Surprisingly high stability of collagen ABC heterotrimer: evaluation of side chain charge pairs.

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Abstract

Type I collagen is a major component of skin, tendon, and ligament and forms more than 90% of bone mass. It is an AAB heterotrimer assembled from two identical alpha1 and one alpha2 chains. However, the majority of studies on the effects of amino acid substitution on triple helix stability have been performed on collagen homotrimeric helices. In a homotrimer, it is impossible to determine whether the contribution to stability is from the polyproline II helix propensity of the amino acids or from interhelix amino acid interactions. The presence of amino acids in all three chains further exaggerates their contribution. In contrast, in a heterotrimer, the individual chains may be tailored in order to have the substitution in one, two, or all three chains. Therefore, a heterotrimer can divulge specific information about any interaction based upon the substitutions in individual chains. In this paper, we evaluate the contribution of electrostatic interactions between side chain charge pairs on the stability of heterotrimers. We synthesize and analyze the stability of four AAB and four ABC heterotrimers including a surprisingly stable ABC heterotrimer composed of (DOG)10, (PKG)10, and (POG)10 chains (O = hydroxyproline). This heterotrimer has a stability comparable to that of a (POG)10 homotrimer even though D and K occur 20 times in the heterotrimeric helix and have been previously shown to significantly destabilize the triple helix compared to the P and O imino acids. These results show that the stability of heterotrimers cannot be directly determined from the analysis of charge pairs in homotrimers. Because collagen heterotrimers can be designed to have substitution in one, two, or three chains, it gives us the ability to decode cross-strand interactions in

collagen in a similar fashion to alpha-helical coiled-coil interactions and DNA duplex hydrogen bonding.

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