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Review

Wasting mechanisms in muscular dystrophy☆

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ABSTRACT

Muscular dystrophy is a group of more than 30 different clinical genetic disorders that are characterized by progressive skeletal muscle wasting and degeneration. Primary deficiency of specific extracellular matrix, sarcoplasmic, cytoskeletal, or nuclear membrane protein results in several secondary changes such as sarcolemmal instability, calcium influx, fiber necrosis, oxidative stress, inflammatory response, breakdown of extracellular matrix, and eventually fibrosis which leads to loss of ambulance and cardiac and respiratory failure. A number of molecular processes have now been identified which hasten disease progression in human patients and animal models of muscular dystrophy. Accumulating evidence further suggests that aberrant activation of several signaling pathways aggravate pathological cascades in dystrophic muscle. Although replacement of defective gene with wild-type is paramount to cure, management of secondary pathological changes has enormous potential to improving the quality of life and extending lifespan of muscular dystrophy patients. In this article, we have reviewed major cellular and molecular mechanisms leading to muscle wasting in muscular dystrophy.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

1. Introduction

Muscular dystrophy comprises a group of genetic diseases that cause progressive degeneration of skeletal muscle fibers resulting in severe pain, disability, and eventually death (Emery, 2002). The primary cause for various forms of muscular dystrophies is the mutations in individual genes that encode a wide variety of proteins, including extracellular matrix (ECM) proteins, transmembrane and membrane-associated proteins, cytoplasmic enzymes, and nuclear matrix proteins (Blake et al., 2002; Campbell, 1995). However, the most severe forms of muscular dystrophies occur due to mutations in the components of the dystrophin–glycoprotein

Abbreviations: CMD, congenital muscular dystrophy; DGC, dystrophin glycoprotein complex; DMD, Duchenne muscular dystrophy; ECM, extracellular matrix; IKK, inhibitor of I kappa B kinase α; LGMD, limb-girdle muscular dystrophy; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; MMPs, matrix metalloproteinases; MuRF1, muscle RING-finger protein-1; NIK, NF-κB-inducing kinase; NO, nitric oxide; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TRPC, transient receptor potential canonical.

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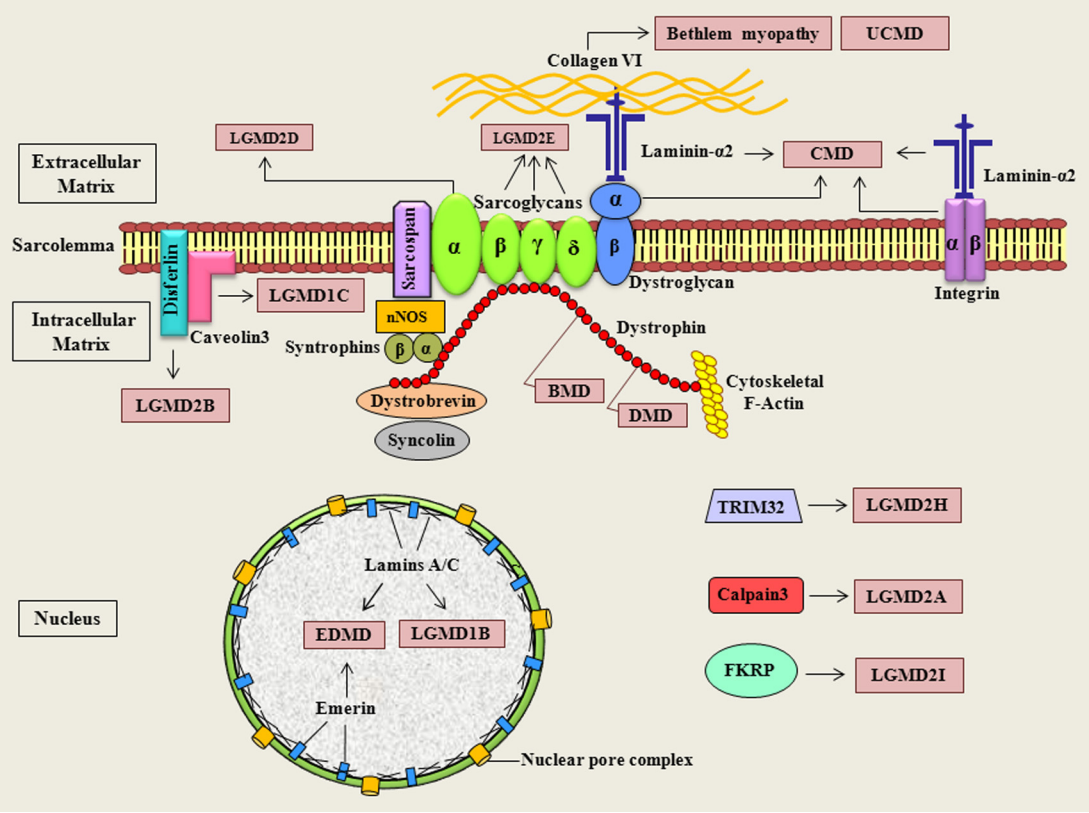

Fig. 1. Genetic basis of muscular dystrophy. Schematic representation of various proteins and associated muscular dystrophy caused by their loss is presented. BMD, Baker's muscular dystrophy; CMD, congenital muscular dystrophy; DMD, Duchenne muscular dystrophy; EDMD, Emery–Dreifuss muscular dystrophy; FKRP, fukutin-related protein; LGMD, limb girdle muscular dystrophy; nNOS, neuronal nitric oxide synthase; TRIM, tripartite motif proteins; UCMD, Ullrich congenital muscular dystrophy.

complex (DGC), a molecular scaffold which is localized to sarcolemma and provides mechanical stability to striated muscle (Fig. 1). For example, mutations in dystrophin or any of the sarcoglycans leads to destabilization of sarcolemma (i.e. muscle membrane) and a dystrophic phenotype.

Duchenne muscular dystrophy (DMD) is one of the most prevalent forms of muscular dystrophies that results from total or partial deficiency of functional dystrophin protein (Fig. 1). Dystrophin is a critical component of DGC, which links the cytoskeleton of the muscle fibers to the ECM (Hoffman et al., 1987). Dystrophin has also been suggested as an important cytolinker that stabilizes cells by linking actin filaments, intermediate filaments, and microtubules to transmembrane complexes (Prins et al., 2009). In the absence of dystrophin, the DGC is functionally impaired and the mechanical stress associated with muscle contraction leads to sarcolemmal damage and fiber necrosis (Petrof et al., 1993; Rando, 2001). While mechanical injury and sarcolemmal defects are important triggering mechanisms promoting dystrophic phenotype, neither fully explains the onset or progression of DMD. Studies in animal models and humans have shown that partial or complete loss of DGC proteins results in the activation of several pathological cascades which aggravate disease progression (Chakkalakal et al., 2005; Engvall and Wewer, 2003; Khurana and Davies, 2003; Rando, 2001; Spencer and Tidball, 2001).

Besides acting as a molecular scaffold serving mechanical function, DGC also has an important signaling role in striated muscle. Disruption of DGC leads to the aberrant activation of a number of signaling pathways (Acharyya et al., 2007; Bhatnagar and Kumar, 2010; Dogra et al., 2006; Kumar and Boriek, 2003; Kumar et al., 2004a). Intriguingly, many signaling pathways that have been found to be involved in pathogenesis of muscular dystrophy are activated before the onset of fiber necrosis signifying that loss of functional DGC is sufficient to disrupt physiological signaling in striated muscle (Bhatnagar and Kumar, 2010). Abnormal myogenic signaling has also been reported in other forms of muscular dystrophies that result from loss of nuclear membrane protein (e.g. lamins A/C, Emerin) or cytoplasmic enzymes (e.g. calpain-3) suggesting that signaling defect is a common pathological mechanism in all types of muscular dystrophies (Bhatnagar and Kumar, 2010). Because activation of different signaling cascades results in altered gene expression, aberrant myogenic signaling could be critical for the onset and perpetuation of pathology in muscular dystrophy.

While it is obvious that gene therapy and stem cell-based therapy would likely provide the cure for DMD and other types of muscular dystrophy (Davies and Grounds, 2007; Goyenvalle et al., 2011), it is not yet clear when these approaches will be developed in near future to be useful for patients with muscular dystrophy. Dystrophin gene size is considerably large which has been a major impediment in the development of effective gene therapy protocols for DMD patients. Systemic delivery of the gene therapy vectors (e.g. plasmids and adeno-associated viruses) to muscles that are distributed all over the body also creates another obstacle (Goyenvalle et al., 2011). Use of antisense oligonucleotides (AON) to modulate splicing of the dystrophin gene to restore a translatable mRNA transcript has also been proposed on the basis of in vitro data. However, in vivo studies showed that the dystrophin expression was highly variable within and between muscles and there is no detectable expression of dystrophin in cardiac muscle even after repeated intravenous injections of AON (Lu et al., 2011). Premature termination codon (PTC) mutations occur in ~15% of patients with DMD. It has been suggested that boys with DMD can potentially be treated by drugs that promote read-through. Aminoglycosides restore protein translation in cultured cells. However, aminoglycosides and related compounds have long-term toxic effects and