Opinion
Volume 16:1, 2022

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 Open Access

Molecular mechanism of Duchenne Muscular Dystrophy

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Opinion

Mutations in the gene that codes for the 427-kDa cytoskeletal protein dystrophin cause Duchenne muscular dystrophy (DMD). A better understanding of dystrophin's function and role in muscle has led to a better understanding of DMD's pathophysiology. This, combined with developments in the molecular biologist's genetic toolkit, has resulted in a plethora of therapy options. Mutations can be corrected using chimaeraplasts and short DNA fragments, exon skipping of mutations can be induced using oligonucleotides, and readthrough of nonsense mutations can be achieved using aminoglycoside antibiotics. Any truncated dystrophin protein can be stabilized by blocking the proteasome degradation pathway, and upregulation of other proteins can also prevent the dystrophic process. Myoblasts or stem cells can be used to repopulate muscle. All these approaches, or a combination of them, hold great promise for the treatment of this devastating disease.

Duchenne muscular dystrophy is an X-linked recessive disorder that affects one i every 3,500 males and is caused by dystrophin gene mutations. The gene is the largest in the human genome, containing 79 exons and encompassing 2.6 million base pairs of DNAs. Approximately 60% of dystrophin mutations are large insertions or deletions that result in downstream frameshift errors, while 40% are point mutations or small frameshift rearrangements. The dystrophin protein is missing in the vast majority of DMD patients. Becker muscular dystrophy, a much milder form of the disease, is caused by a decrease in the amount of the dystrophin protein or an alteration in its size. Because of the high occurrence of sporadic DMD (1 in 10,000 sperm or eggs), genetic screening will never be able to eliminate this disease, so an effective therapy is highly desirable [1].

Pathogenesis

Dystrophin is a structural protein that connects the internal cytoskeleton to the extracellular matrix in muscle. Dystrophin's amino terminus binds to F-actin, and its carboxyl terminus binds to the dystrophin-associated protein complex (DAPC) at the sarcolemma. Dystroglycans, sarcoglycans, integrins, and caveolin are all components of the DAPC, and mutations in any of these components cause autosomal inherited muscular dystrophies. When dystrophin is absent, the DAPC is destabilized, resulting in lower levels of the member proteins. As a result, the fibers gradually deteriorate and the membrane leaks. The DAPC plays a signaling role, and its loss contributes to pathogenesis.

Patients with DMD are typically wheelchair-bound by the age of 12 and die of respiratory failure in their late teens or early twenties. By the age of 18, many boys have an abnormal electrocardiogram, indicating that any therapeutic agent must also target the diaphragm and cardiac muscle. The basement membrane is an extracellular matrix that surrounds skeletal muscle fibers. The basement membrane is divided into two layers. The basal lamina is a felt-like layer that connects to the plasma membrane directly. The external and fibrillar reticular lamina is another layer. The basement membrane is thought to be involved in the lateral force transmission of contractile force generated by myofibrils and provides the muscle structure's tensile strength. As a result, genetic evidence suggests that congenital muscular dystrophies can result from the loss of extracellular matrix proteins and their membrane receptors. Because premature stop codons cause between 5% and 15% of DMD cases, the use of aminoglycoside antibiotics (such as gentamycin and negamycin), which promote translational readthrough of stop codons, has been studied [2-3].

Despite promising results in mdx mice (6 percent dystrophin-positive fibers, 10–20 percent of normal dystrophin levels), no dystrophin expression has been achieved in human studies of DMD and BMD patients, and a replication of the mdx results has not yet been published. Recent cell-culture experiments with eight different patient mutations show that aminoglycosides suppress some sequences better than others. Short fragments or chimaeraplasts (double-stranded RNA–DNA chimeric oligonucleotides) designed to contain the correct nucleotide can be used to precisely correct a dystrophin mutation. Unfortunately, intramuscular injections of chimaeraplasts produced only a small amount of dystrophin protein in the GRMD dog and mdx mouse, with dystrophin-positive cells restricted to the injection site. Dystrophin is a large cytoskeletal protein that helps the cytoskeleton, cell membrane, and extracellular matrix interact. It is found in both muscle and non-muscle tissues at the plasma membrane [4].

Dystrophin is an essential component of the dystrophin-glycoprotein complex (DGC), which serves as a structural unit of muscle. Both dystrophin and DGC proteins are missing in DMD, resulting in excessive membrane fragility and permeability, calcium homeostasis dysregulation, and oxidative damage. These elements are critical in the necrosis of muscle cells. The regenerative capacity of the muscles appears to be exhausted in DMD patients as they age, and connective and adipose tissue gradually replaces muscle fibers. Endomysial connective tissue proliferation, scattered degeneration, and regeneration of myofibers, muscle fiber necrosis with a mononuclear cell infiltrate, and muscle replacement with adipose tissue and fat will all be seen in a muscle biopsy. All patients have intellectual impairment; however, only 20% to 30% of patients have an intelligence quotient (IQ) less than 70. The degree of impairment is unrelated to the severity of the disease. Most patients have only a mild form of learning disability and can function in a regular classroom setting

Epilepsy is more common than in the general population, and autism-like behavior has been described on rare occasions. Patients with DMD have a complete or nearly complete absence of the dystrophin gene. Dystrophin immunoblotting can be used to predict disease severity. Patients with DMD are found to have less than 5% of the normal amount of dystrophin. Polymerase chain reactions (PCR) are another method that can detect up to 98 percent of mutations. MPLA (multiplex ligation-dependent probe amplification) is another technique for detecting duplications and deletions. Duplications can result in in-frame or out-of-frame transcription. FISH (Fluorescence In Situ Hybridization) is used less frequently but is useful for detecting small point mutations. Dystrophin immunocytochemistry can also be used to identify cases that have not been identified by PCR [5].

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Received: 05-Jan-2022, Manuscript No: jmgm-22- 52704; **Editor assigned:** 07-Jan -2022, Pre QC-No. P- 52704; **Reviewed:** 12- Jan -2022, QC No. Q- 52704; **Revised:** 17- Jan -2022, Manuscript No. R- 52704; Published: 22- Jan -2022, DOI: 10.37421/1747-0862.22.16.529

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How to cite this article: Priyadarshini, Veena. "Molecular Mechanism of Duchenne Muscular Dystrophy." *J Mol Genet Med* 16(2022): 529.