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OC.9- MIR-181a AND MIR-181b DOWNREGULATION PROTECTS FROM MITOCHONDRIA-ASSOCIATED NEURODEGENERATION BY ENHANCING MITOCHONDRIAL BIOGENESIS AND MITOPHAGY

A. Indrieri[1,2], S. Carrella[1,3], A. Romano[1], A. Spaziano[1], F. Golia[1], M. Pizzo[1], R. Tammaro[1], E. Marrocco[1], N. Giordano[1,4], A. Carboncino[4,5], L. Ciampi[1], S. Barbato[1], E. De Leonibus[1,4], E.M. Surace[1,3], S. Banfi[1,3], and B. Franco[1,2]

[1]Telethon Institute of Genetics and Medicine (TIGEM), Italy;
[2]Department of Translational Medical Science, University of Naples "Federico II", Italy; [3]Department of Biochemistry, Biophysics and General Pathology, University of Campania "L. Vanvitelli", Italy;
[4]Institute of Genetics and Biophysics (IGB), CNR, Italy; [5]Department of Neuroscience, Biomedicine and Movement Science, University of Verona, Italy

Mitochondrial dysfunction underlies the pathogenesis of a variety of human neurodegenerative disorders, either directly, e.g., in the case of mitochondrial diseases, or indirectly, e.g. in the case of Parkinson's disease. The complexity of these disorders has so far prevented the development of effective therapeutic strategies. We demonstrate that the microRNAs miR-181a and miR-181b (miR-181a/b) regulate key genes involved in mitochondrial biogenesis and function. We also show that these miRNAs are involved in the global regulation of mitochondrial turnover in the central nervous system through the simultaneous and fine tuning modulation of different gene pathways. We sought to verify whether the modulation of these miRNAs could be therapeutically exploited in neurodegenerative conditions associated to impaired mitochondrial activity. We show that miR-181a/b downregulation strongly protects neurons from cell death and significantly ameliorates the disease phenotype in in vivo models of both primary and secondary mitochondria-mediated neurodegeneration, such as Microphthalmia with Linear Skin Lesions, Leber hereditary optic neuropathy and Parkinson's disease. Altogether our results indicate that miR-181a/b act as hubs in mitochondrial homeostasis in the central nervous system and represent novel gene-independent therapeutic targets for a wide-range of neurodegenerative diseases caused by mitochondrial dysfunction.