Gasdermin-D coopts horizontal mitochondrial transfer to propagate sterile neuroinflammatory responses in Alpha-Synucleinopathy

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A recent body of work shows that metabolically active mitochondria can be exported from one cell to another, in a process called horizontal mitochondria transfer. This process has been demonstrated in the settings of Alpha Synucleinopathy, where microglia-mediated transfer of mitochondria to neurons and other microglia prevents neurodegeneration and attenuates neuroinflammatory responses. Mitochondrial dysfunction within brain myeloid cells such as microglia licenses the assembly of innate-immune signaling mechanisms such as the NLRP3 (Nod-like Receptor Protein 3) Inflammasome and the STING(Stimulator of Interferon Genes) pathways, whose hyperactivation has been documented in Parkinson's Disease(PD) and Dementia with Lewy Bodies (DLB) models. Gasdermin-D (GSDMD) is a protein that is activated/cleaved downstream of NLRP3 inflammasome assembly and is best associated with an inflammatory cell death mechanism known as pyroptosis, where it forms pores in the cell membrane. Recent evidence in peripheral immune cells, as well as our preliminary data using cultured primary microglia, within the αSyn pre-formed fibril (PFF) model and postmortem DLB tissue indicate that cleaved/activated GSDMD (CL-GSDMD) accumulates at mitochondria and amplifies mitochondrial damage within microglia. Our data also indicate that CL-GSDMD-laden mitochondria can be horizontally transferred from donor to recipient cells, mediating ligand-independent propagation of neuroinflammatory signaling. Horizontal mitochondrial transfer has thus far been explored as a neuroprotective mechanism. Showing that this process can be “corrupted” by GSDMD to spread neuroinflammation represents a paradigm shift in the fields of horizontal mitochondrial transfer and neuroinflammatory signaling mechanisms.

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