior sagittal sinus or sigmoid sinus. Transarterial embolization was performed and subsequently DSA showed obliteration of the fistula. This patient experienced no clinical decline or rehemorrhage during the 12 months follow-up period. We summarized 41 cases of TDAVF with hemorrhage of cerebral parenchyma which were reported before March 30, 2021 with detailed clinical and imaging data. The average age of onset of this group of patients was 57.2 years, and the ratio of male to female was about 3:1. The hemorrhage located in superior of the tentorium in 17 cases, while in inferior of the tentorium in 17 cases. Supratentorial intracerebral hemorrhage mainly occurred in occipital lobe and thalamus. DSA showed that the arteriovenous fistula was classified as Borden type III or Cognard type IV in 36 cases. 29 patients underwent a single surgical procedure while 12 cases underwent combined surgical or other treatments. Overall, 37 patients achieved angiographically documented obliteration of the fistula and 39 patients experienced good or excellent outcomes. **Conclusion:** TDAVF often presents as cerebral parenchymal hemorrhage which is common in supratentorial region, but rare in basal ganglia region. The cause of cerebral hemorrhage in patients with hypertension may not be attributed to hypertension. Early diagnosis and intervention are of great significance to improve the prognosis of patients.

Isolation and proteomic profiling of amyloid fibril core with ultra-high purity from AD mouse brains

Arun Upadhyay, Robert Vassar, Jeffrey N. Savas

Department of Neurology, Northwestern University Feinberg School of Medicine Chicago IL USA

ABSTRACT

Alzheimer's disease (AD) is a condition of progressive degeneration of neuronal cells and impaired memory over time. AD is primarily a consequence of the deposition of amyloid plaques outside of the cells. Our understanding of the detailed structural arrangements, amyloid formation pathways, and proteomic composition of the fibrils or plaques is in infancy. Alzheimer's diseaseassociated amyloid-beta 42 (Aβ42) peptide may assemble into multiple structural conformations inside and out of the cells, for example, oligomers, protofibrils, fibrils, plaques. We lack a clear understanding of the structural, physiological, biochemical, and clinical features of different conformations primarily due to the unavailability of purification methods of amyloid material from the AD mouse or human brain tissues. We have taken on the challenge, improved the previously described biochemical methods for amyloid isolation, and have drastically increased the purity and yield by more than a hundred fold. We identified numerous proteins associated with amyloid fibrils and plaques, which could be dissociated by putting them under high shear force generated during ultrasonication. Negative staining electron microscopy shows several micrometer-long fibrils and thicker fibrillar bundles consisting of several parallel fibers. The proteomic profile indicates an enrichment of Aβ42 content and dissociation of non-specifically bound proteins from the amyloid plaque cores. Future NMR studies and detailed proteomic characterization of these purified amyloids may help get better insights into the conformation, structural arrangements and composition of amyloid fibrils and plaques.

Title:
Dr.

Name:
Arun Upadhyay

Company:
Northwestern University

Email:
arun.upadhyay@northwestern.edu

Phone:
7086548713

Message:

Category:
YoungAward

Alpha-synuclein aggregation in the Amygdala

Nolwazi Gcwensa

UAB

Parkinson’s disease is a neurodegenerative disease characterized by pathological inclusions termed Lewy Pathology. These inclusions are primarily comprised of a ubiquitous protein, alpha-synuclein, which accumulates at the synapses. In some cases, this protein misfolds and aggregates forming toxic inclusions that correspond with cell death in dopaminergic neurons of the substantia nigra pars compacta (SNpc). This SNpc degeneration is a hallmark feature of PD and is thought to cause the motor symptoms associated with the disease. However, some 80% of PD sufferers also experience non-motor symptoms along with and sometimes preceding the motor symptoms. These symptoms, like apathy, hallucinations, anxiety and depressions do not correlate well with degeneration of the SNpc and might better be explained by looking at the effect of inclusions in other brain regions. Alpha-synuclein aggregation has been observed in the amygdala in a number of diseases like dementia with Lewy bodies and Alzheimer's disease. The amygdala, a region of the brain thought to facilitate emotional memory, shows robust Lewy Pathology in PD patients however, the effect of pathology on the amygdala has not been well studied. In our lab, we have shown that inducing aggregation in the amygdala results in robust inclusion formation that corresponds with significant reduction in contextual fear conditioning during behavioral analysis. Unexpectedly, there was no significant differences in cell death as a result of inclusion formation in the amygdala compared to control mice. Synucleinopathy has been demonstrated to affect spine maturation and dendritic spine density in mouse primary hippocampal neurons. During development, microglial activation facilitates pruning of synapses marked for degradation. This mechanism of action has been considered more recently in relation to synaptic degeneration as investigators show affected neurons may be marked for microglial clearance. We propose that alpha-synuclein aggregation activates microglia for synaptic clearance distances at time points preceding cell death.

Title:

Name:
Nolwazi Gcwensa

Company:
UAB

Email:
gcwenolw@uab.edu

Phone:
2052434837

Neuronal Mfn2 alleviates tau pathology–induced neurodegeneration and cognitive decline

Luwen Wang

ABSTRACT

Mitochondrial dynamics have long been implicated in Alzheimer's disease (AD). Neurofibrillary tangles are known as a hallmark feature of AD and commonly considered as likely causes of neurodegeneration in AD. P301S mice, the widely used transgenic mice of tauopathy, exhibited mitochondrial fragmentation and a consistent decrease in mitofusin2 (Mfn2), a conserved dynamin-like GTPase protein predominantly localized in the mitochondrial outer membrane regulating mitochondrial fusion. To understand the pathological role of mitochondrial dynamics in the context of tauopathy, this study studies the impact of neuronal Mfn2 overexpression in P301S mice. We crossed P301S mice with our previously reported TMFN transgenic mice, which overexpress Mfn2 specially in neurons. We found that neuronal Mfn2 could greatly suppress mitochondrial fragmentation and ameliorate mutant tau-mediated neuronal loss. P301S mice with neuronal Mfn2 overexpression also showed greatly suppressed neuroinflammation as evidenced by Iba1 and GRAP immunostaining. Furthermore, tau pathology and cognitive deficits in P301S mice were also alleviated by neuronal Mfn2. Our findings imply that neuronal Mfn2 inhibits mutant tau accumulation and associated neuronal loss, which may be a promising approach for the treatment of AD and related tauopathies

Title:
Postdoc.

Name:
Luwen Wang

Company:
University of Nebraska Medical Center

Email:
luwang@unmc.edu

Phone:
216-375-0865

Message:

Category:
youngaward

Member:
agree

Young Investigator Session 2, 7/23, 8:15-9:55Am

DOPAL initiates αSynuclein-mediated proteinopathy leading to enhanced vulnerability in Parkinson's disease.

Anna Masato

A full understanding of Parkinson's Disease (PD) etiopathogenesis, as well as the causes of the preferential vulnerability of nigrostriatal dopaminergic neurons, is still an unsolved puzzle. Among the various determinants of the degeneration of the Substantia Nigra pars compacta, a pivotal role has been addressed to the endotoxicity associated with dopamine dyshomeostasis. An altered dopamine metabolism generates increasing levels of the reactive catabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL), with serious consequences on neuronal proteostasis and down-stream toxic effects. Interestingly, αSynuclein (αSyn), whose altered proteostasis is a recurrent trait of PD pathology, is particularly affected by DOPAL modification. By combining biochemical studies with the advanced imaging technique of correlated light and electron microscopy (CLEM), we observed a DOPAL-induced αSyn accumulation among neuronal compartments and impaired αSyn clearance in primary neuronal cultures. In addition, we provided evidence that DOPAL neurotoxicity strongly depends on its interaction with αSyn, leading to hindered neuronal resilience, compromised synaptic integrity, and overwhelmed protein quality control pathways. Finally, *in vivo* models of DOPAL impaired detoxification, displayed a progressive dopaminergic neuron loss and motor impairment, corroborating the αSyn-DOPAL interplay as molecular mechanism of enhanced neuronal vulnerability in PD.

Title:
Dr.

Name:
Anna Masato

Company:
University of Padova

Email:
anna.masato@unipd.it

Phone:
0498276340

Message:

Category:
YoungAward

Member:
agree

Mutant TMEM230 induced neurodegeneration and impaired axonal mitochondrial transport

Xiaobo Wang[1,2], Gongbo Guo[1], Jinru Zhang[1,3], Nicolas Aebez[1], Zhaohui Liu[4], Chun-Feng Liu[2,3], Christopher A. Ross[1] and Wanli W. Smith[1*]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

[2]Institute of Neuroscience, Soochow University School of Medicine, Suzhou, Jiangsu 215123, China

[3]Department of Neurology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China

[4]Department of Human Anatomy and Cytoneurobiology, School of Biology and Basic Medical Sciences, Soochow University, Suzhou, Jiangsu 215123, China

Abstract

Parkinson's disease (PD) is a neurodegenerative disease with movement disorders including resting tremor, rigidity, bradykinesia, and postural instability. Recent studies have identified a new PD associated gene, *TMEM230* (transmembrane protein 230). However, the pathological roles of TMEM230 and its variants are not fully understood. *TMEM230* gene encodes two protein isoforms. Isoform2 is the major protein form (~95%) in human. In this study, we overexpress isoform2 TMEM230 variants (WT or PD-linked *184Wext*5 mutant) or knockdown endogenous protein in cultured SH-5Y5Y cells and mouse primary hippocampus neurons to study their pathological roles. We found that overexpression of WT and mutant TMEM230 or knockdown of endogenous TMEM230 induced neurodegeneration and impaired mitochondria transport at the retrograde direction in axons. Mutant TMEM230 caused more severe neurotoxicity and mitochondrial transport impairment than WT-TMEM230 did. Our results demonstrate that maintaining TMEM230 protein levels is critical for neuron survival and axon transport. These findings suggest that mutant-TMEM230-induced mitochondrial transport impairment could be the early event leading to neurite injury and neurodegeneration in PD development.

Title: Ph.D. student.
Name: Xiaobo Wang
Institution: Johns Hopkins University School of Medicine
Email: xiaobowang86@hotmail.com
Abstract Category: Young investigator award

Title: **The activities of LRRK2 and GCase are positively correlated in clinical biospecimens and experimental models of Parkinson's disease**

Maria Kedariti[1], Emanuele Frattini[2,3], Pascale Baden[4], Susanna Cogo[5,9], Laura Civiero[5,10], Elena Ziviani[5], Alice Kaganovich[5,6], Mark R Cookson[6], Leonidas Stefanis[1,7], Roy Alcalay[8], Michela Deleidi[4], Alessio di Fonzo[2,3], Hardy Rideout[1], Elisa Greggio[5] and **Nicoletta Plotegher[5]**

Affiliations:

[1] Division of Basic Neurosciences, Biomedical Research Foundation of the Academy of Athens; Athens, Greece

[2] Neurology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[3] Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

[4] German Center for Neurodegenerative Diseases (DZNE), Tübingen, 72076, Germany

[5] Department of Biology, University of Padova, Italy

[6] Laboratory of Neurogenetics, NIA, Bethesda, USA

[7] Department of Neurology, University of Athens Medical School; Athens, Greece

[8] Movement Disorders Division, Dept of Neurology; Columbia University School of Medicine; New York, USA

[9] Current address: School of Biological Sciences, University of Reading, UK

[10] IRCCS San Camillo Hospital, Venice, Italy

Glucocerebrosidase (GCase) is an enzyme involved in ceramide metabolism, key for lysosomal function. Heterozygous mutations in *GBA1*, the gene encoding GCase, are the most common genetic risk factors for Parkinson's disease (PD). Moreover, GCase activity and function were found to be altered in idiopathic PD and in other genetic forms of the disease.

LRRK2 is a kinase involved in different cellular functions, including autophagy and endolysosomal pathways, vesicle trafficking and inflammation. Mutations in *LRRK2*, including the common hyperactive G2019S mutation, cause autosomal dominant forms of PD and are all associated to an increased LRRK2 kinase activity.

Sparse evidence suggests that LRRK2 kinase activity can regulate GCase function, with a mechanism that is still unknown.

To gain insights into the impact of LRRK2 on GCase, we investigated GCase levels and activity in clinical biospecimens (PBMCs and plasma) from PD patients carrying the G2019S-LRRK2 mutation, finding a positive correlation between the activities of LRRK2 and GCase. These results were further confirmed in patient-derived cellular models, i.e., fibroblasts and iPSC-derived neurons. Genetic and pharmacological manipulation of LRRK2 kinase activity in simpler cellular models allowed to further highlight that LRRK2 impacts both GCase activity and levels, possibly by affecting its intracellular trafficking or specific activity.

Name: Nicoletta Plotegher
Company:
Department of Biology, University of Padova

Email:
nicoletta.plotegher@unipd.it

Phone:+390478276337

Category:
YoungAward

Characterization of Lysosomal Protein Interactions and Structures by Cross Linking Mass Spectrometry

Jasjot Singh

Jasjot Singh, Hadeer Elhabashy, Felipe Merino, Markus Stepath, Martin Eisenacher, Oliver Kohlbacher, Volkmar Gieselmann, and Dominic Winter

The lysosomal proteome consists of luminal proteins, which are predominantly hydrolases responsible for the degradation of lysosomal substrates, and membrane proteins fulfilling various functions. Those include, but are not limited to, lysosomal acidification, nutrient transport/sensing, and interaction with other proteins, organelles, or complexes. The latter are e.g. related to metabolic signaling, lysosomal transport, and vesicle fusion. While certain proteins and complexes have been investigated in great detail, the function, structure, and interaction partners of a significant number of lysosomal proteins has not been analyzed yet. Recent developments in cross-linking mass spectrometry and interactive computational modeling allow to characterize protein-protein interactions (PPIs) on a large scale in complex biological systems, providing an ideal tool for the investigation of the lysosome. We present the first cross-linking mass spectrometry study of lysosomes. The data contain a highly interconnected network of 847 proteins forming 1024 PPIs. This includes 33% known PPIs, confirming the validity of the dataset, and 67% potentially novel PPIs, of which two were confirmed by co-immunoprecipitation. Furthermore, 118 cross-links of 36 lysosomal proteins provide structural information, confirming for some of them crystal-structure based models in a physiological state, and providing evidence for a novel tetrameric structure of Palmitoylprotein thioesterase 1. For the lysosome-interacting proteins Flotillin 1/2, we further propose the first ab initio structures for the monomer, dimer, and oligomeric state. Further experiments with immunoprecipitation of Flotillin-containing vesicles, blue native gel electrophoresis, computational modeling, and LC-MS resulted in a model for oligomeric Flotillin assembly at endosomes and their putative cargo.

Title: Mr.

Name: Jasjot Singh

Company: University of Bonn

Email: jsin@uni-bonn.de

Phone: +49 228 4742

Category:
YoungAward

Title: Understanding the importance of LRRK2 GTP-binding in macrophages

Susanna Cogo1,2, Susanne Herbst3 , Anna Masato2 , Eva Van Acker2 , Giulia Favetta2 , Ilaria Battisti4 , Giulia Tombesi2 , Lucia Iannotta2 , Rachael Chandler1 , Claudia Manzoni5 , Giorgio Arrigoni4 , Nicoletta Plotegher2 , Eva Kevei1 , Patrick Lewis3 & Elisa Greggio2 1 School of Biological Sciences, University of Reading, UK 2 Department of Biology, University of Padova, Italy 3 Royal Veterinary College, London, UK 4 Department of Biomedical Sciences, University of Padova, Italy 5 Department of Pharmacology, University College London School of Pharmacy, UK

Leucine-rich repeat kinase 2 (LRRK2) represents an attractive player in neurodegeneration since mutations in this gene cause familial Parkinson's disease (PD) and more common variants increase lifetime PD risk. In addition to that, the LRRK2 protein hosts dual GTPase/Roc (Ras of complex) and kinase catalytic functions within the same molecule, bridged by a COR (C-terminal Of Roc) platform for dimerization and surrounded by scaffold moieties. The evidence that multiple PD mutations are located within the Roc domain and can lead to both defective GTPase activity and augmented kinase activity in cells supports a crosstalk between GTPase and kinase domains, although with an as yet unclear mechanism. Moreover, the potential druggable nature of both enzymatic activities has prompted the understanding of the interplay between the two domains and with the surrounding scaffold regions. In this frame, we explored the consequence of endogenous LRRK2 GTP-binding loss on autophagy and response to lysosomal damage in macrophage models. I will specifically discuss how the lack of GTP-binding – hence GTPase activity – affects LRRK2 steady-state levels and kinase activity endogenously as well as LRRK2 interactome under basal conditions or upon induction of autophagy and lysosomal damage response

Susanna Cogo,

PhD School of Biological Sciences, University of Reading, UK

s.cogo@reading.ac.u

Trafficking of the glutamate transporter is impaired by pathogenic LRRK2

Iovino L1 , Giusti V1 , Pischedda F2 , Giusto E3 , Tombesi G1 , Marte A4 , Battisti I5 , Di Iacovo A6 , Marku A7 , Piccoli G2 , Bandopadhyay R8 , Perego C7 , Bonifacino T9 , Bonanno G9 , Roseti C6 , Bossi E6 , Arrigoni G5 , Bubacco L1 , Greggio E1 , Hilfiker S10, Civiero L1,3 *

1 Department of Biology, University of Padova, Italy; 2 University of Trento, Department of Cellular, Computational and Integrative Biology – CIBIO, Trento, Italy; 3 IRCCS San Camillo Hospital, Venice, Italy; 4 University of Genova, Department of Experimental Medicine, Genova, Italy; 5 Department of Biomedical Sciences, University of Padova, Padua, Italy; 6 Center for Research in Neuroscience, University of Insubria, Varese; 7 University of Milano, Department of Pharmacological and Biomolecular Sciences, Milano, Italy; 8 Reta Lila Weston Institute of Neurological Studies, London, United Kingdom; 9 University of Genova, Department of Pharmacology-DIFAR, Genova, Italy; 10Rutgers New Jersey Medical School, Department of Anesthesiology, Newark, New Jersey, United States of America

Excitatory amino acid transporter 2 (EAAT2) accounts for 80% of brain glutamate clearance and it is mainly expressed in astrocyte perisynaptic processes. Functional EAAT2 is regulated by endocytic events, recycling at the plasma membrane and degradation. Deficits in EAAT2 have been associated to neuronal excitotoxicity and neurodegeneration. In this study, we show that EAAT2 trafficking is affected by the pathogenic variant G2019S of Leucine-rich repeat kinase 2 (LRRK2), which is involved in the onset of familiar forms of Parkinson's disease (PD). EAAT2 protein level is significantly decreased and matches with elevated gliosis in LRRK2 G2019S human brains and experimental animal models. The altered expression of the transporter correlates with its reduced functionality in mouse LRRK2 G2019S purified astrocytic terminals and in Xenopus laevis oocytes injected with human LRRK2 G2019S mRNA. In the brain, the endogenous transporter misplaces its correct surface localization and interacts with a plethora of endo-vesicular proteins. By coupling imaging techniques and specific pharmacological treatments, we revealed that LRRK2 G2019S delays the receptor recycling to the plasma membrane contributing to its intracellular accumulation in striatal astrocytes. Finally, we showed that LRRK2-mediated trafficking perturbation favors the degradation of the transporter, further exacerbating its functional deficits. Overall, our results reported that the pathogenic variant LRRK2 G2019S interferes with the physiology of EAAT2 facing extracellular glutamate as a possible contributor of neurodegeneration in PD

Title:PhD

Name: LUDOVICA IOVINO

Company: University of Padova, Department of Biology

Email: ludovica.iovino@unipd.it

Phone: 3895792551

Category: YoungAward

PAK6 enhances neuronal autophagy via TFEB

Francesco Agostini1 , Nicoletta Plotegher1 , Rossella Agostinis2 , Susanna Cogo1,3, Marco Bisaglia1 , Elisa Greggio1

1 Department of Biology, University of Padova, Italy. 2 Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy. 3 School of Biological Sciences, University of Reading, UK.

Autophagy is a degradative process mainly controlled by the activity of TFEB, a transcription factor that enhances the expression of several autophagy and lysosomal-related genes. In turn, TFEB activity is controlled by the binding of 14-3-3 proteins, which prevent its nuclear translocation. As accumulating evidence links TFEB dysregulation to neurodegenerative diseases, the aim of this project is to characterize and validate a novel mechanism to enhance autophagy in neurons. In fact, considering that the neuronal-enriched kinase PAK6 has been recently demonstrated to regulate the interaction of 14-3-3 proteins with their binding partners (Civiero et al., Front Mol Neurosci 2017), we hypothesized that PAK6 may induce TFEB nuclear translocation by phosphorylating 14-3-3s and promoting their dissociation from TFEB. Taking advantage of both in vivo and in vitro models we assessed the effect of PAK6 kinase activity on TFEB. Our data revealed that PAK6 activation in cells promotes TFEB nuclear translocation. Moreover, PAK6 overexpression stimulates autophagy as assessed by the analysis of several autophagic markers and the level of TFEB. To explore the role of PAK6 in vivo, we used Drosophila melanogaster downregulating mbt, the fly orthologue of PAK6. We found that neuronal-specific silencing of mbt results in a reduction of autophagic activity and lysosomal function. Overall, these results show a novel and conserved mechanism of TFEB regulation. Moreover, since TFEB activity is essential in every cell, our data point to PAK6 as a potential key target to regulate autophagy specifically in neurons

Name:
Francesco Agostini

Company:
University of Padova

Email:
francesco.agostini.6@phd.unipd.it

Phone:
3494767275

Message:

Category:
Regular

Unravelling the involvement of the PAK6-LRRK2 axis in modulating ciliogenesis in the brain

Lucia Iannotta1 , Claudia Ciriani1 , Giulia Tombesi1 , Michael Lu 2 , Elisa Greggio1

1 Department of Biology, University of Padova, Via Ugo Bassi 58/B, Padova 35131, Italy 2 Department of Biomedical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton 33431, FL, USA.

Accumulating evidence links a very specialized signalling platform at primary cilia to Parkinson's disease (PD). Indeed, primary cilia were shown to be crucial for dopaminergic neurogenesis induction and Sonic Hedgehog signalling mediated by primary cilia was found to increase the resilience of dopaminergic neurons exposed to toxins that mimic PD. Furthermore, the PD-linked kinase Leucine-rich repeat kinase 2 (LRRK2) was recently shown to block primary cilia formation through the phosphorylation of its substrate Rab10. We previously found that LRRK2 interacts with p21 activated kinase 6 (PAK6), which leads to Ser935-LRRK2 dephosphorylation through phosphorylation of 14-3-3γ. Importantly, the overexpression of a constitutively active form of PAK6 rescues the neurite shortening phenotype associated with the LRRK2 mutation G2019S, indicating that PAK6 activity is protective in mutant LRRK2 models. Our preliminary data shows that PAK6 is present at the basal body and in the cilium shaft in mouse embryonic fibroblasts. Moreover, PAK6 activity correlates with reduced Rab10 phosphorylation. Based on these data, we hypothesize that PAK6 may influence primary cilia dynamics via interaction with LRRK2. To this aim, we explored the role of PAK6 in ciliogenesis taking advantage of SH-SY5Y cells overexpressing or downregulating PAK6 or LRRK2, as well as primary neurons and astrocytes from PAK6/7 double knock-out mice. Our results indicate a mechanistic interplay between LRRK2 and PAK6 in ciliogenesis, suggesting novel opportunities to disclose additional targets for the treatment of PD

Name:
Lucia Iannotta

Company:
University of Padova, Italy

Email:
lucia.iannotta@unipd.it

Phone:
+393285657271

Message:

Category:
YoungAward

Unraveling the role of DJ-1 in the bioenergic homeostasis

F. De Lazzari[1], F. Agostini[1], N. Plotegher[1], E. Greggio[1], A. Megighian[2], L. Bubacco[1], A.J. Whitworth[3], F. Sandrelli[1], M. Bisaglia[1,*]

[1] Department of Biology, University of Padua, Italy

[2] Department of Biomedical Sciences, University of Padua, Italy

[3] Medical Research Council Mitochondrial Biology Unit, University of Cambridge, UK

Alterations in the function of the protein DJ-1 have been associated with different neurodegenerative disorders, ranging from Parkinson's disease to amyotrophic lateral sclerosis, and dementia. DJ-1 is a small cytosolic protein that has mainly been implicated in the protection against conditions of cellular stress, such as redox alterations. However, the precise function of the protein remains still elusive. To get insights into the physiological role of DJ-1 *in vivo*, we took advantage of *Drosophila melanogaster* as a model organism. Similarly to the murine model, DJ-1 null flies do not display overt abnormalities, showing a normal lifespan and no signs of neurodegeneration. Nonetheless, insights into the mitochondrial homeostasis revealed that DJ-1 null flies present an altered mitochondrial morphology and functionality, though preserving total ATP levels, even under starvation. Moreover, DJ-1 deficiency sensitizes flies to nutrient deprivation, resulting in premature death and more bodyweight loss as compared to controls. Interestingly, analysis of catabolic pathways indicated that DJ-1 knockout flies have an impaired autophagic response under both basal conditions and starvation. Therefore, here we showed that DJ-1 plays an important role in the bioenergetic homeostasis *in vivo*, by acting at both the mitochondrial and autophagic levels.

Name:
Federica De Lazzari

Company:
University of Padova

Email:
federica.delazzari@unipd.it

Phone:
+39 3475029393

Message:

Category:
Regular

Giulia Tombesi1 , Giulia Favetta1 , Antonella Marte2 , Ilaria Battisti3 , Susanna Cogo1,4, Lucia Iannotta1 , Giorgio Arrigoni3 , Franco Onofri2 and Elisa Greggio1

1 Department of Biology, University of Padova, Italy 2 Department of Experimental Medicine, University of Genova, Italy 3 Department of Biomedical Sciences, University of Padova, Italy 4 School of Biological Sciences, University of Reading, UK

Title: **The Parkinson's disease kinase LRRK2 orchestrates dendritic spine dynamics via BDNF signaling pathway**

Dendritic spines (DS), small protrusions originating from neuronal dendrites, constitute the postsynaptic element of most excitatory synapses and are particularly abundant in some classes of neuronal cells such as striatal medium spiny neurons (MSNs). DS possess the ability to change their number, density and morphology within short timeframes, representing highly dynamic elements. Structural plasticity of striatal dendritic spines is well known to be influenced by brain derived neurotrophic factor (BDNF) released from glutamatergic cortical afferents. Accumulating evidence indicate synaptic vulnerability, including alterations in DS, as common feature of neurodegenerative disorders. In Parkinson's disease (PD) synaptic dysfunction is an early event that precedes neuronal death and disease clinical manifestation. Here, I will present data suggesting that the PD-associated kinase LRRK2 influences dendritic spine and synapse dynamics, including the pathological effects of the most common LRRK2 mutation, the G2019S. I will further show how LRRK2 responds to BDNF in cultured neurons and how attenuated BDNF signaling due to LRRK2 deficiency may underlying the observed DS alterations.

Giulia Tombesi

Company:
University of Padova

Email:
giulia.tombesi@studenti.unipd.it

Phone:
3472268495