VDAC1-based gene therapy recovers mitochondrial respiration by enhancing the complex I-sirtuins axis in a mice model of ALS

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On the outer mitochondrial membrane, the Voltage-Dependent Anion-selective Channel 1 (VDAC1) stands out as the most abundant pore-forming protein and the main permeability pathway for ions and small metabolites (ATP/ADP, NAD^+/NADH, Krebs's cycle intermediates)[1]. However, in neurodegeneration, VDAC1 behaves as a hub for the selective recruitment of misfolded proteins on the cytosolic surface of mitochondria. Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease, and ~20% of inherited cases depends on mutations in the gene encoding the antioxidant enzyme Cu/Zn Superoxide Dismutase (SOD1). The mitochondrial accumulation of SOD1 mutants affects VDAC1 conductance, ADP/ATP exchanges and oxygen consumption, triggering the organelle dysfunction[2]. As a matter of fact, VDAC1 downregulation in SOD1 transgenic rats accelerates the pathology onset and decreases the animals' lifespan.
In the attempt to counteract the mitochondrial malfunctioning in ALS, we enhanced the expression of VDAC1 in the spinal cord of SOD1 transgenic mice by a neonatal intraspinal injection of an adeno-associated virus. For the first time, here we demonstrate that a stable VDAC1 upregulation rescues the whole respiratory profile of pre-symptomatic mice. Mechanistically, VDAC1 activates a mitochondrial quality control pathway involving the TOM complex, the main gateway for the import of proteins within the organelle, leading to the selective increase of expression and function of the electron transport chain (ETC) complex I and the NAD^+-dependent deacetylases sirtuin 3 (Sirt3). Overall, by stabilizing the complex I-Sirt3 axis, VDAC1 emerges as a highly promising for advancing ALS therapeutics, establishing a 'virtuous cycle' in affected mitochondria: it increases the NADH availability and reoxidation by complex I, and the derived NAD^+ strongly stimulates Sirt3 activity, a pivotal regulator of the ETC.

1 Magrì et al, Front Chem, 2018, 6: 10
2 Magrì et al, Cell Death Dis, 2023, 14: 122