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Introduction: molecular and biomechanical basis of osteoarthritis

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Abstract. Osteoarthritis has developed into the most common chronic disease in the highly industrialized nations. Moreover, because of the prevalence of the disease in the elderly, this trend occurs worldwide as a consequence of increasing longevity due to the overall improvement in living conditions and health status. In contrast, research on osteoarthritis is still financially marginalized within biomedical research, so that the molecular and biophysical bases for disease initiation and progression are largely unmapped. The following sequence of five reviews highlights a remarkable change in that body of knowledge taking place at the beginning of the World Health Organization (WHO) 'Bone and Joint Decade 2001–2010'. The data and ideas presented in these articles reflect to some extent the guidelines set up by the WHO and by the National Institutes of Health of the USA and therefore allow a glimpse into the directions that research in osteoarthritis will take in the future.

Key words. Arthritis; cartilage degeneration; cartilage metabolism.

When in May 1994, the World Health Organization Conference for Guidelines in Osteoarthritis Research, Diagnosis, and Treatment took place in Monterey, California, issues ranging from molecular biology of connective tissue to clinical outcome studies of treatment were discussed, and always with one striking result: joint replacement is today the only successful 'therapeutic' procedure nowadays against osteoarthritis (OA). On top of the clinical problems, OA is the single most expensive disease for any developed nation, simply because of the decades of disease progression. A very frustrating baseline for clinicians but also a very motivating one for researchers.

The conference updated the definition of OA as a disease and it now reads as follows: 'Osteoarthritic diseases (OA) are a result of both mechanical and biologic events that uncouple the normal balance between degradation and synthesis by articular cartilage chondrocytes and extracellular matrix, and subchondral bone. OA diseases involve all of the tissues of the diarthrodal joint. Ultimately, OA diseases are manifested by morphologic, biochemical, and biomechanical changes. When clinically evident, OA diseases are characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation.'

Looking more closely into that definition, OA is seen not as a single disease entity but potentially as a group of several independent disease mechanisms leading to the same clinical phenotype. Furthermore, metabolic elements are put on an equal footing with biomechanic features to drive the pathomechanisms, certainly a unique platform for any chronic disease. And, finally, the element that defines OA nowadays, the clinical stage, is placed at the very end and leaves no doubt about the role of clinical observations: such data are from the end stage of the disease and help little in defining the origins of pathomechanisms that finally cause pain and dysfunction.

From the start, OA follows a very complex pathological metabolism. Since the functional compartment of joint cartilage is the extracellular matrix and not the cell, at least in the immediate actions (= compressibility) during cycles of loading and unloading the joint, mechanical wear contributes to loss of material properties. Slow to very slow degradative processes are likely to erode the normal function of the articular cartilage. Based on this slow pace of degradation, a gradual process of regenera-

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tion restores and maintains healthy structures. Overlapping these endogenous mechanisms within cartilage are metabolic processes in the underlying bone and neighboring synovial membrane such as renewal of synovial joint fluid and mineral recycling in the bone. In other words, cartilage metabolism is an aspect of the integrated function of the entire joint as an organ. But there are also episodes of diseases, ranging from the common cold to trauma. At one point in time, the continuous attempts of the joint cartilage cells, the chondrocytes, fail to repair cartilage tissue, leaving behind initially damaged tissue.

Such a scenario requires complex methods of analysis. Until very recently, one investigator could monitor only a very few parameters of cartilage metabolism, mainly due to technical restrictions. Aigner and McKenna (p. 5, this issue) demonstrate in their contribution how modern technology-oriented pathology can overcome these hurdles. Gene expression chips allow for the simultaneous screening of thousands of expressed genes at a time and generate a fairly reliable image of the complex changes occurring in, for example, OA cartilage. Using this initial qualitative information, more detailed analysis of quantitative alterations may subseqently follow, although certain potential candidate genes may reveal qualitative rather than quantitative expression patterns to indicate particular stages of the disease.

OA in one joint may not be the OA of another joint. Evidence for this seemingly paradoxical situation has existed for sometime: most people develop OA in the hip, or in the knee, or somewhere else, but it is rarely generalized. Indeed, generalized OA is seen as an additional disease group. So, does OA prefer some joint groups because of usage patterns or because of genetically fixed metabolic expression patterns in various joint groups? Cole and Kuettner (p. 19) put forward the hypothesis of joint-specific metabolic baseline features that render cartilage more or less susceptible to disease, and present some intriguing evidence to support such a hypothesis.

Certain features of cartilage at the molecular level will generate biomechanical tissue properties which in turn influence material performance under loading. As Kerin et al. (p. 27) explain, cartilage has very unique biomechanical properties, both in terms of stiffness and elasticity. These parameters are a function of the molecular composition varying with age. In addition, changes in the molecular composition during regeneration, repair, or pathological processes further influence the tissue biomechanics to foster or break the vicious circle of cartilage degeneration in OA.

Biomechanic forces can be transmitted into the cell by a variety of structures: deformation of the cell membrane, stress and strain on the cytoskeleton, deformation of the nucleus, and direct signaling pathways via receptors of the extracellular matrix. Two prominent families of such matrix receptor are the integrins and CD44 isoforms. Both families have specific members expressed on cartilage cells. The ligands for these receptors are collagens, glycoproteins and, in case of CD44, hyaluronic acid. As Knudson and Loeser (p. 36) report, occupation of the receptors with their natural ligands or degraded metabolites from these ligands has profound effects on chondrocyte metabolism. Their observations allow them to postulate that chondrocytes can be governed by mechanical forces and by metabolic events (such as degradation) that assign additional functions to the matrix receptors and their (degraded) ligand molecules.

One of these extraordinary metabolic events is inflammation. Even today, the therapy for OA is essentially the same as in medieval times: protection of the damaged joint from excessive use and application of medication for the relief of pain. Pain, however, is a sign of inflammation. Although OA is considered a disease dominated by noninflammatory processes, occasionally fulminant inflammation, in particular in late-stage OA, accompanies the disease and is the major reason for medical treatment and hospitalization. How do chondrocytes contribute to the inflammatory episodes? How do they cope with inflammatory cytokines, will they recover, and to what extent? These questions are essential for the development of effective drug treatment. Hedbom and Häuselmann (p. 45) describe some aspects of this pressing set of questions.

As complex pathomechanisms are expected to be the driving forces behind the disease patterns, interdisciplinary research is demanded. Unfortunately, current administrative structures of research funding do not always foster such interdisciplinary approaches. The following series of reviews is written by scientists who undertook to attack the ‘fund-a-mental’ problems and to attempt to generate innovative interdisciplinary research approaches to tackle the disease questions.