Mitochondrial medicine and translational aspects of mitochondrial diseases

IST1-04

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Mitochondrial myopathies are genetic disorders caused by mutations in mitochondrial or nuclear DNA, leading to defective oxidative phosphorylation and severe muscle dysfunction. While no cure currently exists, promising therapeutic strategies are emerging, including pharmacological and gene therapy approaches.
Our previous work demonstrated that rapamycin, an mTORC1 inhibitor, improved motor function and reduced myopathy in a Cox15 muscle-specific knockout (Cox15sm) mouse model by activating TFEB-mediated autophagy and lysosomal biogenesis. Given rapamycin's broad systemic effects, we explored alternative TFEB activators, such as Urolithin A (UA), a natural polyphenol known to stimulate mitophagy. Cox15sm mice expressing the mitophagy reporter MitoQC were treated with UA for nine weeks. By the end of the study, treated mice exhibited significant motor improvement, enhanced mitophagy in skeletal muscle, and improved mitochondrial ultrastructure, although cytochrome c oxidase (COX) activity remained unchanged.
In parallel, we investigated AAV-based gene therapy using a novel liver-detargeted, myotropic AAV vector to restore Cox15 expression in Cox15sm mice. Following systemic AAV-Cox15 administration, treated mice showed a marked increase in motor performance—up to tenfold improvement—beginning as early as two to four weeks post-injection. Muscle histology confirmed reduced myopathy and partial restoration of COX activity. EM analysis showed rescued mitochondrial ultrastructure. Importantly, this new AAV vector demonstrated superior efficacy compared to AAV9 at equivalent doses.
Together, these studies highlight two complementary therapeutic strategies: UA as a pharmacological approach to enhance mitophagy and an optimized AAV gene therapy for direct genetic correction. These findings pave the way for further exploration of combinatorial or standalone treatments for mitochondrial myopathies.