Increased polyamines as protective disease modifiers in Congenital Muscular Dystrophy.

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Abstract
Most Mendelian disorders, including neuromuscular disorders, display extensive clinical heterogeneity that cannot be solely explained by primary genetic mutations. This phenotypic variability is largely attributed to the presence of disease modifiers, which can exacerbate or lessen the severity and progression of the disease. LAMA2-deficient Congenital Muscular Dystrophy (LAMA2-CMD) is a fatal degenerative muscle disease resulting from mutations in the LAMA2 gene encoding Laminin-α2. Progressive muscle weakness is predominantly observed in the lower limbs in LAMA2-CMD patients, whereas upper limbs muscles are significantly less affected. However, very little is known about the molecular mechanism underlying differential pathophysiology between specific muscle groups. Here, we demonstrate that the triceps muscles of the dy2j/dy2j mouse model of LAMA2-CMD demonstrate very mild myopathic findings compared to the tibialis anterior (TA) muscles that undergo severe atrophy and fibrosis, suggesting a protective mechanism in the upper limbs of these mice. Comparative gene expression analysis reveals that S-Adenosyl-methionine decarboxylase (Amd1) and Spermine oxidase (Smox), two components of polyamine pathway metabolism, are downregulated in the TA, but not in the triceps of dy2j/dy2j mice. As a consequence, the level of polyamine metabolites is significantly lower in the TA than triceps. Normalization of either Amd1 or Smox expression in dy2j/dy2j TA ameliorates muscle fibrosis, reduces overactive pro-fibrotic TGF-β pathway and leads to improved locomotion. In summary, we demonstrate that a deregulated polyamine metabolism is a characteristic feature of severely affected lower limb muscles in LAMA2-CMD. Targeted modulation of this pathway represents a novel therapeutic avenue for this devastating disease.

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