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Anabolic events in osteoarthritis

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Homeostasis of normal cartilage in adults represents a delicate balance between the degradation and the synthesis of extra-cellular matrix components to maintain the functional integrity of the joint. Under the influence of mechanical stress or joint inflammation, this dynamic equilibrium is broken and catabolic events progressively become prevalent leading to cartilage destruction.

Animal models in the study of the development of osteoarthritis have identified two types of repair reactions that correspond to the depth of the injury. The reparative process of osteochondral defects involves the release of mesenchymal cells from subchondral bone. The extent of the repair is influenced by the width, direction and site of the injury. Better repair is observed when the injury is parallel to the direction of joint motion [1]. However, the histologic, biochemical and biomechanical characteristics of the repair tissue are different from normal cartilage. The repair of chondral defects occur early following the induced cartilage lesion. The repair tissue is characterized by chondrocyte clustering (mitosis and/or migration), cartilage hypertrophy, an increase in glycosaminoglycan (GAG), fibronectin, and water cartilage content, and an enhancement of GAG and collagen (types II and III but not type I) synthesis by chondrocytes [2].

Unfortunately, the repair tissue ultimately fails and cartilage destruction ensues. Chondrocytes progressively decompensate, start secreting more proteolytic enzymes and catabolic cytokines and finally die probably by apoptosis (Fig. 1).

Questions remain concerning the repair process. It is unknown at what point the repair process ends and cartilage damage becomes irreversible. Many of the circumstances leading to aborted repair reaction remain unknown. Several factors could be involved, including alteration in the cartilage macromolecule structure, chondrocyte phenotypic change, IL-1 overproduction, increase susceptibility of chondrocytes to cytokine-induced degradation, focal over-expression of IL-1 and tumor necrosis factor (TNF) α receptors, growth factor synthesis and bioactivity down-regulation, reduction of chondrocyte sensitivity to growth factors, chondrocytes apoptosis, etc. [3–6].

The cartilage repair reaction is regulated by soluble factors produced locally by chondrocytes and neighboring tissues, mainly synovial membrane and bone. The most important factors involved in the control of the repair reaction are tranforming growth factor (TGF)-β, basic fibroblast derived growth factor (bFGF), insulin like growth factor (IGF)-1, interleukin (IL)-1 (α and β) and TNFα. Nevertheless, factors including platelet derived growth factor (PDGF), bone morphogenic proteins (BMPs) or cartilage-derived morphogenetic proteins (CDMPs) could also have an important regulatory function. TGFβ and IGF-1 play a significant role in promoting chondrocyte anabolism and inhibiting chondrocyte catabolism whereas IL-1β and TNFα inhibit cartilage matrix component synthesis and promote cartilage destruction by increasing metalloproteinase synthesis by chondrocytes. TGF-β and IGF-1 may partially reverse IL-1β-mediated degradation of articular cartilage [7, 8].

The imbalance between anabolic growth factors and catabolic cytokine synthesis and/or bioactivity could be the key of cartilage repair failure. Several mechanisms can control growth factors and cytokine bioactivity during the development of osteoarthritis. Interactions with binding proteins, soluble receptors, matrix components (e.g., decorin), or with other growth factors or cytokines may modulate their effects on chondrocyte metabolism.

On the basis of these experimental considerations, therapeutic intervention to promote the cartilage reparative process in osteoarthritis becomes more evident. Intraarticular injection of growth factors, interleukin-1 receptor antagonist (IL-1ra), docyxycline or nitric oxide (NO) synthase inhibitors has been tested successfully on experimental models of osteoarthritis [9, 10]. These substances

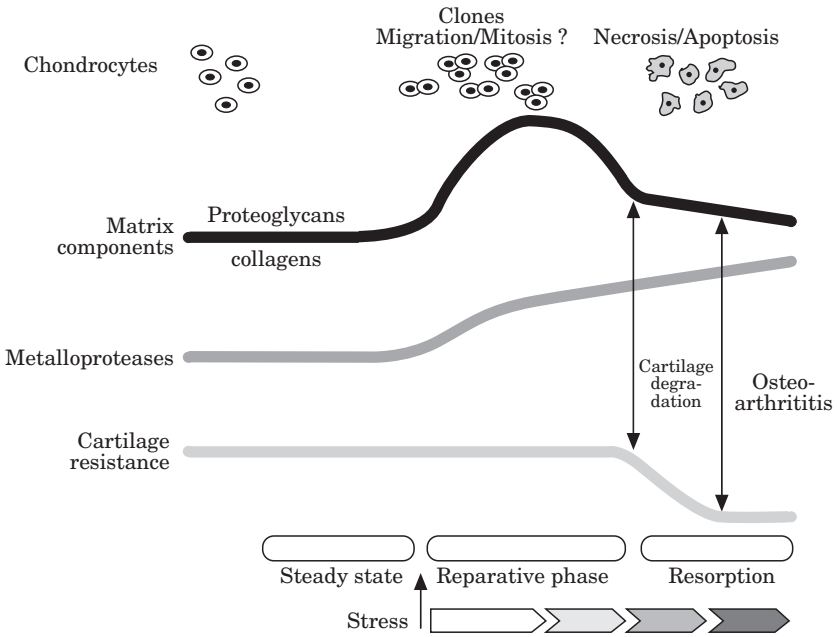

FIG. 1. The reparative attempt of chondral defect in which injury is limited to cartilage.

can prevent the development of osteoarthritis or reduce the severity of the lesions. Gene therapy offers an elegant therapeutic alternative. Transfer of an appropriate gene(s) into chondrocytes or synoviocytes prior to transplantation, may allow a high level of expression of growth factors in vivo for an extended period of time [11, 12].

However, prolonged high expression of growth factor transgene could lead to focal cartilage hyperplasia with loss of articular surface congruity, promoting osteophyte formation. Drugs which inhibit metalloproteanase activity/synthesis or IL-1 synthesis could also prolong the reparative response. Finally, if administrated during the early period of osteoarthritis, drugs stimulating cartilage matrix synthesis by chondrocytes could also be valuable tools to sustain repair reaction.

In conclusion, it is important to consider that the chondrocyte metabolic activity at the early stage of the osteoarthritis is different from that associated with the progression of the disease. Therefore, the possibility must be considered that therapeutic agents or growth factors, which are effective in the initial stage , may lose their effectiveness at the later stages of the disease and vice versa. This possibility must be taken in account in the design of experimental protocol studying the effect of potential structure or disease modifying osteoarthritis drugs (DMOAD).

References

1. Yoshioka M, Kubo T, Coutts R, Hirasawa Y. Differences in the repair process of longitudinal and transverse injuries of cartilage in the rat knee. Osteoathritis Cart 1998;6:66–75.
2. Kouri J, Jimenez S, Quintero M, Chico A. Ultrastructural study of chondrocytes from fibrillated and non-fibrillated human osteoarthritic cartilage. Osteoarthritis Cart 1996;4:111–26.
3. Chambers M, Bayliss M, Mason R. Chondrocyte cytokine and growth factor expression in murine osteoarthritis. Osteoarthritis Cart 1997;5:301–8.
4. Towle C, Hung H, Bonassar L, Treadwell B, Mangham D. Detection of interleukin-1 in the cartilage of patients with osteoarthritis: possible autocrine/paracrine role in pathogenesis. Osteoarthritis Cart 1997;5:293–300.
5. Webb G, Westacott C, Elson C. Chondrocytes tumor necrosis factor receptors and focal loss of cartilage in osteoarthritis. Osteoarthritis Cart 1997;5:427–37.
6. Blanco F, Guitan R, Vasquez-Martul E, de Toro F et al. Osteoarthritis chondrocytes die by apotosis: a possible pathway for osteoarthritis pathology. Arthritis Rheum 1998;41:284–9.
7. Trippel S. Growth factor actions on articular cartilage. J Rheumatol 1995;43 (Suppl):129–32.
8. Lotz M, Blanco F, von Kempis J et al. Cytokine regulation of chondrocyte functions. J Rheumatol 1995;43(Suppl):104–8.
9. Pelletier J-P, Jovanovic D, Fernandes J-C et al. Selective inhibition of nitric oxide synthase reduces in vivo the progression of experimental osteoarthritic lesions and production of metalloproteases and interleukin-1. Arthritis Rheum 1997;40 (Suppl):S173.
10. Glansbeek H, van Beuningen H, Vitters E et al. Stimulation of articular cartilage repair in established arthritis by local administration of transforming growth factor-beta into murine knee joints. Lab Invest 1998;78:133–42.
11. Kang R, Marui T, Chivizzani S, Nita I, et al. Ex vivo gene transfer to chondrocytes in full-thickness

articular cartilage defects: a feasibility study. Osteoarthritis Cart 1997;5:139–42.
12. Aigner T, Gluckert K, von der Mark K. Activation of fibrillar collagen synthesis and phenotypic modulation of chondrocytes in early human osteoarthritis cartilage lesions. Osteoarthritis Cart 1997;5:183–9.