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FUNDAMENTAL PATHWAYS IN OSTEOARTHRITIS: AN OVERVIEW

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1. ABSTRACT

Osteoarthritis (OA) is a significant world-wide health problem owing to the progressive and debilitating nature of the condition which results in high morbidity and a marked decrease in the quality of life. Significant advances in the medical and surgical management of OA have resulted from an understanding of the fundamental pathways governing the health and disease of synovial joint tissues. Continuing investigations into the nature of synovial joint pathophysiology at both the molecular and biochemical level should pave the way for the development of novel therapeutic strategies, including gene therapy and tissue engineering, in the treatment of the OA patient.

2. INTRODUCTION

Osteoarthritis (OA) is a debilitating, progressive disease of diarthrodial joints that is associated with aging (1,2). The aging process of synovial joints and OA pathology overlap particularly with respect to synovial joint remodeling. However, in many respects the pathways resulting in cartilage destruction and subchondral bone changes in OA and those governing joint remodeling as a function of age are fundamentally different (3). Thus, while OA is found almost universally among the elderly (2), and aging could be considered one of several risk factors for developing OA, OA does not develop simply as a result of aging and/or "wear-and-tear" of the synovial joints. An understanding of the critical pathways resulting in maintenance of articular cartilage in health, alterations in articular cartilage extracellular matrix (ECM) that may initiate the OA process and the failure of adult articular cartilage to undergo repair after repetitive trauma or acute injury are all critical to the development of novel medical and surgical strategies or gene therapies which may prove useful in the treatment of OA. This special edition of *Frontiers in Bioscience*, entitled, "Fundamental Pathways in Osteoarthritis," addresses the basic concepts required for an understanding of OA pathogenesis, OA progression and potential for medical intervention in the OA disease process.

3. METABOLIC PATHWAYS IN OA

3.1. Pathophysiological pathways

The pathophysiological response of articular cartilage in OA represents a constellation of anabolic and catabolic dysfunctions by the chondrocyte. Dr. A. R. Poole (Shriners Hospital for Children, McGill University, Montréal) reviews how the classic loss of cartilage in OA and the remodeling of bone are at the same time abnormal (cartilage loss) and yet part of the maturation and aging of the synovial joint (bone remodeling), albeit accentuated by the formation of bony osteophytes during the OA process. The pathophysiological response in OA articular cartilage is characterized by an acquired imbalance between anabolic and catabolic pathways resulting in 1) robust proteolytic degradation of the ECM by resident chondrocytes, 2) an attempt at compensatory synthesis of these very same ECM proteins by resident chondrocytes which is ultimately inefficient resulting in net loss of ECM proteins, and 3) the up-regulated expression of cartilage ECM genes that cause a skewing of the normal ECM protein repertoire.

The repair of articular cartilage in OA is feeble. While initial pathophysiological responses of articular cartilage in OA are characterized by chondrocyte proliferation and ECM protein synthesis around chondrocyte lacunae (4), these responses are not sustained. Drs. S. Frenkel and P. E. DiCesare (New York University-Hospital for Joint Diseases, New York) point out that the inherent failure of articular cartilage to undergo repair in OA is likely a result of a lack of the proper repertoire of growth factors and signaling molecules. These serve to support chondrocyte proliferation and migration in the

embryo and during cartilage maturation. The possibility that these growth factors and/or signaling molecules are aberrant or deficient in adult cartilage responses must be entertained. While transplantation of adult chondrocytes to severe cartilage defects have proven to have some success in repair in trauma cases affecting the knee (5), repair of large surface lesions in unstable OA joints remains controversial. The application of gene therapy to restore growth factors locally or suppress catabolic pathways consonant with OA pathogenesis remains an area fertile for advances in the treatment of OA.

While OA has almost always been seen as a focal disorder of synovial joints, Drs. C.W. Denko and C. J. Malemud (Case Western Reserve University School of Medicine, Cleveland, OH) argue that systemic disturbances may also play an important role in OA. Proteins typical of the acute phase response to systemic inflammation are also elevated in OA. Furthermore, the growth hormone/insulin-like growth factor-I (GH/IGF-I) paracrine pathway is skewed. The altered serum levels of GH/IGF-I in OA may alter cartilage repair potentials. In addition, the significantly elevated levels of GH in both plasma and erythrocytes from male patients with OA points to a potential role for elevated GH synthesis in OA pathogenesis and red blood cell sequestration of GH in clinically active OA.

3.2. Metabolic Pathways

3.2.1. Cytokines

It is generally held that OA is a slow, but ultimately progressive and irreversible disorder. Drs. J. Martel-Pelletier, N. Alaaeddine and J.-P. Pelletier (Centre Hospitalier de l'Université de Montréal, Montréal, Canada) discuss the central role that cytokines (i.e. interleukins, tumor necrosis factor) play in up-regulating the expression of metalloproteinase genes. Cytokines are not only responsible for accelerating the destruction of cartilage ECM via their ability to up-regulate metalloproteinase gene expression (6), but they also serve to suppress compensatory ECM protein biosynthesis by chondrocytes. Chondrocytes isolated from OA cartilage and fibroblasts derived from the synovium of OA patients also appear to develop exquisite sensitivity to the presence of cytokines such as TNF-alpha (7), presumably because they produce elevated levels of TNF-alpha receptors (8). Another pathway involving the induction of nitric oxide in cartilage appears relevant to programmed cell death (apoptosis) and OA pathology (9). The important role played by cytokines in OA has resulted in numerous experimental protocols designed to inhibit the biological activity of these mediators (10).

3.2.2. Metalloproteinases and endopeptidases

The metabolic imbalance of OA cartilage characterized by significant up-regulation of metalloproteinase (MMP) genes without concomitant elevated synthesis of tissue inhibitor of metallo-proteinases (TIMPs) is a fundamental pathway generating cartilage destruction without cartilage repair. The endogenous ECM proteins (i.e. collagen, proteoglycans, link protein, fibronectin) are degraded in this process. This event irreversibly compromises the integrity of cartilage ECM. The synthesis and activation of MMPs in OA is a focus for future therapeutic intervention. Dr. R. L. Smith (Stanford University Medical Center, Stanford, CA) reviews the many MMPs present in OA cartilage and addresses the all important mechanism of activation which involves, at least in part, the activity of endopeptidases such as Cathepsin B and other MMPs such as the membrane-type MMPs (MMP-14) and gelatinase A [MMP-2] (11,12). The inability of TIMPs which are also produced by chondrocytes (both constitutively and in OA) to inhibit activated MMPs appears more to do with an overwhelming level of MMPs produced in OA cartilage than with a structural abnormality in TIMP which might render TIMP ineffective as an MMP inhibitor. The mechanism underlying stromelysin-1 (MMP-3) inhibition by TIMP which has recently been elucidated (13) may now provide sufficient information for the production of synthetic TIMPs which are more effective in neutralizing MMP activity.

3.2.3. Amplification of catabolic pathways.

While cytokines are clearly important in up-regulating MMP gene expression, other pathways relevant to the process include the potent biological activity of fibronectin fragments (fibronectin is itself a substrate for MMPs) as discussed by Dr. G. A. Homandberg (Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL). Fibronectin fragments enhance levels of catabolic cytokines and also up-regulate MMP expression, significantly enhance loss of proteoglycans from cartilage and transiently suppress proteoglycan synthesis. Other peptides produced from ECM proteins, such as link protein, may also be biologically active in OA cartilage (14).

4. MOLECULAR AND DEVELOPMENTAL PATHWAYS

An understanding of the molecular events governing the morphogenesis of articular cartilage in development may be germane to OA, if in order for cartilage to repair itself, adult cartilage must recapitulate growth and developmental events produced in the embryo. Drs. L. Sandell and P. Adler (Washington University, St. Louis, MO) elucidate the large number of differentiation proteins and signaling molecules and pathways they regulate during cartilage formation. The remodeling of synovial joints clearly represents the inherent capacity for chondrocyte proliferation and migration. The re-expression in human OA cartilage of an alternative splice variant of Type II procollagen (type IIA) present in embryonic cartilage could represent an attempt to restructure OA cartilage ECM or could represent inappropriate repair (15). The mechanism by which the transcription of ECM genes are regulated could very well provide important information allowing for manipulation of ECM protein gene expression. Dr. T. Hering (Case Western Reserve University School of Medicine, Cleveland, OH) discusses what is known about the structural genes and coding regions of cartilage proteoglycans, collagens and other cartilage accessory ECM proteins. These studies not only provide the structural basis for understanding the mechanism by which cartilage ECM protein synthesis is

regulated in development, but also points to ways in which the expression of these genes may be manipulated in adult OA cartilage.

5. FUTURE DIRECTIONS

The clinical management of OA involves periodic physical and radiographic assessment of OA progression, use of corticosteroids and non-steroidal anti-inflammatory drugs, and often surgical removal of the OA joint with prosthetic replacement. An understanding of the fundamental pathways governing OA pathogenesis and the molecular mechanisms governing OA progression has emerged over the past decade and now provide the impetus for novel gene, medical and surgical therapies to be developed (16-18). Drs. C. J. Malemud and V. M. Goldberg (Case Western Reserve University School of Medicine, Cleveland, OH) discuss how the emerging understanding of the mechanisms regulating anabolic and catabolic pathways in cartilage and the potential of human bone-marrow-derived mesenchymal progenitor cells (17,18) to be employed to repair damaged cartilage has resulted in a wide variety of experimental and human studies designed to alter the rate of cartilage destruction and support of cartilage repair in the OA patient.

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