Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: The mitochondrial quality control pathway mediated by PINK1 pathway and its relevance for Parkinson's disease

Synopsis:

The brain relies heavily on mitochondrial energy production and Calcium buffering, which is fundamental to neuronal transmission and normal synaptic function. Besides their role in metabolism, mitochondria are key regulators in the control of neuronal apoptosis. In addition, the diverse functionality of the mitochondria is mirrored by their complex morphology and dynamic alterations. Therefore, it may come as no surprise that many genetic mutations in genes encoding mitochondrial proteins can cause neurodegeneration.

The identification of mutations in PTEN induced putative kinase (PINK1) and Parkin, causing autosomal recessive Parkinson's Disease (PD), provides a fantastic inroad to unravel the role of mitochondrial dysfunction in neurodegeneration. Although all clinical mutations result in loss-of-function in different cellular assays, Pink1 deficient mice do not display overt neurodegeneration, indicating that additional mechanisms are deregulated in autosomal recessive PD. A series of highly interesting observations suggest that a protein upstream of PINK1 might provide a clue to a broader understanding of the pathway. This protein is the protease, presenilin associated rhomboid like (PARL), which cleaves PINK1 in a constitutive fashion. When mitochondria get damaged, this cleavage does not longer occur and PINK1 accumulates at the outer membrane, which initiates mitophagy. Intriguingly, when PINK1 cleavage becomes inhibited, a second substrate of PARL becomes cleaved. This substrate is the phosphatase, phosphoglycerate mutase 5 (PGAM5). A functional relationship between PINK1 and PGAM5 is further deduced from genetic experiments in Drosophila which show that loss of PGAM5 rescues PINK1 phenotypes. As PGAM5 has been shown to interact with RIP1 and RIP3 kinases, proteins involved in necroptosis, this protein seems to play a central role in the integration of different cell death signals. In this project, we will focus on PARL and the proteolytic cleavage of PINK1 and PGAM5. PARL itself has anti-apoptotic activity, while PINK1 and PGAM5 are linked to mitophagy and necroptosis. Thus, PARL is at the cross roads of several mitochondrial death pathways.

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