Sarcolemma-specific collagen VI deficiency in Ullrich disease

Mutations in collagen VI are a cause of the severe congenital muscular dystrophy, Ullrich disease. Ishikawa et al. report eight patients with Ullrich disease with a different abnormality: collagen was present in the interstitium but absent from the sarcolemma. They suggest that the failure of collagen VI to anchor the basal lamina to the interstitium can cause Ullrich disease.

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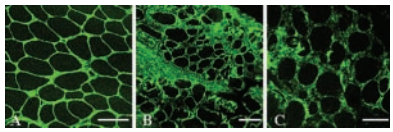
Collagen VI expression and muscle weakness

Commentary by Carolyn Sewry, MD

There is growing interest in the role of the extracellular matrix in neuromuscular disorders. Protein complexes associated with dystrophin connect the cytoskeleton of the muscle fiber to the extracellular matrix via transmembrane proteins. The precise function(s) of the complexes have not been fully elucidated but current hypotheses favor membrane stability and signaling as the most probable. What is clear, however, is that defects in several of the components can lead to malfunctioning of the muscle fiber, and can result in primary and secondary alterations in protein expression, giving rise to specific neuromuscular phenotypes. Collagen VI is unusual in that recessive mutations usually give rise to Ullrich disease, a form of congenital muscular dystrophy (UCMD), but dominant mutations lead to a milder disorder, Bethlem myopathy. UCMD



Immunostaining for collagen VI (A: normal, B: Fukuyama-type congenital muscular dystrophy, and C: Ullrich disease). Collagen VI is present in the interstitium but is markedly reduced or absent in the sarcolemma in an Ullrich disease patient.

is a severe disorder with onset at birth or in early infancy and characterized by hypotonia, contractures of proximal joints, and distal joint laxity. Affected UCMD patients often are unable to walk and develop respiratory failure. Muscle weakness in Bethlem myopathy, however, is milder and only slowly progressive. The article by Ishikawa et al. highlights the general role of immunohistochemistry in identifying alterations in protein expression in recessively inherited conditions, especially subtle ones, and emphasizes the importance of assessing the basal lamina. It also illustrates the fact that ultrastructural studies can provide new information when combined with the molecular genetic characterization of disease. In addition, their results lend further support to molecular heterogeneity associated with the Ullrich phenotype. It is, however, surprising that mutations in collagen VI were found in only one of their eight patients, suggesting either that a molecular deficit was overlooked or that other genes are more commonly mutated. However, two potential candidates, biglycan and decorin, were excluded.

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