Mitochondrial autoimmune mechanisms in neurodegenerative diseases

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Two important hallmarks of neurodegenerative diseases (ND) are inflammation and mitochondrial dysfunction. We recently discovered a new pathway of antigen presentation for mitochondrial antigens: Mitochondrial Derived Vesicles (MDV)/MitAP (mitochondrial antigen presentation) pathway. MDV/MitAP pathway represents a link between mitochondrial dysfunction and inflammation and directly implicate autoimmunity in PD pathogenesis. MitAP is absent in steady state conditions and gets activated only under a mitochondrial stress that jeopardizes mitochondrial homeostasis and quality control (mitophagy inhibition and MDV generation), a context that could be induced by infection and deficiency in PD-related genes that control mitophagy (PINK1 and Parkin). Indeed, during infection or fever, the stress signals are transmitted to mitochondria and under conditions where the mitochondrial quality control is compromised, these stress signals induce MitAP. Thus, imbalance in mitochondrial quality control, a dysfunction that is closely related to several ND, is the main trigger for MitAP. Therefore, ***we hypothesize that in ND, dysregulation of mitochondrial homeostasis institutes susceptibility for MitAP induction, and this is associated with mitochondrial autoimmune/autoinflammatory response.*** Our research focuses on defining the role of MitAP in ND, such as PD, amyotrophic lateral sclerosis (ALS) and multiple sclerosis, and to characterize the mechanisms by which mitochondrial autoimmune/autoinflammation responses are induced. Our approach is based on the initial identification and characterization of mitochondria-related autoimmune responses in patients and secondly, based on the human data, we dig into the mechanistic aspect of mitochondrial autoimmunity using ND models. Our preliminary data strongly suggest that MitAP and mitochondrial autoimmunity are not only active in PD patients, but they are also found in MS and ALS patients. We also found an unexpected role for the MDV/MitAP pathway in the regulation of autoinflammation and the consequent generation of autoimmune-related Th17 cells. Characterization of MitAP in ND likely identifies novel therapeutic targets and opens new avenues for the treatment of ND. Unraveling these pathways will help us to better comprehend ND pathogenesis and how immune tolerance breakdown can contribute to the disease process.