INVITED LECTURE 1

Collagen Fibril Formation; an Extracellular Target to Limit the Formation of Fibrotic Deposits.

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Collagen fibrils form biological scaffolds that in physiological conditions provide mechanical strength to connective tissues and facilitate attachment of the cells that build them. The main element of collagen fibrils is the collagen molecule. Collagen I is the most abundant structural protein of connective tissues such as skin, bone, and tendon. This protein is first synthesized as a precursor molecule, procollagen, that is characterized by the presence of a central triple-helical domain flanked by short linear telopeptides and globular N-terminal and C-terminal propeptides. The formation of collagen fibrils is initiated by the enzymatic cleavage of N-terminal and C-terminal propeptides. Such removal of procollagen propeptides exposes telopeptides, which drive collagen self-assembly by engaging in site-specific intermolecular interactions.

In physiological conditions the homeostasis of tissue collagens is constantly maintained, but during pathological processes, the balance is shifted toward fibrosis, a process of excessive collagen production and accumulation. Fibrosis is a reactive process modulated by various factors propagated by an inflammatory tissue reaction. These factors trigger the local expansion of resident fibroblast subpopulations, modulate anabolic and catabolic processes taking place in these cells, and influence reactions governing the biosynthesis and degradation of the connective tissue components. Localized fibrotic reactions are quite common and frequently develop as a consequence of trauma or surgical procedures.

Current therapeutic interventions to limit localized fibrosis include application of anti-inflammatory and anti-proliferative agents. Those approaches, however, are not fully effective and are frequently associated with significant side effects. The novel approach presented here targets the extracellular process of the formation of collagen fibrils, a key element of fibrotic deposits. Specifically, a few variants of antibody-based inhibitors of critical collagen-collagen interactions that drive fibril formation were engineered and employed in models mimicking a localized fibrotic process. Preliminary data indicate that the antibody-based inhibitors prevent excessive fibril formation not only by blocking the collagen-collagen interaction but also by interfering with the processing of procollagen C-terminal propeptide by procollagen C proteinase.

We expect that the utility of inhibitors of the collagen-collagen interaction in preventing localized fibrosis will be high. This notion is based on the fact that excessive deposition of collagen fibrils is a characteristic of fibrotic processes occurring in all connective tissues.