Alpha synuclein impairs structural and functional integrity of mitochondria in human dopaminergic neurons

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Alpha synuclein (aSyn) is strongly linked to Parkinson's disease but the molecular targets for its toxicity remains elusive. Rapidly evolving concepts of PD pathology suggest that variants of aSyn accumulate within mitochondria leading to neuronal demise. Nevertheless, the role of aSyn in mitochondrial physiology is poorly defined. We aim to investigate the deleterious effects of mitochondrial localization of aSyn in human dopaminergic LUHMES cells. Therefore, we have generated neuron specific, adeno associated virus type 2 (AAV2) expressing cytosolic as well as mitochondrial targeting aSyn, and EGFP expressing viruses for respective controls.

Overexpression of either form of aSyn severely disrupted dendritic network, electrical activity and induced dopaminergic cell death. Both cytosolic and mitochondrial aSyn induced mitochondrial ROS formation, loss of ATP production and membrane depolarization. Real-time analysis of mitochondrial bioenergetics using Seahorse Bioscience system following AAV infection elicited a complete damage to mitochondrial respiration capacity in dopaminergic neurons. Transmission electron microscopy illustrated a number of deformed cristae in cytosolic form and a complete loss of cristae structure and massively swollen mitochondria in mitochondrial targeted aSyn in expressing cells. Furthermore, we could show for the first time that inhibition of caspases by QVD significantly ameliorated aSyn-induced cell death and improved mitochondrial function in human dopaminergic neurons. Overall, our findings show that cytosolic as well as mitochondrial targeted expression of aSyn is detrimental to dopaminergic neurons and inhibition of caspases amended this aSyn toxicity. Thus, caspase inhibitors may provide therapeutic potential to prevent neuronal degeneration in synucleinopathies, including PD.

Speaker Biography

Goutham Kumar Ganjam is a Principal Investigator in University of Marburg, Germany. He is an expert in mitochondrial bioenergetics, neurodegeneration, inflammation, Parkinson's disease, mentoring, design, plan, execute, training graduates, etc.

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