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Collagen VI disorders: insights on form and function in the extracellular matrix and beyond

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Highlights

- Collagen VI mutations produce mild to severe muscular dystrophies with skin and tendon involvement.
- The mutations compromise collagen VI intracellular and extracellular assembly and alter extracellular matrix structure and biomechanical properties.
- We discuss the downstream cellular consequences and how these could be targeted therapeutically.
- We review emerging roles for collagen VI in cancer, obesity and diabetes.

Abstract

Mutations in the three canonical collagen VI genes, *COL6A1*, *COL6A2* and *COL6A3*, cause a spectrum of muscle disease from Bethlem myopathy at the mild end to the severe Ullrich congenital muscular dystrophy. Mutations can be either dominant or recessive and the resulting clinical severity is influenced by the way mutations impact the complex collagen VI assembly process. Most mutations are found towards the N-terminus of the triple helical collagenous domain and compromise extracellular microfibril assembly. Outside the triple helix collagen VI is highly polymorphic and discriminating mutations from rare benign changes remains a major diagnostic challenge. Collagen VI deficiency alters extracellular matrix structure and biomechanical properties and leads to increased apoptosis and oxidative stress, decreased autophagy, and impaired muscle regeneration. Therapies that target these downstream consequences have been tested in a collagen VI null mouse and also in small human trials where they show modest clinical efficacy. An important role for collagen VI in obesity, cancer and diabetes is emerging. A major barrier to developing effective therapies is the paucity of information about how collagen VI deficiency in the extracellular matrix signals the final downstream consequences – the receptors involved and the intracellular messengers await further characterization.

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