P.40

SRT2104, a new specific SIRT1 activator, promotes muscle recovery enhancing mitochondrial metabolism in DMD

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Duchenne Muscular Dystrophy (DMD) is an X-linked degenerative genetic disease caused by mutations of the DMD gene encoding dystrophin protein. While remarkable progress has been made in genetic approaches to restore dystrophin or its function, targeting secondary pathological mechanisms remains an important issue to address. SIRT1 belongs to a class of NAD+-dependent class III deacetylase that controls several key cellular processes. Different attempts have been done to increase SIRT1 activation in mdx mice, however, despite the initial promise, the current opinion reveals the need for developing better and more selective activators of sirtuins. Among these, the SRT2104 molecule is the most advanced in clinical studies. We have challenged the effects of SRT2104 administration in mdx mice and 12 weeks of SRT2104 supplementation with the diet improved muscle performance and muscle phenotype. SRT2104 administration also boosted muscle OxPhos capacity, as further confirmed by respiratory complexes' activity, supporting the idea of SRT2104 as a good metabolic enhancer.
To mechanistically characterize the SRT2104 mode of action, a series of molecular dynamics simulations have been performed on the available structures of SIRT1. They support the idea that a conformational selection mechanism is responsible of the activity of SRT2104, i.e., the open inactive conformation of the protein explores a more compact intermediate state that is stabilized by the drug, then converted into its active form.
We have further investigated SRT2104 action by exploring the proteomic profiles of muscles through quantitative mass spectrometry, revealing the SRT2104-dependent enhancement of the muscle contraction system. Moreover, we have also characterized the acetylated landscape of mdx muscle after SRT2104 administration pointing out some interesting deacetylated metabolic enzymes, therefore both approaches proved muscle improvements and specific metabolic effects of the drug.