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Histone Deacetylase 4 is crucial for proper skeletal muscle development and disease

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Epigenetics plays a pivotal role in modulating gene response to physiological or pathological stimuli.

Histone Deacetylase inhibitors (HDACi) have been used in the treatment of various cancers[1], are effective in several animal models of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), and are currently in clinical trial to promote muscle repair in muscular dystrophies[2]. However, long-term use of pan-HDAC inhibitors is not tolerated[3]. The assignment of distinct biological functions to individual HDACs in skeletal muscle is a prerequisite to improve the efficacy of pharmacological treatments based on HDACi. HDAC4 is a member of class II HDACs that mediates many cellular responses. Clinical reports suggest that inhibition of HDAC4 can be beneficial to cancer cachexia, dystrophic or ALS patients. All the above conditions are characterized by progressive muscle wasting and up-regulation of HDAC4 expression in skeletal muscle, suggesting a potential role for this protein in regulating these diseases. To study the role of HDAC4 with a genetic approach, we generated several models of muscle disease in mice lacking HDAC4 in skeletal muscle: cancer cachexia, by implanting Lewis lung carcinoma (LLC), muscular dystrophy, by using mdx mice, or ALS, by using SODG93A mice. Lack of HDAC4 worsens skeletal muscle atrophy induced by both LLC and ALS, demonstrated by a reduction in muscle mass and myofibers size. Conversely, dystrophic mice lacking HDAC4 in skeletal muscle show an increased number of necrotic myofibers and run less efficiently than mdx mice. The aggravation of the dystrophic phenotype may be partially due to the impairment in skeletal muscle regeneration observed in mice lacking HDAC4 in skeletal muscle. Our results indicate that HDAC4 is necessary for maintaining skeletal muscle homeostasis and function. Current studies aim to investigate the molecular mechanisms underlying the role of HDAC4 in skeletal muscle maintenance in response to cancer cachexia, ALS or muscular dystrophy.

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Keywords

Cancer; Amyotrophic lateral sclerosis; muscular dystrophy; Histone Deacetylases.