Synthetic collagen heterotrimers: structural mimics of wild-type and mutant collagen type I.

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Abstract

Collagen type I is an AAB heterotrimer assembled from two alpha1 chains and one alpha2 chain. Missense mutations in either of these chains that substitute a glycine residue in the ubiquitous X-Y-Gly repeat with a bulky amino acid leads to osteogenesis imperfecta (OI) of varying severity. These mutations have been studied in the past using collagen-like peptide homotrimers as a model system. However, homotrimers, which by definition will contain glycine mutations in all the three chains, do not accurately mimic the mutations in their native form and result in an exaggerated effect on stability and folding. In this article, we report the design of a novel model system based upon collagen-like heterotrimers that can mimic the glycine mutations present in either the alpha1 or alpha2 chains of type I collagen. This design utilizes an electrostatic recognition motif in three chains that can force the interaction of any three peptides, including AAA (all same), AAB (two same and one different), or ABC (all different) triple helices. Therefore, the component peptides can be designed in such a way that glycine mutations are present in zero, one, two, or all three chains of the triple helix. With this design, we for the first time report collagen mutants containing one or two glycine substitutions with structures relevant to native forms of OI. Furthermore, we demonstrate the difference in thermal stability and refolding half-life times between triple helices that vary only in the frequency of glycine mutations at a particular position.

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