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Development of Collagen Mimetic Mini-Fibrils to Study the MMP Susceptibility of Collagen Fibrils.

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Collagen fibrils are the major molecular scaffold of all connective tissues, and are organized in a complex molecular hierarchy. Within the fibrils, the enzyme and cell receptor binding sites of collagen triple helix are further organized by the super twist of the triple helix and the *D*-periodic packing of the fibrils. How such supramolecular structure of collagen fibrils modulate the interactions of collagen with other molecular ligands are not fully understood. In particular, how the fibril packing affects the interactions of collagen with matrix metalloprotease (MMP) is of great interests in the research of wound healing ad tissue remodeling. The enzymatic cleavage of collagen fibrils by MMPs is hypothesized to lead to a range of biochemical and physiological reactions during various physiological processes. Additionally, the susceptibility of collagen fibrils to MMP is of vital importance for the development of collagen-based biomaterials having controllable turnover rate for applications.

While there has been extensive study of how MMP interacts with the triple helix, specifics about how MMPs degrade collagens in the fibril form remains unclear. Questions like how exposed are the MMP cleave sites on the fibrillar surface, do fibrils use the same residues like those in a triple helix to tether MMP, how does the MMP recognize the cleavage site given the uniform overall conformation of the triple helix and the tight packing of the triple helices in a fibrillar arrangement, especially considering the narrow catalytic center of the MMP which is only wide enough to fit a single triple helix, remain unanswered. The exact mechanism of the interaction of MMP on fibrils is important to know since the functional form of collagen is fibrillar in the body.

Our lab has succeeded in generating collagen mimetic mini-fibrils using designed genes in a bacterial expression system. These collagen-like mini-fibrils provide a unique opportunity to investigate the interactions of MMPs at the fibril level. Using this design strategy, we have developed several peptides modelling regions of type III collagen. The peptides are engineered to have varying number of MMP digestion sites. In this presentation we will present our recent results on the studies of 1) the effects of fibril-assembly on the susceptibility of collagen triple helices to MMPs, and 2) the effects of the structural hierarchy and the amino acid sequences on the sensitivity of the mini-fibrils to MMPs. The ultimate goal of the research is to expand the mini-fibrils into a platform for developing collagen materials having tuneable functionalities for medical applications.