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Pharmacological NAD-Boosting Strategies Improve Mitochondrial Homeostasis in Human Complex I-Mutant Fibroblasts.

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Abstract

Mitochondrial disorders are devastating genetic diseases for which efficacious therapies are still an unmet need. Recent studies report that increased availability of intracellular NAD obtained by inhibition of the NAD-consuming enzyme poly(ADP-ribose) polymerase (PARP)-1 or supplementation with the NAD-precursor nicotinamide riboside (NR) ameliorates energetic derangement and symptoms in mouse models of mitochondrial disorders. Whether these pharmacological approaches also improve bioenergetics of human cells harboring mitochondrial defects is unknown. It is also unclear whether the same signaling cascade is prompted by PARP-1 inhibitors and NR supplementation to improve mitochondrial homeostasis. Here, we show that human fibroblasts mutant for the NADH dehydrogenase (ubiquinone) Fe-S protein 1 (NDUFS1) subunit of respiratory complex I have similar ATP, NAD, and mitochondrial content compared with control cells, but show reduced mitochondrial membrane potential. Interestingly, mutant cells also show increased transcript levels of mitochondrial DNA but not nuclear DNA respiratory complex subunits, suggesting activation of a compensatory response. At variance with prior work in mice, however, NR supplementation, but not PARP-1 inhibition, increased intracellular NAD content in NDUFS1 mutant human fibroblasts. Conversely, PARP-1 inhibitors, but not NR supplementation, increased transcription of mitochondrial transcription factor A and mitochondrial DNA-encoded respiratory complexes constitutively induced in mutant cells. Still, both NR and PARP-1 inhibitors restored mitochondrial membrane potential and increased organelle content as well as oxidative activity of NDUFS1-deficient fibroblasts. Overall, data provide the first evidence that in human cells harboring a mitochondrial respiratory defect exposure to NR or PARP-1, inhibitors activate different signaling pathways that are not invariantly prompted by NAD increases, but equally able to improve energetic derangement.

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