CRIMIPRIM - The relationship between cristae shape and mitochondrial protein import in mitochondrial disease models

The majority of mitochondrial proteins are imported from the cytosol into the organelle. The main mitochondrial protein import pathways account for the import of mitochondrial matrix and mitochondrial inner membrane (IM) proteins, e.g. the subunits of the respiratory chain complexes (RCC). This import process is facilitated by mitochondrial IM and outer membrane (OM) contact sites. Furthermore, the aforementioned pathways depend on the IM elechtrochemical gradient and ATP to take place. The host lab showed that mild overexpression of the dynamin-related protein optic atrophy 1 (OPA1) protects against IM proton electrochemical gradient lost upon complex III inhibition. OPA1 is involved in RCC stabilisation and cristae remodeling, but also in mitochondrial IM and outer membrane contacts. Recently, lower levels of mitochondrial import receptor and channels proteins were linked to Parkinson disease. The hypothesis of this proposal is that OPA1 directly influences TIM23 and TIM22 protein import pathways. This fellowship will follow three main aims; a) define the relationship between OPA1 and protein import in models of Leigh syndrome, b) determine cristae integrity in TOM20, TIM23 and TIM22 deficient cells and c) define protein import machinery molecular partners of OPA1. I will use classical biochemistry and BN-PAGE gels to determine the integrity of TIM23 and TIM22 and to assess the mitochondrial import capacity in the mouse models. Next, I will measure by electron microscopy the shape of the cristae and perform detailed morphometric analyses to determine if the protein import plays a role in cristae biogenesis. Finally, using complexomic analysis, I will aim to identify potential import pathway partners of Opa1 and establish their role by their deletion by CrispR/Cas9 in Opa1tg cells. This research will open the possibility to target the import machinery to remodel cristae in mitochondria in an OPA1-dependant manner as an alternative to treat mitochondrial disorders.

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