Unraveling the molecular mechanism underlying neuroinflammation in Parkinsonian Syndrome

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PIZZA SERVED!

In vitro cell culture, ex vivo brain slice culture, and in vivo model systems of Parkinson's disease (PD), as well as postmortem brains from PD patients, have implicated microglial hyperactivation, mediated by inflammatory ligands, in the loss of dopaminergic neurons in the substantia nigra region of the brain. The signaling pathways leading to this chronic, sustained microglial activation in response to environmental stressors or disease-associated molecular patterns (DAMPs) are not clearly understood. We show herein the role of mitochondrial dysfunction in mediating pro-inflammatory signaling cascades in microglial cells in response to environmental factors such as pesticides and metals. Exposure to the pesticides rotenone and tebufenpyrad as well as the neurotoxic divalent metal manganese (Mn) leads to the activation of the NLRP3 pro-inflammatory signaling cascade in microglial cells. Mitochondrial superoxide generation plays a key role in activation of the NLRP3 inflammasome. Furthermore, activation of NLRP3 produces neurotoxic factors, like IL-1β and IL-18, that lead to neurodegeneration. The novel mitochondria-targeted antioxidant mito-apocynin was able to reduce mitochondrial superoxide generation and NLRP3 inflammasome activation. We also demonstrated that Mn leads to mitochondrial dysfunction by downregulation of mitochondrial fusion protein (Mfn2). Lastly, we show that Mn exposure leads to the propagation of the NLRP3 inflammasome through the mechanism of exosomal release of ASC, an inflammasome component. This finding has high translational relevance since exosomes isolated from welder cohorts known to have been exposed to Mn fumes carry a higher exosomal load of ASC.

Alpha-synuclein aggregates are a major component of Lewy bodies and neurites, which are pathological hallmarks of PD. Classical activation of microglial cells has been shown to be mediated by pre-formed fibrillar α-synuclein (αSynAgg), but the signaling mechanism is not well understood. We sought to identify the role of microglial potassium channels in regulating αSynAgg-induced neuroinflammation. We show conclusively, in both cell culture and animal models of PD, that αSynAgg-induced neuroinflammation is associated with upregulation of the voltage-gated potassium channel Kv1.3. Remarkably, Kv1.3 was also highly induced in post-mortem PD patient tissues, as well as in peripheral blood mononuclear cells (PBMC) isolated from PD patients. We show that Fyn kinase, a src family kinase, regulates Kv1.3 transcriptionally through the p38 MAPK and NFκB pathways. Fyn was also observed to directly bind to Kv1.3, phosphorylating tyrosine 139 to modulate the channel's activity. Lastly, we demonstrate that Kv1.3 inhibition reduces neuroinflammation and neurodegeneration in vitro and in preclinical setups. Overall, we identify key mechanistic pathways in response to both environmental stressors and DAMPs which strongly contribute to the chronic microglial pro-inflammatory responses that characterize PD-associated neuroinflammation.