PHARMACOLOGICAL CONTROL OF COLLAGEN SYNTHESIS

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D.J. Prockop and KI. Kivirikko. Collagen: Molecular Biology, Diseases and Potentials for Therapy. Annual Review of Biochemistry 64:403-434 (1995).

Comprehensive review of the unique pathway whereby fibroblasts and other cells synthesize the soluble precursor of collagen (procollagen) and then use it to assemble collagen fibers that have the strength of steel wires. One section reviews mutations in collagen genes that decrease collagen synthesis or synthesis of abnormal collagens. The mutations thereby cause severe skeletal diseases such as osteogenesis imperfecta and chondrodysplasias. More rarely, they cause common diseases such as osteoporosis and osteoarthritis. Mutations in one collagen (type VII) cause dystrophic epidermolysis bullosa. One section discusses ways of designing antifibrotic agents that are inhibitors of specific steps in collagen biosynthesis.

M.R. Duncan, K.S. Frazier, S. Abramson, S. Williams, H. Klapper, X. Huang, G.R. Grotendorst. Connective tissue growth factor mediates transforming growth factor β-induced collagen synthesis: down-regulation by cAMP. FASEB J. 13:1774-1786 (1999).

A recent review on Connective Tissue Growth Factor (CTGF). CTGF or its receptor is an attractive target for anti-fibrotics because it mediates the effects of TGF-β on fibroblasts. The binding of TGF-β to fibroblasts releases CTGF. The CTGF then acts on the same cells to increase collagen biosynthesis. CTGF does not appear to play a role in the multiple other effects of TGF-β. Therefore, an antibody to TGF-β or an antagonist to its receptor should specifically block the important role that TGF-β has on increasing collagen deposition during wound repair.

D.J. Prockop, A.L. Sieron and S.-W. Li. Procollagen N-proteinase and procollagen C-proteinase. Two unusual metalloproteinases that are essential for procollagen processing probably have important roles in development and cell signaling. Matrix Biology 16;399-408 (1998).

A review that compares the similarities and differences between these two enzymes that are required for processing the soluble precursor (procollagen) to collagen and, therefore, for the assembly of normal collagen fibrils. The good news is that both enzymes have important differences in structure and function from each other and from the over 200 similar enzymes known as zinc-metalloproteinases, i.e. enzymes that cleave proteins and have a zinc ion in their active site. Zinc metalloproteinases include degradative enzymes such as collagenases and stromolysins. These also include a large number of enzymes involved in early development of embryos. There has been great interest by drug companies in developing inhibitors of metalloproteinases such as collagenases as a therapy for arthritis. However, the similarities between the enzymes has made it difficult to design a drug that inhibits one metalloproteinase without inhibiting others. The unique features of procollagen N-proteinase and procollagen C-proteinase is good news in that these unique features suggest it will be possible to develop specific drugs to inhibit the enzymes and thereby decrease the amount of collagen that is deposited during wound repair. The bad news is that each of these enzymes recently have been found to play unexpected roles in early development of embryos, Therefore, it may be necessary to take great precautions in giving drugs that inhibit the enzymes to pregnant women and perhaps chi1dren.