



COMMENTARY

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The Role of Utrophin Upregulation in Muscular Dystrophy: Potential for Therapeutic Intervention

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About the Study

Muscular Dystrophy (MD) surround a group of genetic disorders characterized by progressive weakness and degeneration of the skeletal muscles that control movement. These disorders are primarily caused by defects in genes responsible for muscle structure and function, leading to abnormalities in the proteins that these genes encode. Muscular dystrophies are often categorized by the specific genetic mutations and corresponding proteins affected. The most well-known forms include Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD), Limb Girdle Muscular Dystrophy (LGMD), and Myotonic Dystrophy (MD). The pathogenesis of these disorders involves several interconnected molecular mechanisms.

One of the primary molecular defects in many forms of muscular dystrophy, particularly DMD and BMD, involves the Dystrophin Glycoprotein Complex (DGC). Dystrophin is an important protein that links the cytoskeleton of a muscle fiber to the surrounding extracellular matrix through the cell membrane. This connection is essential for maintaining the structural integrity of muscle fibers during contraction and relaxation. A damaged DGC is the outcome of dystrophin deficit or absence caused by mutations in the DMD gene. The muscle cell membrane becomes less stable when dystrophin is absent, increasing the possibility of damage occurring during muscle contraction. This membrane instability allows for increased calcium influx, which activates proteolytic enzymes and leads to muscle cell necrosis.

In BMD, mutations in the DMD gene result in the production of a partially functional but shorter dystrophin protein. Although the dystrophin is present, it is not as effective in stabilizing the DGC, leading to a milder, yet progressive, muscle degeneration

compared to DMD. In MD, the sarcolemma's integrity is impacted by the disruption of the DGC, which leads to increased permeability. This altered permeability is particularly detrimental because it disrupts calcium homeostasis within muscle cells.

The amounts of calcium in muscle cells are strictly controlled in a normal state. However, in the absence of functional dystrophin, the increased influx of calcium into the cell activates various calcium-dependent enzymes, such as calpains and phospholipases. These enzymes degrade essential cellular components, including proteins and lipids, leading to muscle fiber damage and necrosis. Additionally, the excess intracellular calcium disrupts mitochondrial function, contributing to increased oxidative stress and further cellular damage. The muscle damage in MD triggers an inflammatory response, which, while initially intended to repair tissue, becomes chronic and pathological in the context of continuous muscle degeneration. Immune cells, including macrophages and T cells, infiltrate the damaged muscle tissue and release pro-inflammatory cytokines such as Tumor Necrosis Factor Alpha (TNF- α) and Inter Leukin-6 (IL-6). These cytokines increase oxidative stress and subsequent inflammation, which worsens muscle injury.

Chronic inflammation in MD also leads to fibrosis, characterized by the excessive deposition of extracellular matrix components such as collagen. Fibrosis replaces functional muscle tissue with non-contractile fibrotic tissue, impairing muscle function and contributing to the progressive weakness seen in MD patients. Satellite cells are muscle stem cells responsible for muscle regeneration and repair. In healthy muscle, satellite cells become activated in response to injury, proliferate, and differentiate into mature muscle fibers to repair the damaged tissue.

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The ongoing process of muscle deterioration in MD precedes host cells' ability to regenerate.

Similar to dystrophin, utrophin is a protein that could make up for dystrophin deficiency in muscle cells. Utrophin is expressed in the sarcolemma throughout fetal development, but as dystrophin expression rises

after formation, utrophin expression is downregulated. Up regulating utrophin expression has been considered as a potential treatment for MD, especially DMD. The sarcolemma's integrity can be partially regained by raising utrophin levels, which may lessen the muscular deterioration associated with MD.