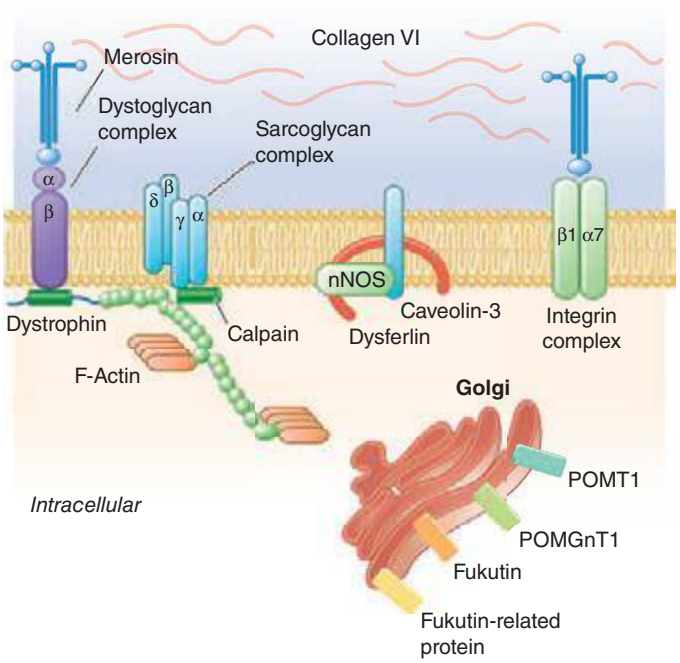

FIGURE 462e-6 **Selected muscular dystrophy–associated proteins** in the cell membrane and Golgi complex.

Dystrophin localizes to the cytoplasmic face of the muscle cell membrane. It complexes with two transmembrane protein complexes, the dystroglycans and the sarcoglycans. The dystroglycans bind to the extracellular matrix protein merosin, which is also complexed with β_1 and α_7 integrins (Tables 462e-5, 462e-6, and 462e-7). Dysferlin complexes with caveolin-3 (which binds to neuronal nitric oxide synthase, or nNOS) but not with the dystrophin-associated proteins or the integrins. In some of the congenital dystrophies and limb-girdle muscular dystrophies (LGMDs), there is loss of function of different enzymes that glycosylate α-dystroglycan, which thereby inhibits proper binding to merosin: POMT1, POMT2, POMGnT1, Fukutin, Fukutin-related protein, and LARGE.

The dystrophin-glycoprotein complex appears to confer stability to the sarcolemma, although the function of each individual component of the complex is incompletely understood. Deficiency of one member of the complex may cause abnormalities in other components. For example, a primary deficiency of dystrophin (Duchenne dystrophy) may lead to secondary loss of the sarcoglycans and dystroglycan. The primary loss of a single sarcoglycan (see "Limb-Girdle Muscular Dystrophy," below) results in a secondary loss of other sarcoglycans in the membrane without uniformly affecting dystrophin. In either instance, disruption of the dystrophin-glycoprotein complexes weakens the sarcolemma, causing membrane tears and a cascade of events leading to muscle fiber necrosis. This sequence of events occurs repeatedly during the life of a patient with muscular dystrophy.

TREATMENT DUCHENNE MUSCULAR DYSTROPHY

Glucocorticoids, administered as prednisone in a dose of 0.75 mg/kg per day, significantly slow progression of Duchenne dystrophy for up to 3 years. Some patients cannot tolerate glucocorticoid therapy; weight gain and increased risk of fractures in particular represent a significant deterrent for some boys. As in other recessively inherited dystrophies presumed to arise from loss of function of a critical muscle gene, there is optimism that Duchenne disease may benefit from novel therapies that either replace the defective gene or missing protein or implement downstream corrections (e.g., skipping mutated exons or reading through mutations that introduce stop codons).

BECKER MUSCULAR DYSTROPHY

This less severe form of X-linked recessive muscular dystrophy results from allelic defects of the same gene responsible for Duchenne dystrophy. Becker muscular dystrophy is ~10 times less frequent than Duchenne.

Clinical Features The pattern of muscle wasting in Becker muscular dystrophy closely resembles that seen in Duchenne. Proximal muscles, especially of the lower extremities, are prominently involved. As the disease progresses, weakness becomes more generalized. Significant facial muscle weakness is not a feature. Hypertrophy of muscles, particularly in the calves, is an early and prominent finding.

Most patients with Becker dystrophy first experience difficulties between ages 5 and 15 years, although onset in the third or fourth decade or even later can occur. By definition, patients with Becker dystrophy walk beyond age 15, whereas patients with Duchenne dystrophy are typically in a wheelchair by the age of 12. Patients with Becker dystrophy have a reduced life expectancy, but most survive into the fourth or fifth decade.

Mental retardation may occur in Becker dystrophy, but it is not as common as in Duchenne. Cardiac involvement occurs in Becker dystrophy and may result in heart failure; some patients manifest with only heart failure. Other less common presentations are asymptomatic hyper-CK-emia, myalgias without weakness, and myoglobinuria.

Laboratory Features Serum CK levels, results of EMG, and muscle biopsy findings closely resemble those in Duchenne dystrophy. The diagnosis of Becker muscular dystrophy requires Western blot analysis of muscle biopsy samples, demonstrating a reduced amount or abnormal size of dystrophin or mutation analysis of DNA from peripheral blood leukocytes. Genetic testing reveals deletions or duplications of the dystrophin gene in 65% of patients with Becker dystrophy, approximately the same percentage as in Duchenne dystrophy. In both Becker and Duchenne dystrophies, the size of the DNA deletion does not predict clinical severity; however, in ~95% of patients with Becker dystrophy, the DNA deletion does not alter the translational reading frame of messenger RNA. These "in-frame" mutations allow for production of some dystrophin, which accounts for the presence of altered rather than absent dystrophin on Western blot analysis.

TREATMENT BECKER MUSCULAR DYSTROPHY

The use of glucocorticoids has not been adequately studied in Becker dystrophy.

LIMB-GIRDLE MUSCULAR DYSTROPHY

The syndrome of LGMD represents more than one disorder. Both males and females are affected, with onset ranging from late in the first decade to the fourth decade. The LGMDs typically manifest with progressive weakness of pelvic and shoulder girdle musculature. Respiratory insufficiency from weakness of the diaphragm may occur, as may cardiomyopathy.

A systematic classification of LGMD is based on autosomal dominant (LGMD1) and autosomal recessive (LGMD2) inheritance. Superimposed on the backbone of LGMD1 and LGMD2, the classification uses a sequential alphabetical lettering system (LGMD1A, LGMD2A, etc.). Disorders receive letters in the order in which they are found to have chromosomal linkage. This results in an ever-expanding list of conditions summarized in Tables 462e-6 and 462e-7. None of the conditions is as common as the dystrophinopathies; however, prevalence data for the LGMDs have not been systematically gathered for any large heterogeneous population. In referral-based clinical populations, Fukutin-related protein (FKRP) deficiency (LGMD2I), calpainopathy (LGMD2A), anoctaminopathy (LGMD2L), and to a lesser extent dysferlinopathy (LGMD2B) have emerged as the most common disorders.