

THE REGULATION OF CARTILAGE MATRIX TURNOVER AND THE PATHOLOGY OF OSTEOARTHRITIS

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INTRODUCTION: Osteoarthritis (OA) is a degenerative joint disease involving the whole diarthrodial joint. Extensive remodelling of bone, changes in ligaments, menisci and synovia accompany the progressive degeneration of articular cartilage (AC). With the damage to AC there is a progressive loss of joint function.¹

Idiopathic OA involves the formation of focal lesions that progressively enlarge, leading to the eburnation of subchondral bone and changes in the congruency of articulating surfaces. The development of these lesions involves excessive degradation of extracellular matrix, in particular the resident collagen fibrils (composed mainly of type II collagen), more remote from chondrocytes.^{2, 3} In healthy cartilages only pericellular molecules are ordinarily degraded in young individuals (up to 35 years).⁴ The degradation is generally seen in the same sites where the collagenases, matrix metalloproteinases (MMP)-1 and -13 are localized.⁴ MMP-13 appears to be involved in the excessive cleavage of 'resident' collagen molecules: MMP-1 may often be more involved in the degradation of newly synthesized molecules.⁵ Both aggrecanase and MMPs are involved in the excessive cleavage of aggrecan⁶ There is also an increase in synthesis of these matrix molecules in OA. This involves onset of gene expression of the type IIA COL2A1 gene and especially upregulation of type IIB collagens.¹ Collagen synthesis is increased as revealed by radiochemical analyses and the increased generation of the c-propeptide of these type II molecules.⁷ This frequently occurs in the same sites where cleavage is observed which, as discussed above, involves cleavage of newly made molecules.

The degenerative process is initiated at the articular surface, extending progressively into the deeper layers⁴ – probably over a period of 10-20 years or more. It is normally very slow but can be accelerated in the presence of joint inflammation or following joint injury causing changes in joint loading. As the collagen network degenerates, so chondrocytes differentiate and become hypertrophic, expressing type X collagen, annexin V and other genes associated with hypertrophy. These also include MMP-13 and COL2A1, including type IIA collagen. There is partial calcification of cartilage matrix. Eventually this results in chondrocyte apoptosis as in the growth plate and fracture callous, as part of endochondral ossification.¹

The excessive degeneration of type II collagen and chondrocyte hypertrophy can be induced by a single small peptide of this same collagen working via a specific cell surface receptor. This is dependent upon increased expression and activity of interleukin-1 or tumour necrosis factor α , both of which are often involved in the excessive degradation seen in OA cartilages in culture.⁸ The chondrocyte is very sensitive to its environment and to the degradative changes that it creates through the excessive generation of MMPs. It is also very sensitive to changes in mechanical loading and there is evidence to indicate that mechanical loading combined with excessive proteolysis is required for the development of focal lesions.⁹

Through the work of many laboratories we now have a much clearer understanding of the pathobiology of this disease—one where the events seen in OA are likely also encountered in the engineering of new cartilage. Comparative studies of both OA and cartilage engineering may provide a better understanding of the problems we face in each field. Since the management of OA needs more effective cartilage repair and often cartilage repair results in a degenerative process..

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