Exploiting redox-active molecules against mitochondrial diseases

S-01.8-1

D. Bonesso[I], M. Donadon[I], L. Biasutto[II], A. Rossa[III], M. Favero[I], E. Giannoni[IV], P. Chiarugi[IV], M. Zeviani[V], A. Mattarei[III], C. Viscomi[II], **I. Szabo**[I]

[I]University of Padova, Department of Biology, Padova, Italy, [II]University of Padova, Department of Biomedical Sciences Padova, Padova, Italy, [III]Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy, [IV]Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Morgagni 50, 50134, Florence, Italy, [V]University of Padova, Department of Neurology, Padova, Italy

Mitochondrial diseases result from a decreased oxidative phosphorylation (OXPHOS) that leads to a broad spectrum of incurable pathologies [1,2]. Our goal was to understand whether membrane-permeant small molecule(s) can be exploited to treat OXPHOS-related diseases as an alternative to gene therapy. Therefore, we selected some molecules for their ability to replace the redox functions of complex III and among them identified a few promising agents. Sub-μM dose of these drugs is harmless, restores respiration and increases ATP production in Ttc19-/- mouse embryonic fibroblasts as well as in fibroblasts from patients harboring pathogenic mutations in three different assembly/stabilization factors of complex III, including TTC19. The drugs normalized the mitochondrial membrane potential, mildly increased ROS production, and triggered mitochondrial biogenesis. These in vitro effects were confirmed also in vivo, in both Drosophila melanogasterTTC19KO, in Danio rerioTTC19KD [3]. Here we show that redox cyclers and their derivatives with enhanced life-time and tissue distribution exhibited a benefit in Ttc19 KO mouse model. Administration of low, non-toxic concentrations of the drugs significantly ameliorated movement and coordination proficiency, without inducing toxicity. Likewise, drugs able to receive electrons from NADH, showed a beneficial effect also in the case of cells and mice with complex I disease. Our results point to exploitation of redox cyclers for therapy against diseases due to OXPHOS dysfunction.

[1] Suomalainen A, Battersby BJ. Nat Rev Mol Cell Biol. (2018) 19, 77.

[2] Viscomi C, Zeviani M. J Intern Med. 2020 Jun;287(6):665-684.

[3] Peruzzo R, Corrà S, Costa R, Brischigliaro M, Varanita T, Biasutto L, Rampazzo C, Ghezzi D, Leanza L, Zoratti M, Zeviani M, De Pittà C, Viscomi C, Costa R, Szabò I. Nature Communications (2021) 12, 2103.