- *Conditions with abnormalities in receptors for extracellular matrix*. In this group are diseases that disrupt the post-translational modification of alpha-dystroglycan (Fig. 27-10) by O-linked glycosylation. Mutations of alpha-dystroglycan itself result in fetal demise but defects in its post-translational modification result in milder forms of dystroglycan deficiency. Alpha-dystroglycan expression is important for CNS and eye development. Severe cases exhibit features of congenital muscular dystrophy as well as developmental defects of the CNS and eyes that cause seizures, mental retardation and blindness. Milder forms may only cause skeletal muscle disease. Some of these mutations are also linked to a presentation described as limb girdle muscular dystrophy (see below).

The following section focuses on the most common and best understood forms of inherited myopathies.

Muscular Dystrophies

Muscular dystrophies include several inherited disorders of skeletal muscle that have in common progressive muscle damage that typically manifests itself between childhood and adulthood. As mentioned earlier, with the exception of congenital muscular dystrophies, these diseases do not present in infancy.While our focus is on X-linked muscular dystrophies, other forms in which the disease pathogenesis is reasonably well understood are also briefly discussed.

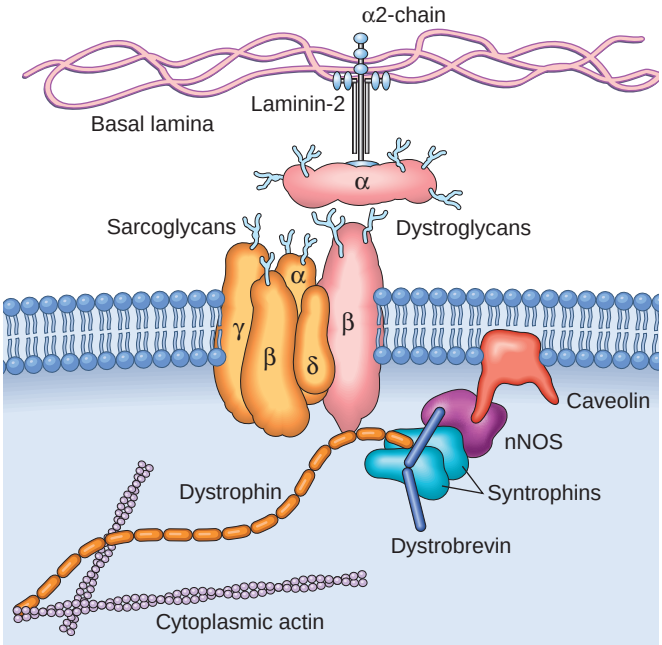

Figure 27-10 Relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins. Dystrophin, an intracellular protein, forms an interface between the cytoskeletal proteins and a group of transmembrane proteins, the dystroglycans and the sarcoglycans. These transmembrane proteins have interactions with the extracellular matrix, including the laminin proteins. Dystrophin also interacts with dystrobrevin and the syntrophins, which form a link with neuronal type nitric oxide synthetase (nNOS) and caveolin. Mutations in dystrophin are associated with the X-linked muscular dystrophies; mutations in caveolin and the sarcoglycan proteins with the limb-girdle muscular dystrophies, which can be autosomal dominant or recessive disorders; and mutations in the α_2-laminin (merosin) with autosomal recessive congenital muscular dystrophy.

X-Linked Muscular Dystrophy with Dystrophin Mutation/ Duchenne and Becker Muscular Dystrophy

The most common muscular dystrophies are X-linked and stem from mutations that disrupt the function of a large structural protein called *dystrophin*. As a result, these diseases are sometimes referred to as *dystrophinopathies*. The most common early onset form is referred to as *Duchenne muscular dystrophy*. It has an incidence of 1 per 3500 live male births and has a severe progressive phenotype. Becker muscular dystrophy is a second relatively common dystrophinopathy that is characterized by later disease onset and a milder phenotype. Other rare dystrophinopathies may present with isolated cardiomyopathy, asymptomatic elevations of creatine kinase levels, or exercise intolerance because of myalgias and cramps. As with many X-linked diseases, female carriers of dystrophin mutations may be mildly symptomatic due to unfavorable X-chromosome inactivation.

Pathogenesis. **Duchenne and Becker muscular dystrophy are caused by loss-of-function mutations in the dystrophin gene on the X chromosome.** Dystrophin is one of the largest human genes, spanning 2.3 million base pairs and composed of 79 exons. The encoded protein, dystrophin, is a key component of the dystrophin glycoprotein complex (DGC) (Fig. 27-10). This complex spans the plasma membrane and serves as a link between the cytoskeleton inside the myofiber and the basement membrane outside of the cell. The amino terminus of dystrophin binds actin filaments in the cytoplasm of myofibers, while the carboxy terminus binds β-dystroglycan, one of the transmembrane proteins of the DGC. By doing so, dystrophin is thought to provide mechanical stability to the myofiber and its cell membrane during muscle contraction. Defects in the complex may lead to small membrane tears that permit influx of calcium, triggering events that result in myofiber degeneration. In addition to its mechanical function, dystrophin may have a role in signaling pathways; for example, its carboxy terminus interacts with nitric oxide synthase, which generates NO.

Identification and characterization of specific dystrophin mutations has provided an explanation for some of the phenotypic variation in patients with dystrophinopathies. Duchenne muscular dystrophy is typically associated with deletions or frame shift mutations that result in total absence of dystrophin. In contrast, the mutations in Becker muscular dystrophy typically permit the synthesis of a truncated version of dystrophin, which presumably retains some function.

MORPHOLOGY

The changes in Duchenne and Becker muscular dystrophy are similar, but differ in degree. Both are marked by chronic muscle damage that outpaces the capacity for repair (Fig. 27-11). Muscle biopsies in young boys show ongoing damage in the form of **segmental myofiber degeneration and regeneration** associated with an admixture of **atrophic myofibers**. The fascicular architecture is preserved at this stage of the disease,