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Proinflammatory mediators and osteoarthritis

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Although the etiology of osteoarthritis (OA) remains elusive, it is currently believed that the integrity of articular tissue is maintained through a balance in cytokine-driven anabolic and catabolic processes.

OA is characterized by a degeneration of articular cartilage. Breakdown of the cartilage matrix leads to the development of fibrillation, fissures, the appearance of gross ulcerations, and full thickness loss of the joint surface. Moreover, at the clinical stage of the disease, changes caused by OA involve not only the cartilage, but also the synovial membrane where an inflammatory reaction is often seen. The occurrence of synovial inflammation in OA appears to be of fundamental importance mainly due to the secretion of mediators such as the cytokines [1].

Although the spectrum of factors responsible for the altered function of the cells in OA has not been fully defined, evidence suggests that the production of irregular cytokines and alterations in their amounts or operative mechanisms contribute to the abnormalities present.

Among the proinflammatory cytokines, interleukin (IL)-1β and tumor necrosis factor (TNF)-α appear most involved in the catabolic process of OA [1]. The net effect of these proinflammatory cytokines depends not only on absolute levels, but on a complex interplay among ambient cytokines. Other inflammatory cytokines have been shown to be expressed in synovial membrane or fluid of OA patients (Fig. 1), these being the IL-6, leukemia inhibitory factor (LIF), IL-17 and IL-8. All are upregulated by the proinflammatory cytokines IL-1β and TNF-α, and also have the ability to increase the synthesis of the two latter.

IL-1β is primarily synthesized as a 31 kD precursor (pro-IL-1β) and must be proteolitically processed to be active. In mammals only one protease, which belongs to the cysteine-dependent protease family and is named IL-1β converting enzyme (ICE or Caspase-1), can specifically generate the mature cytokine. TNF-α also occurs in a precursor membrane-bound form, and is released from cells by proteolytic cleavage resulting in a soluble active form. This appears to occur via a TNF-α converting enzyme (TACE) belonging to a subfamily of the adamalysin (ADAM).

IL-6 has also been proposed as a contributor to the OA pathological process by increasing the amount of inflammatory cells in synovial tissue, inducing a proliferation of chondrocytes, and by amplifying the effects of IL-1 on the increased metalloprotease (MMP) synthesis and inhibition of proteoglycan production. However, as IL-6 can induce the production of TIMP and not MMP themselves, it is believed that this cytokine is involved in the feedback mechanism that limits enzyme damage. LIF is another cytokine that can stimulate cartilage proteoglycan resorption as well as MMP synthesis. In OA, however, its role has not yet been clearly defined. IL-17 is a newly discovered cytokine that upregulates a number of gene products involved in cell activation, including the pro-inflammatory factors; the role of LIF in OA remains undetermined. IL-8 is a potent chemotactic cytokine synthesized and secreted mainly by neutrophils, although it has been detected in other cell types including OA synovium macrophages, cells from the lining layer and in chondrocytes. This cytokine enhances the production of oxidative and 5-lipoxygenase products and could synergize with TNF-α to markedly increase PGE_2 production.

It is now clear that an activation of cytokine cascades is involved in OA, however apart from IL-1β and TNF-α, the exact role of other inflammatory cytokines has not been clearly established. As well, it has not yet been determined if they act independently or in concert, or whether a functional hierarchy exists between them. Yet it is claimed, and substantiated by studies on animal models, that IL-1β is of pivotal importance in cartilage destruction, and TNF-α drives the

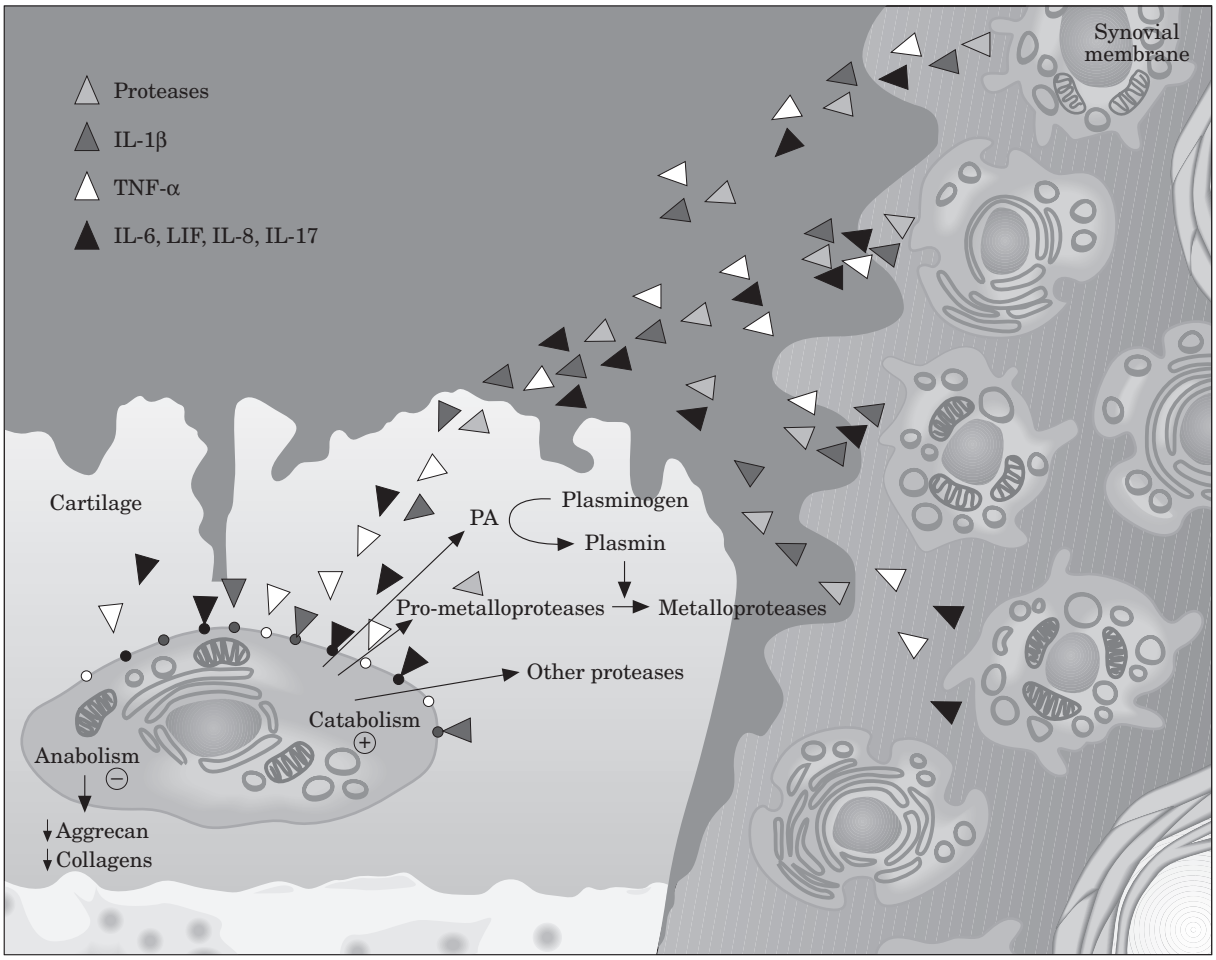

FIG. 1. Process involved in osteoarthritis. At a later stage of the disease, inflammation of the synovial membrane occurs from which proteases and proinflammatory cytokines are released, and diffuse through the synovial fluid into the cartilage. This induces additional breakdown of cartilage matrix macromolecules. At this stage, the chondroyctes are hyperresponsive to cytokine stimulation because of an increased level of cytokine receptors on the cell membrane. (Reproduced with modification with the kind permission of *Arthritis & Rheumatism*.)

inflammatory process. Therefore, these two cytokines are prime targets for therapeutic approach.

The understanding of the release and activity of these cytokines has evolved greatly in recent years, and a clearer comprehension of their modulating factors as well as their major regulators has helped to more accurately identify effective targets that may be potentially therapeutic in the treatment of OA. This may occur via a direct or indirect decrease in the release and/or action of these factors, and various cytokine-related therapies are now being considered.

Novel approaches include the inhibition of IL-1β and TNF-α production. Chemical and biological agents are currently being evaluated including: inhibition of the enzyme responsible for the conversion of IL-1β to an active molecule (ICE), soluble cytokine receptors, (IL-1 receptor antagonist), antiinflammatory cytokines (IL-4, IL-10 and IL-13); and targeting of the intracellular signaling cascades or transcription factors of IL-1β or TNF-α.

Reference

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