Recent Advances in Orthopedics

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Contents

Chapter 6

Targeting Fibrosis to Reduce Post-traumatic Joint Stiffness

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INTRODUCTION

Post-traumatic Joint Stiffness

Joint stiffness, or contracture, is defined as the loss of passive range of motion (ROM) of diarthrodial joints. A common result of traumatic orthopedic injury, joint stiffness can make even basic functions of daily living difficult if they require specific ranges of motion. For instance, people with joint stiffness might not be able to reach the parameters needed for proper knee flexion for the swing-through phase of ambulation (67°), to ascend an 8-inch stair (83°), to descend stairs (90°–100°), to raise from a standing chair (93°), to rise from a low chair (105°) and to kneel (125°).

Joint stiffness occurs, in part, due to fibrotic processes that take place after a joint is injured.[1] The injury triggers inflammation, which releases growth factors that activate fibroblastic cells to produce macromolecules that subsequently form scar tissue. In contrast to the precise architecture of the tissues that build healthy joints, this scar tissue lacks a defined structure. Rather than support joint functioning, this scar tissue impairs joint functioning and causes joint stiffness.[1-3]

Therapeutic approaches to limit joint stiffness focus on reducing this scar tissue formation. No fully effective and safe treatments are yet available that block the development of joint stiffness or improve ROM. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) do not fully reduce the profibrotic inflammatory processes. Intra-articular or intravenous injections of the anti-inflammatory corticosteroids may improve the ROM in patients with arthrofibrosis, but applying corticosteroids can result in significant side effects, including an increased risk of infection, immunosuppression, decreased wound healing, insomnia and weight gain.[4-7] Designing pharmacological therapies that reduce joint stiffness is a particularly challenging problem, since production of macromolecules that form fibrotic scar overlaps with production of elements needed for proper healing of injured joints.

Some nonpharmacological methods are available to treat joint stiffness. Cryotherapy can decrease inflammation in patients suffering from joint trauma. Active physical

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manipulation of the arthrofibrotic joints or passive manipulation, using devices such as continuous passive motion machines, may increase the ROM. Applying these physical methods, however, may accelerate pain and inflammation, thereby reducing their benefits.

PATHOMECHANISMS OF POST-TRAUMATIC JOINT STIFFNESS

Fibrotic Scarring

Reduced joint ROM results from structural aberrations in various tissues that facilitate normal operation of a healthy joint. These tissues include muscles, capsules, ligaments, tendons, cartilage, bone and skin. In post-traumatic joint stiffness, these aberrations result chiefly from the formation of fibrotic scar by collagen-rich fibrotic deposits. These deposits change the architecture of a tissue, thereby inhibiting its normal mechanical functions.

Key processes that drive post-traumatic scarring in injured joints resemble those that drive fibrosis in other organs and tissues, such as skin, liver, kidney and lungs. These processes include inflammation, cell activation, enhanced cell proliferation, and the formation of collagen-rich fibrotic extracellular deposits.[1]

Inflammatory Processes

Shortly after joint trauma, various inflammatory cells infiltrate the sites of injury, triggering an increase in the number of mast cells.[8,9] Hildebrand et al. documented a significant increase in the number of mast cells in capsules of injured knee joints in a rabbit model, and later, they documented a similar increase in anterior elbow capsules in patients with post-traumatic elbow contractures.[10]

The increase in the number of mast cells in these patients was associated with an increase of the number of α-smooth muscle actin (α-SMA)-positive myofibroblasts. Accelerated proliferation of mast cells was also observed in periarticular tissues from patients with idiopathic arthrofibrosis after total knee arthroplasty.[11]

Mast cells also produce profibrotic chymase and tryptase and profibrotic growth factors, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and tissue growth factor β1 (TGF β1).[12,13] The expression of these profibrotic molecules and the close contact of mast cells with fibroblasts that produce collagen-rich matrices both contribute to the pathomechanism that forms fibrotic deposits within and around injured joints.

Other important contributors to the development of post-traumatic joint contracture include neuroinflammatory pathways. Key elements of the neuroinflammatory response, calcitonin gene-related peptide (CGRP) and substance P (SP),[14] are produced in dorsal root ganglia and function mainly as neurotransmitters, but they also act as paracrine factors affecting vasodilation, tissue edema, cell proliferation and production of elements of the extracellular matrix. Studies have demonstrated that, following traumatic injury, CGRP and SP are secreted by peripheral nerve endings in skin, muscle, tendons, ligaments, capsule and other joint tissues. Upon secretion, these peptides stimulate profibrotic activities of various cells, including mast cells and fibroblasts, thereby accelerating the formation of fibrotic scars. The presence of CGRP-positive nerve fibers in knee capsules of experimental rabbits with knee contractures and in patients with post-traumatic elbow stiffness supports the profibrotic role of the neuroinflammatory pathways.[10]

FORMATION OF THE ARCHITECTURE OF JOINT TISSUES IN HEALTH AND IN RESPONSE TO INJURY

Development of Joint Architecture

Joint motion is facilitated by proper architecture of elements that form the synovial joints, including the joint capsule, ligaments and tendons, as well as bone and cartilage. The architecture of these elements is mainly formed by a fibrillar structure of collagenous proteins (**Figure 6.1**). Most notably, collagen I contribute to more than 80% of the dry mass of the key elements of the fibrillar structure.[1,2]

The formation of the collagen-rich architecture of the joints is a complex, well-orchestrated process initiated during embryonic development. Formation of a continuous cartilaginous anlage initiates the joint development. Subsequently, the synovial cavities form within defined regions of the anlages in processes that require mechanical forces, cell necrosis and cell removal by apoptosis.[15-17]

Following the formation of the synovial cavity, other elements start to develop to form a functional joint. Studies of periarticular and intra-articular joint development in rats have shown that the capsular tissue initially appears as a thin lamella of elongated, densely packed cells followed by the emergence of elements of the extracellular matrix.[15,16]

Early studies have also indicated the important role of movement in development of joints.[18] Experimental studies have demonstrated that lack of movement causes severe alterations of the joint structure, including fusions. In humans, decrease in fetal movement (fetal akinesia) causes arthrogryposis, which is characterized by contracture of certain joints. Unlike post-traumatic joint stiffness, joint contracture due to fetal akinesia is not associated with classical signs of inflammation, indicating that the main cause is a lack of mechanical forces.

The importance of mechanical forces to the proper alignment of the collagen fibrils that form the connective tissue architecture is well-recognized. In 1951 MacConaill concluded that "as iron filings are to a magnetic field so are collagen fibrils to a tension field".[19]

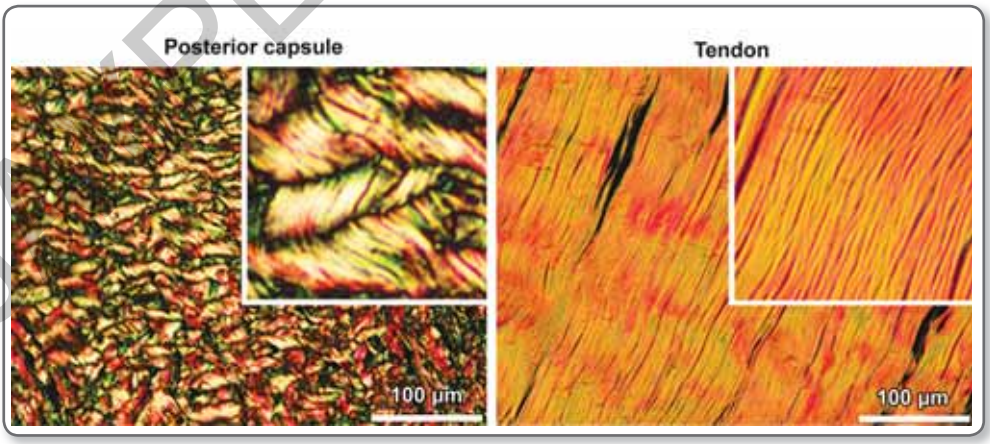


Figure 6.1: Polarized light microscopy of picrosirius stained collagen-rich matrices that form the posterior knee capsule and a tendon. Inserts present detailed views of collagen fibrils. Note highly-organized architectures of the presented tissues in which crimped collagen fibrils are clearly visible.

Since then, the role of mechanical forces in fibril organization has been demonstrated in studies on connective tissues, including meniscus, tendon and ligament.[20,21] Based on these studies, researchers have concluded that the force-fibril orientation relationship is critical for defining micro-structural properties in connective tissues. In a context of post-traumatic contracture, scar tissue formation reflects the body's inability to recapitulate the orchestrated chain of complex events needed for joint tissue to form properly.

Collagen-based Structure of Key Elements of Healthy and Stiff Joints

Biosynthesis of Collagen Molecules

The biosynthesis of the collagen fibrils that form the key elements of the joints is a complex process that includes both intracellular and extracellular steps. Intracellularly, each collagen molecule is formed by assembly of three collagen α-chains that consist of approximately 300 uninterrupted repeats of -Gly-X-Y- amino acid triplets.[22] These collagen molecules are first produced as procollagens, which are characterized by the presence of globular N-terminal and C-terminal propeptides that flank the triple-helical region. Short telopeptide domains separate the propeptides and the triple-helical domain.

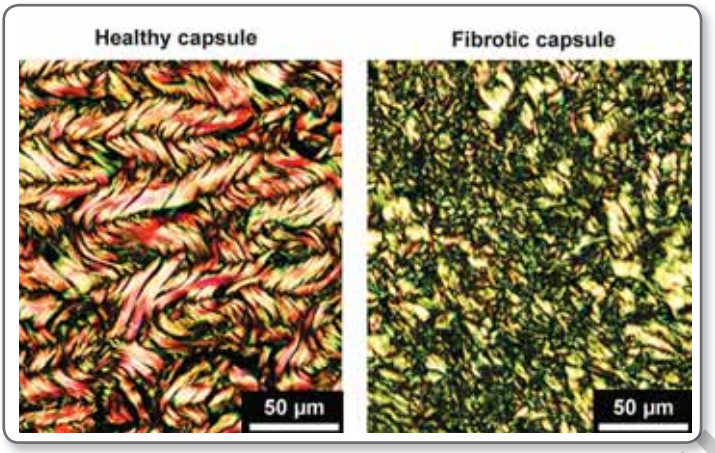
Critical for the function of collagen molecules are post-translational modification of nascent α chains. Most notably, prolyl-4-hydroxylase (P4H) hydroxylates proline residues present in the -Y- position of the -Gly-X-Y- triplets while lysyl hydroxylase (LH) hydroxylates lysine residues present in the –Y- position.[22] P4H consists of two catalytic α units (P4Hα) and two non-catalytic β units (P4Hβ). The P4Hβ subunit also serves as protein disulfide isomerase (PDI) that catalyzes the formation of disulfide bonds and functions as a protein chaperone that prevents premature aggregation of procollagen chains.[23,24] More recently, 3-hydroxyproline residues have also been found in the -X- and -Y- positions of the –Gly-X-Y- triplets.[25,26] While 4-hydroxyproline residues participate in triple helix stabilization, the role of 3-hydroxiproline residues is less clear.

Post-translationally-modified procollagen chains fold into a triple-helical structure in a zipper-like fashion.[27] Chaperone proteins stabilize nascent chains, prevent their nonspecific aggregation, and play a key role in procollagen folding. These chaperone proteins include: (i) heat-shock protein 47 (HSP47), (ii) heat-shock 70 kDa-related luminal binding protein (BiP), and (iii) P4Hβ/PDI.[28]

Collagen Fibril Formation

Following secretion into the extracellular space, procollagen N proteinase cleaves the N-terminal propeptides and procollagen C proteinase cleaves the C-terminal propeptides.[29-31] Cleavage of procollagen propeptides is required to initiate collagen fibril formation. Researchers have demonstrated that procollagen propeptides may also be processed by meprins and mast cell chymases, enzymes whose production increases during inflammation and fibrosis.[32,33]

Collagen fibrils self-assemble in a process driven by site-specific interactions among individual collagen molecules.[34] In particular, telopeptides of one collagen molecule interact with a partner telopeptide-binding region to assemble into fibrils. Following their assembly, individual collagen molecules may be cross-linked by lysyl oxidase (LOX), a process that maintains the structural integrity of collagen fibrils and facilitates proper mechanical functions of collagen-rich tissues.[24]



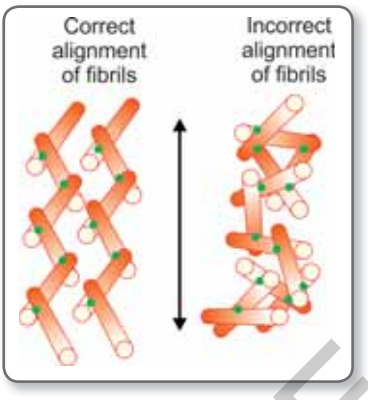


Figure 6.2: Aberration of the fibrillar architecture of the posterior capsule isolated from a rabbit with severe knee contracture. Polarizing light microscopy images illustrate the difference in the fibril organization: the healthy capsule shows a regular crimping pattern of fibril organization while the fibrotic capsule does not. Note that the green color of the fibrils seen in the injured capsule indicates their smaller diameter compared to the red fibrils in the healthy capsule. A schematic illustrating the arrangement of collagen fibrils in healthy and injured posterior capsule is also presented. Green dots represent "hinge-like" points formed by proper crimping. While these areas present in normal tissue allow normal knee movement, their aberrations in fibrotic joints cause joint stiffness. The arrow indicates the direction of forces imposed on the capsules during extension/flexion.

Balanced processes of fibrillogenesis and collagenolysis maintain the homeostasis of collagen-rich extracellular matrices in healthy tissues, but in fibrotic tissues the process of fibrillogenesis dominates. Researchers have demonstrated that this causes an imbalance that significantly alters the fibrillar architecture of fibrotic tissues. Studies on rabbits with post-traumatic knee joint contracture have demonstrated that collagen fibril organization is significantly altered in the posterior joint capsules. **Figure 6.2** illustrates the absence of well-defined crimping of collagen fibrils and fibers that form the structure of the fibrotic posterior capsules. This lack of crimping illustrates poor organization of the collagen matrix, which in healthy capsules is formed by layers of parallel fibers arranged in a wave-like fashion (**Figure 6.2**). Ultimately, this poor organization of the scar tissue is a key cause of post-traumatic contracture of joints (**Figure 6.2**).

NOVEL APPROACHES TO LIMIT POST-TRAUMATIC JOINT STIFFNESS

Targeting Inflammation

There are no effective pharmacological methods to prevent post-traumatic joint stiffness. Surgeons may apply nonsteroid and steroid anti-inflammatory agents to reduce the

profibrotic inflammatory processes, but significant side effects limit their use. Clinical observations associate the use of anti-inflammatory agents with increased risk of infection, immunosuppression, decreased wound healing, insomnia and weight gain.[4-7]

Since established fibrotic tissues around and within injured joints do not remodel easily, scientists have explored novel approaches to block their development. These efforts, which target various elements of the inflammatory process, offer an attractive way to limit the formation of fibrotic tissue and reduce post-traumatic contracture.

Recently, scientists showed how mast cells present in joint capsules express critical profibrotic growth factors that activate fibroblasts to produce structural macromolecules that form the fibrotic scar tissue.[9,10] In addition to their profibrotic inflammatory functions, Steplewski et al. suggested that mast cells may also play more direct role in the production of the collagen-rich fibrillar deposits in injured joints.[1] Specifically, they pointed to the studies by Kofford et al. indicating that mast cell chymases cleave off both procollagen propeptides in a way that enables collagen molecules to assemble into fibrils, thereby accelerating fibrosis.[33]

Scientists have tested whether blocking the profibrotic activities of mast cells would reduce post-traumatic joint contracture. They focused on ketotifen fumarate, a "mast cell stabilizer" that prevents vesicle degranulation and limits the mast cell secretion of profibrotic cargo.[35]

In studies aiming to limit systemic sclerosis, scientists tested the antifibrotic potential of ketotifen in patients with scleroderma and established fibrotic deposits. Treatment with ketotifen did not improve any clinical parameters of these patients, so results of these initial studies were somewhat disappointing.[36] Subsequent studies in animal models of fibrosis showed more promising results. Specifically, instead of applying ketotifen in the late stages of fibrosis, scientists applied it at earlier stages, when the fibrotic processes are taking place in the skin and joint capsules. They found that administering ketotifen right after injury to the knee joints reduced the expression of key markers of fibrosis, including TGF-β1, α-SMA and collagen I, in experimental rabbits.[8] Moreover, the rabbits treated with ketotifen had significantly fewer mast cells and myofibroblasts in their posterior capsules compared to rabbits that were not treated with ketotifen. Mechanical measurement after treatment showed that the treated knees had significantly less flexion contracture compared to the nontreated control.[37]

These promising results indicate that targeting the mast cells represents a valid therapeutic approach to reducing post-traumatic joint stiffness. Moreover, these studies indicate that for intervention to be successful, an anti-fibrotic treatment must be applied in the early stages of the fibrotic process.

Targeting the Assembly of Fibrotic Tissue

Therapeutic approaches to limit fibrosis, including arthrofibrosis, ultimately aim to reduce the excessive production of collagen-rich deposits that alter tissue function. The majority of these approaches target broad cellular processes associated with inflammation and accelerated production of elements of the scar tissue, most notably collagen I. To date, however, targeting these processes has not led to any fully effective and safe treatments for fibrotic disease. Consequently, new targets and therapeutic modalities are needed to reduce the burden of fibrosis.

Recently, scientists identified the very process of collagen fibril assembly as a valid target to reduce injury-related fibrotic deposits.[38] To block collagen fibrillogenesis, researchers targeted the process of site-specific binding that occurs between the telopeptides of one collagen molecule and the telopeptide-binding region of an interacting partner. They proposed that blocking this key interaction could inhibit the formation of collagen fibrils, thereby decreasing the mass of fibrotic deposits.[38,39] They tested this idea by employing a monoclonal antibody that binds the C-terminal telopeptide of the α2 chain of collagen I (α2Ct), based on the fact that collagen I is the most abundant element of fibrotic scars.[38] Initial tests demonstrated that the anti-α2Ct antibody blocks the formation of collagen fibrils in vitro and in organotypic keloid-like constructs in mice.

Subsequently, Fertala et al. developed a clinically-relevant recombinant IgG-form of the anti-α2Ct antibody suitable for preclinical tests in animal models.[40] Employing a rabbit-based model of posttraumatic joint contracture, the researchers tested the utility of the anti-α2Ct antibody to reduce joint stiffness. In brief, following knee injury, the anti-α2Ct antibody was delivered directly to the knee cavities for eight weeks using programmable subcutaneous pumps. At the end of experiment, the rabbits were sacrificed and then mechanical, biochemical, and histological assays of the knees were performed.[2] Mechanical assays demonstrated that treatment with the anti-α2Ct antibody significantly reduced the flection contracture in the treated of rabbits compared to the nontreated control. Detailed analyses of collagen fibrils present in the posterior capsules of treated joints suggested the mechanism of the observed improvements. Specifically, microscopic analyses indicated that significantly fewer collagen fibrils had formed in the treated joints compared to the controls.[2]

Based on results of tests of the anti-fibrotic activity of the anti-α2Ct antibody, the authors concluded that collagen fibril formation is a valid target to reduce post-traumatic joint contracture. Unlike antifibrotic approaches that target broad intracellular processes associated with inflammation and cell proliferation, the anti-α2Ct antibody approach targets a well-defined extracellular process, thereby potentially reducing unwanted side effects. In this sense, this approach is similar to blocking extracellular LOX as a method to reduce fibrosis in idiopathic pulmonary fibrosis.[41,42] Although promising in initial tests, clinical trials of the antibody-based blocking of LOX in lung fibrosis were recently terminated due to lack of efficacy. As LOX catalyzes formation of the crosslinks among collagen molecules incorporated into a fibril, blocking a downstream process of the fibril formation using the anti-α2Ct antibody could represent a more effective way to reduce buildup of the fibrotic deposits.

The initial study on the efficacy of anti-α2Ct antibody to reduce post-traumatic joint stiffness had certain limits that do not allow to a full determination of the utility of this novel approach.[2] This approach did not fully prevent development of joint stiffness since flexion contracture was still observed in the rabbits, despite the antibody treatment. The authors offered some possible explanations for this limitation: (i) the antibodies did not reach a fully effective concentration, (ii) the antibodies were unable to access all sites of fibrosis and (iii) the antibodies did not target the formation of noncollagenous elements of fibrotic tissue.

Future efforts should focus on improved targeting of the extracellular processes of collagen fibrillogenesis, including optimizing antibody concentration, employing more effective antibody delivery systems, and designing small-molecule inhibitors able to penetrate target sites more effectively than antibodies.

REFERENCES

1. Steplewski A, Fertala J, Beredjiklian PK, et al. Auxiliary proteins that facilitate formation of collagen-rich deposits in the posterior knee capsule in a rabbit-based joint contracture model. J Orthop Res. 2016;34(3):489-501.
2. Steplewski A, Fertala J, Beredjiklian PK, et al. Blocking collagen fibril formation in injured knees reduces flexion contracture in a rabbit model. J Orthop Res. 2017;35(5):1038-46.
3. Akeson WH, Amiel D, Woo SL. Immobility effects on synovial joints the pathomechanics of joint contracture. Biorheology. 1980;17(1-2):95-110.
4. Aoki M, Kato F, Mimatsu K, et al. Histologic changes in the intervertebral disc after intradiscal injections of methylprednisolone acetate in rabbits. Spine. 1997;22(2):127-31.
5. Gold EW, Fox OD, Weissfeld S, et al. Corticosteroid-induced avascular necrosis: an experimental study in rabbits. Clin Orthop Relat Res. 1978(135):272-80.
6. Oikarinen A, Haapasaari KM, Sutinen M, et al. The molecular basis of glucocorticoid-induced skin atrophy: topical glucocorticoid apparently decreases both collagen synthesis and the corresponding collagen mRNA level in human skin in vivo. Br J Dermatol. 1998;139(6):1106-10.
7. Taguchi T, Kubota M, Saito M, et al. Quantitative and Qualitative Change of Collagen of Achilles Tendons in Rats With Systemic Administration of Glucocorticoids. Foot Ankle Int. 2016;37(3):327-33.
8. Monument MJ, Hart DA, Befus AD, et al. The mast cell stabilizer ketotifen reduces joint capsule fibrosis in a rabbit model of post-traumatic joint contractures. Inflamm Res. 2012;61(4):285-92.
9. Monument MJ, Hart DA, Salo PT, et al. Posttraumatic elbow contractures: targeting neuroinflammatory fibrogenic mechanisms. J Orthop Sci. 2013;18(6):869-77.
10. Hildebrand KA, Zhang M, Salo PT, et al. Joint capsule mast cells and neuropeptides are increased within four weeks of injury and remain elevated in chronic stages of posttraumatic contractures. J Orthop Res. 2008;26(10):1313-9.
11. Freeman TA, Parvizi J, Dela Valle CJ, et al. Mast cells and hypoxia drive tissue metaplasia and heterotopic ossification in idiopathic arthrofibrosis after total knee arthroplasty. Fibrogenesis Tissue Repair. 2010;3:17.
12. Pennington D, Thomas P, Lopez A, et al. Transforming growth factor-beta production by dog mastocytoma cells. Storage and release from mast cell granules. Chest. 1991;99(3 Suppl):66S.
13. Gruber BL. Mast cells in the pathogenesis of fibrosis. Curr Rheumatol Rep. 2003;5(2):147-53.
14. Monument MJ, Hart DA, Salo PT, et al. Neuroinflammatory Mechanisms of Connective Tissue Fibrosis: Targeting Neurogenic and Mast Cell Contributions. Adv Wound Care (New Rochelle). 2015;4(3):137-51.
15. Mitrovic DR. Development of the metatarsophalangeal joint of the chick embryo: morphological, ultrastructural and histochemical studies. Am J Anat. 1977;150(2):333-47.
16. Mitrovic D. Development of the diarthrodial joints in the rat embryo. Am J Anat. 1978;151(4):475-85.
17. Nalin AM, Greenlee TK, Sandell LJ. Collagen gene expression during development of avian synovial joints: transient expression of types II and XI collagen genes in the joint capsule. Dev Dyn. 1995;203(3):352-62.
18. Lelkes G. Experiments in vitro on the role of movement in the development of joints. J Embryol Exp Morphol. 1958;6(2):183-6.
19. Macconaill MA. The movements of bones and joints. The mechanical structure of articulating cartilage. J Bone Joint Surg Br. 1951;33-B(2):251-7.
20. Parry DA. The molecular and fibrillar structure of collagen and its relationship to the mechanical properties of connective tissue. Biophys Chem. 1988;29(1-2):195-209.
21. Provenzano PP, Vanderby R Jr. Collagen fibril morphology and organization: implications for force transmission in ligament and tendon. Matrix Biol. 2006;25(2):71-84.
22. Prockop DJ, Berg RA, Kivirikko KI, Uitto J. Intracellular Steps in the Biosynthesis of Collagen. In: Ramachandran GN, Reddi AH, editor. Biochemistry of Collagen. New York: Plenum; 1976. p. 163-237.
23. Bottomley MJ, Batten MR, Lumb RA, et al. Quality control in the endoplasmic reticulum: PDI mediates the ER retention of unassembled procollagen C-propeptides. Curr Biol. 2001;11(14):1114-8.
24. Prockop DJ, Kivirikko KI. Collagens: molecular biology, diseases, and potentials for therapy. Annu Rev Biochem. 1995;64:403-34.
25. Fietzek PP, Rexrodt FW, Wendt P, et al. The covalent structure of collagen. Amino-acid sequence of peptide 1-CB6-C2. Eur J Biochem. 1972;30(1):163-8.
26. Morello R, Bertin TK, Chen Y, et al. CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta. Cell. 2006;127(2):291-304.

27. Engel J, Prockop DJ. The zipper-like folding of collagen triple helices and the effects of mutations that disrupt the zipper. Annu Rev Biophys Biophys Chem. 1991;20:137-52.
28. Lamande SR, Bateman JF. Procollagen folding and assembly: the role of endoplasmic reticulum enzymes and molecular chaperones. Semin Cell Dev Biol. 1999;10(5):455-64.
29. Kadler KE, Hojima Y, Prockop DJ. Assembly of collagen fibrils de novo by cleavage of the type I pC-collagen with procollagen C-proteinase. Assay of critical concentration demonstrates that collagen self-assembly is a classical example of an entropy-driven process. J Biol Chem. 1987;262(32):15696-701.
30. Colige A, Vandenberghe I, Thiry M, et al. Cloning and characterization of ADAMTS-14, a novel ADAMTS displaying high homology with ADAMTS-2 and ADAMTS-3. J Biol Chem. 2002;277(8):5756-66.
31. Li SW, Sieron AL, Fertala A, et al. The C-proteinase that processes procollagens to fibrillar collagens is identical to the protein previously identified as bone morphogenic protein-1. Proc Natl Acad Sci U S A. 1996;93(10):5127-30.
32. Broder C, Becker-Pauly C. The metalloproteases meprin alpha and meprin beta: unique enzymes in inflammation, neurodegeneration, cancer and fibrosis. Biochem J. 2013;450(2):253-64.
33. Kofford MW, Schwartz LB, Schechter NM, et al. Cleavage of type I procollagen by human mast cell chymase initiates collagen fibril formation and generates a unique carboxyl-terminal propeptide. J Biol Chem. 1997;272(11):7127-31.
34. Prockop DJ, Fertala A. The collagen fibril: the almost crystalline structure. J Struct Biol. 1998;122(1-2):111-8.
35. Craps LP, Ney UM. Ketotifen: current views on its mechanism of action and their therapeutic implications. Respiration; Int Rev Thor Dis. 1984;45(4):411-21.
36. Gruber BL, Kaufman LD. A double-blind randomized controlled trial of ketotifen versus placebo in early diffuse scleroderma. Arthritis Rheum. 1991;34(3):362-6.
37. Monument MJ, Hart DA, Befus AD, et al. The mast cell stabilizer ketotifen fumarate lessens contracture severity and myofibroblast hyperplasia: a study of a rabbit model of posttraumatic joint contractures. J Bone Joint Surg Am. 2010;92(6):1468-77.
38. Chung HJ, Steplewski A, Chung KY, et al. Collagen fibril formation. A new target to limit fibrosis. J Biol Chem. 2008;283(38):25879-86.
39. Prockop DJ, Fertala A. Inhibition of the self-assembly of collagen I into fibrils with synthetic peptides. Demonstration that assembly is driven by specific binding sites on the monomers. J Biol Chem. 1998;273(25):15598-604.
40. Fertala J, Steplewski A, Kostas J, et al. Engineering and characterization of the chimeric antibody that targets the C-terminal telopeptide of the alpha2 chain of human collagen I: a next step in the quest to reduce localized fibrosis. Connect Tissue Res. 2013;54(3):187-96.
41. Cox TR, Bird D, Baker AM, et al. LOX-mediated collagen crosslinking is responsible for fibrosis-enhanced metastasis. Cancer Res. 2013;73(6):1721-32.
42. Rodriguez HM, Vaysberg M, Mikels A, et al. Modulation of lysyl oxidase-like 2 enzymatic activity by an allosteric antibody inhibitor. J Biol Chem. 2010;285(27):20964-74

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