INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Small Molecule Activation of Lysosomal TRP Channels Ameliorates Duchenne Muscular Dystrophy in Mouse Models

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OVERVIEW

Duchenne Muscular Dystrophy is a X-linked disease that leads to progress muscle weakening and death

- Researchers have created a mouse model lacking mucolipin 1 (TPRML1), causing muscular defects similar to DMD
- Increasing TPRML 1 function ameliorates muscle weakness symptoms in these mice, suggesting a potential treatment of DMD in humans

BACKGROUND

Duchenne Muscular Dystrophy (DMD) is a rare, X-linked disease with a prevalence of 18,000 cases in the United States. The illness is caused by the loss of dystrophin, a structural protein that connects muscle cells to the extracellular matrix to stabilize muscle fibers. The primary symptom of DMD is muscle weakness, which usually presents first in the hips, thighs, and shoulders, and then later in the arms, legs, and trunk. In the final stages of the disease, respiratory muscles and the heart become weakened, and death ensues. Life expectancy for these patients historically has been limited to early adulthood, though improving technologies for cardiac and respiratory support have extended the lives of some DMD patients into their fourth or fifth decade.

Treatment options for DMD are limited and primarily focused on the management of symptoms rather than addressing the underlying cause of the disease. The current therapeutic approaches for DMD patients include corticosteroids to reduce inflammation and maintain muscle strength, physical therapy to strengthen and maintain muscle function for as long as possible,

medications to treat dilated cardiomyopathy, and mechanical assistive breathing devices. A need exists for a DMD treatment that addresses the causes of the disease rather than merely managing symptoms.

INNOVATION

Researchers have generated mice lacking mucolipin 1 (TRPML 1), a lysosomal calcium channel protein that regulates lysosomal exocytosis which, when mutated, causes muscular defects phenotypically similar to DMD. Pharmacologic activation of TRPML 1 improves muscle function in this mice model, suggesting a potential therapeutic agent for patients with DMD by upregulation of mucolipin 1. This transgenic overexpression or pharmacological activation of ML1 in vivo facilitates sarcolemma repair and alleviates the dystrophic phenotype in both skeletal and cardiac muscles in mice. The hallmark dystrophic features of DMD, including myofiber necrosis, central nucleation, fibrosis, elevated serum creatine kinase (CK) levels, reduced muscle force, and impaired motor ability, are all ameliorated by increasing ML1 activity. Hence, the present work indicates that manipulating lysosome function by targeting lysosomal calcium channels represents a promising approach to treating DMD and related muscle diseases.