Targeting mitochondria to treat rare and common neurodegenerative disorders

Mitochondrial dysfunction underlies the pathogenesis of a variety of human neurodegenerative diseases, either directly, in the case of the rare Mitochondrial Diseases (MDs), or indirectly, as in more common and complex neurodegenerative disorders, such as Parkinson’s disease. In particular a tight connection between vision and mitochondrial dysfunction has been extensively described. Several MDs are associated with some form of vision impairment. In particular Leber Hereditary Optic Neuropathy (LHON) and Autosomal Dominant Optic Atrophy (ADOA) are the most frequent hereditary optic neuropathies, and are both characterized by degeneration of retinal ganglion cells and loss of vision. Interestingly, also the most common optic neuropathies such as glaucoma and diabetic retinopathy show signs of mitochondrial dysfunction and share clinical similarities with the hereditary MDs.

Despite a vast amount of research these pathologies are still only treated symptomatically, and, in this respect, mitochondria could represent the common denominator and hence a promising therapeutic target.

MicroRNAs (miRNAs) are key regulators of gene expression representing promising therapeutic tools for their capability to modulate multiple pathways involved in disease pathogenesis and progression. The miR-181 family, composed of four members, is highly expressed in brain and retina, where they regulate neurotrophic signaling, axon guidance, immunity and mitochondrial-related pathways (Indrieri et al., 2020). We recently demonstrated that the microRNAs miR-181a and miR-181b (miR-181a/b) regulate key genes involved in mitochondrial biogenesis function and clearance. We also show that these miRNAs are involved in the global regulation of mitochondrial turnover in the central nervous system (CNS) through the coordination of mitochondrial biogenesis and mitophagy. Interestingly miR-181a/b downregulation protects neurons from cell death and ameliorates the disease phenotype in different in vivo models of MDs, including LHON (Indrieri et al., 2019). Our unpublished results also showed an amelioration of the disease phenotype in chemical models of Parkinson’s disease indicating that miR-181a/b may represent novel gene-independent therapeutic targets for a wide-range of neurodegenerative disorders caused by mitochondrial dysfunction. Moreover, our results strongly suggest that the coordinated enhancement of mitophagy and mitochondrial biogenesis may be an effective therapeutic tool in mitochondrial-associated neurodegenerations (Indrieri et al., 2019).

The main interest of my laboratory is to develop and validate new therapeutic strategies enhancing mitochondrial turnover in the CNS to treat mitochondrial-associated neurodegeneration in a mutation-independent manner. In particular we are developing Adeno Associated Viral vectors carrying miR-181a/b inhibitors in order to test their therapeutic efficacy in vivo. Moreover, we are also screening FDA-approved libraries to identify compounds able to increase mitochondrial turnover in the CNS to further expand therapeutic opportunities for mitochondrial-associated neurodegenerations. Our strategies will be applied in models of rare diseases such as mitochondrial optic neuropathies, as well as in model of common disorders such as Glaucoma, Diabetic Retinopathy and Parkinson’s disease.

References:

**Keywords**: Mitochondria, MicroRNA, Neurodegenerative Disorders.

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