Inhibition of aerobic glycolysis curbs the neuroinflammatory response of astrocytes

Daniel Esteve[1], Mariana Bresque[1], Sandhya Ramachandran[2], Mariana Pehar[2,3] and Marcelo R. Vargas[1]

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

ABSTRACT

Astrocytes are glial cells essential for metabolic homeostasis in the central nervous system. Aerobic glycolysis is considered to be a primary energy source in astrocytes. Even in conditions of normoxia, astrocytes are considered to have higher glycolytic rate than neurons, with the resulting lactate serving as an energy source for coupled neurons via the glia-neuron lactate shuttle. In neurodegenerative diseases, like amyotrophic lateral sclerosis (ALS), astrocytes undergo a phenotypic transformation. This phenotype is characterized by an increase in glycolysis, the development of an inflammatory response, and neurotoxicity. The exact contribution of metabolic changes to the phenotype of reactive astrocytes is not yet fully understood. However, it seems clear that astrocytes undergo a metabolic reprograming to support a pro-inflammatory response. Here, we investigate the relationship between glycolysis and the inflammatory response in astrocytes. Using different inflammatory stimuli including, TNFα or a cytokine cocktail, we explored the effect of lactate dehydrogenase (LDH) inhibition in astrocytes in NF-kB signaling-activation and the development of neurotoxicity. We found that LDH inhibition decreased the NF-κB-driven pro-inflammatory response in spinal cord astrocyte cultures treated with inflammatory stimuli. Moreover, LDH inhibition decreased the toxicity of stimulated astrocytes towards co-cultured motor neurons. Similar results were observed following LDH inhibition in astrocyte cultures obtained from the spinal cord of symptomatic hSOD1^{G93A} ALS mouse models, as well as in iPSC-derived astrocytes from ALS patients. Taking all together, our data highlights the importance of metabolic reprogramming in the astrocyte inflammatory response and in its potential role in astrocyte-mediated neurotoxicity in ALS.

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Presenter Name and contact information:
Daniel Esteve, Ph.D.
Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA.
Phone: 608-640-1809
Email: d.estevemoreno@neurology.wisc.edu