

Poster Presentation

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Fibrillar Collagen Trimerization: Structural Basis and Related Genetic Disorders

U. Sharma¹, N. Mariano², D. Hulmes², N. Aghajari^{1 2}

¹CNRS/Université Lyon 1, Bases Moléculaires et Structurales des Systèmes Infectieux, Institut de Biologie et Chimie des Protéines, Lyon, France,

²CNRS/Université Lyon 1, Biologie Tissulaire et Ingénierie Thérapeutique, Institut de Biologie et Chimie des Protéines, Lyon, France

The C-propeptides of fibrillar procollagens play crucial roles in tissue homeostasis and remodeling by controlling both the intracellular assembly of procollagen molecules and the extracellular assembly of collagen fibrils. Mutations in the C-propeptides affecting molecular assembly are associated with several, often lethal, genetic disorders affecting bone, cartilage, blood vessels and skin. Cells often produce multiple collagen types, each with the correct chain composition. In fibrillar collagens, molecular assembly begins with the C-propeptides which contain chain recognition sequences specific for each collagen type. Our recent crystal structure of a C-propeptide trimer from procollagen III (Bourhis et al, 2012), revealed specific interactions at the trimer interface. Unlike collagen III, a homotrimer, collagen I is normally a heterotrimer, though small amounts of homotrimer are found in embryonic tissue and cancer. To investigate the molecular basis of homo- versus hetero-trimer formation, further structural information is required. We have initiated structural studies on homo- and hetero-trimers of the C-propeptide domain of human procollagen I, to study the molecular basis of chain selectivity within the same cells. CPI homotrimer crystallizes in the monoclinic spacegroup P21, and data were collected to 2.2 Å resolution. The crystal structure solved by MR shows a structure resembling CPIII with the overall shape of a flower. At the trimerization interface however, interactions between chains are specific to CPI and these give insights into the mechanism of molecular recognition. These interactions will be compared to those in CPIII. Structural mapping indicates striking correlations between the sites of numerous disease-related mutations in different C-propeptide domains and the degree of phenotype severity. The results have broad implications for the understanding of genetic disorders of connective tissues and also for new therapeutic approaches against fibrosis.

[1] Bourhis, J.M., Mariano, N., Zhao, Y., et al, N. & Hulmes, D.J.S. (2012) Structural Basis of Fibrillar Collagen Trimerization and Related Genetic Disorders. *Nature Structural & Molecular Biology*. 19: 1031-1036., [2] Bourhis, J.M., Mariano, N., Zhao, Y., et al, N. & Hulmes, D.J.S. & Aghajari, N. (2012) Production and crystallization of the C-propeptide trimer from human procollagen III. *Acta Cryst F*. 68: 1209-1213.

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