

A PRIMER OF COLLAGEN BIOLOGY: SYNTHESIS, DEGRADATION, SUBTYPES AND ROLE IN DUPUYTREN'S CONTRACTURE

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Collagen is the primary structural protein of the extracellular matrix. To date, 28 structurally distinct subtypes of collagen have been identified which serve not only as structural components of the interstitial matrix but also function as adhesive and occlusive components of basement membranes, as anchoring fibrils between cells and the interstitium, and as integrative transmembrane proteins. In addition to their structural functions, collagens have a number of physiologically important roles as well. Collagens can serve as an extracellular "sink" for a number of growth factors and cytokines that are released in active form during the process of collagen degradation; additionally, the degradation products of collagen have a number of physiologic activities that are important to the process of wound healing.

The extracellular matrix collagens are not static but are constantly being remodeled in response to the local environment. Collagen remodeling is tightly regulated in vivo, resulting in a balance between synthesis and degradation which allows the quantity and quality of the extracellular matrix to be adapted precisely to physiologic need. Disregulation of the balance between these two processes has been shown to have a role in the pathogenesis of a number of fibrotic conditions, notably in Dupuytren's contracture.

Despite their broad structural and functional diversity, all collagens have some features in common. They are the only proteins which contain hydroxyproline as well as an unusually high content of the amino acids glycine and proline. Furthermore, all collagen subtypes contain within their structure at least one domain composed of a cross-linked triple-helical motif. The triple helical structure renders collagen impervious to enzymatic degradation by most proteases as long as it is intact; only a few proteases (known as collagenases) have the ability to recognize and digest this triple helical motif. In mammals, interstitial collagens are primarily degraded by several members of the matrix metalloproteases (MMPs), with lesser contributions from the cysteine proteases cathepsins L and K. In contrast, a number of enzymes isolated from a variety of bacteria and marine organisms have been shown to have potent collagenolytic activity; the best characterized of these are the collagenases secreted by *Clostridium histolyticum*. These were discovered over fifty years ago and have had broad application as research tools for cell culture, tissue transplantation and disease modeling, and are currently being investigated in therapeutic applications (most recently in the non-surgical management of Dupuytren's contracture and similar pathologic fibrotic conditions).