Effects of PARP inhibition on *in vitro* and *in vivo* models of Mitochondrial Complex I Deficiency

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Mitochondrial disorders are devastating genetic diseases for which efficacious treatment is still an unmet need. To reach this goal it is mandatory to understand the pathogenetic mechanisms triggered by the primary genetic defects, and whether mitochondrial dysfunction can be reduced by targeting alternative metabolic pathways. It has been speculated that excessive production of ROS is the leading cause of cell demise in patients affected by Complex I Deficiency (CID). Of note, PARP-1 activation is a key event in ROS-dependent neuronal death but, at present, its relevance to cell demise in the periphery and the CNS of patients with CID is completely unknown. However, it has been recently demonstrated both *in vitro* and *in vivo* that genetic or pharmacological suppression of PARP-1 increases intracellular NAD contents and boosts SIRT1-dependent PGC1alpha-mediated mitochondrial biogenesis and function. On these basis, we evaluated the impact of pharmacological PARP inhibition in a mouse model of CID, the NDUFS4 knockout (KO) mice, characterized by a severe mitochondrial encephalomyopathy. We found that treatment with the PARP inhibitor improved NDUFS4 KO mice phenotype, with increased limb tone and balance ability, reduced ataxia and hindlimb clasping. However, at later stage of disease development, both control and treated mice became lethargic, stopped gaining weight and died. These therapeutic effects were associated to mitochondrial biogenesis. The latter was also found in human fibroblasts from patients carrying mutation in NDUFS1 subunit of Complex I exposed *in vitro* to different PARP inhibitors. Taken together these findings indicate that PARP inhibition might be considered a promising strategy to improve energy metabolism in condition of oxidative phosphorylation defects.