Abstract

Collagen VI is a heterotrimeric extracellular matrix protein in connective tissues. It belongs to the beaded-filament forming collagens and maintains structural integrity in skeletal muscle. The assembly of collagen VI is a complex multi-step process and the sensibility and vulnerability of the process is manifested in muscular diseases. The assembly begins with the trimerization of the collagen VI α chains with subsequent dimerization and formation of tetramers, which are finally linked in form of microfibrils in the ECM. The collagenous regions of the α chains are flanked by N- and C-terminal von Willebrand factor A (VWA) domains, protein-protein interaction domains found in several ECM proteins. The N-terminal end of the collagen VI α3 chain consists of up to ten VWA domains and harbours flexible linker regions that enable the correct domain arrangement. In this study it was shown that the flexibility is an intrinsic feature of the linker region but adjacent VWA domains can influence the extent. The linker regions between the N5 and N4 domains, as well as between the N4 and N3 domains, harbour short α-helices which may act as spacers to enable spatial separation of domains or as extensile elements which react to mechanical forces in the ECM.

Mutations in *COL6A1, COL6A2* and *COL6A3* lead to muscular diseases like Bethlem myopathy on the milder end of the spectrum or the severe Ullrich Congenital Muscular Dystrophy (UCMD). Unlike other UCMD patients, patients with the dominant *de novo* intronic mutation in *COL6A1* (c.930+189C>T) have no or only minor symptoms at birth but symptoms progress severely within the first decade. The mutation leads to the in-frame insertion of a pseudoexon between exon 11 and exon 12, which is translated into 24 amino acid residues in the N-terminal region of the triple helix and results in the interruption of the typical G-X-Y motif. In this study it was shown that the mutant chain is translated and secreted as a single α chain, while the collagen VI tetramers are assembled only with the wildtype α1 chain. The mutant chain cannot be incorporated into collagen VI tetramers, but forms large aggregates in the ECM. Here, the mutant α1 chain interacts with collagen VI and potentially with other molecules. Fibrillar aggregates of unknown composition are found in patient's muscle sections. The study provides novel insights into the disease progression of UCMD patients with the *COL6A1* (c.930+189C>T) mutation.