PATHOPHYSIOLOGY OF OSTEOARTHRITIS

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Introduction

Osteoarthritis (OA) is one of the most common diseases worldwide and certainly the most common joint disorder. There is sound data verifying the fact that the majority of individuals over the age of 65 (about 60% of men and 70% of women) have radiographic and/or clinical evidence of OA in at least one major joint of their bodies. The most frequently affected sites are the hands, knees, hips and spine. The disease is characterized by progressive destruction of articular cartilage, but it also affects the entire joint, including the synovial membrane, the joint capsule, the ligaments, the peri-articular muscles and tendons and the subchondral bone. It is important to mention that the symptoms of OA are often associated with significant functional impairment, as well as signs and symptoms of inflammation, including pain, stiffness and loss of mobility.

Primary OA is characterized by late onset and has no obvious cause, whereas secondary OA has an earlier onset and an identifiable cause, such as injury or a developmental abnormality. Although the precise etiology of the disease in most cases is unknown, it is generally accepted that OA is a multi-factorial disorder involving both genetic and environmental components. Primary OA in particular is usually the end-result of mechanical and/or several biological and genetic factors (acting in unison or not) which destabilize the physiological metabolism of the cartilage and the subchondral bone. Primary OA may be the consequence of "pathological" strain on "normal" cartilage, "normal" strain on "pathological" cartilage or "pathological" strain on "pathological" cartilage.

The physiology of articular cartilage and osteoarthritis

A rather controversial issue regarding the pathogenesis of OA is whether the functional status of the chondrocytes in osteoarthritic cartilage is biomechanically

modified. Recently published papers report that through the normal function of several biomechanical sensors (e.g. CD44 and integrin), chondrocytes seem to modify their normal cellular activities, following even mild modification of their biomechanical properties. As a result, several substances acting destructively on the normal cartilage (proteinases, cytokines, chemokines, MMP-13) are produced. The production of these biochemical molecules initiate a series of destructive pathways which lead to the development of OA.

Another issue regarding the pathophysiology of OA is the phenotypic modification of the functional status of chondrocytes. "Adult" chondrocytes are fully differentiated cells, "living" in a state of "rest", following the successful synthesis of Extracellular Matrix (ECM). Provided that there is no external factor acting on chondrocytes, the exchange rate of the proteins which are contained in ECM is extremely slow (e.g. the half-life of collagen fibers is 100 years and of aggregan 3-24 years). However, this status quo changes dramatically in patients suffering from early osteoarthritis. The chondrocytes are activated and this leads to the development of fibrillation, to the pathological accumulation of cells, to the depletion of the ECM and to changes in the quantity, distribution and composition of the proteins of the ECM. The phenotypic modification of the functional status of chondrocytes in patients with osteoarthritis is further proved by the detection of type X collagen fibers (normally they do not exist in the cartilage of adults) and the expression of genes which differentiate chondrocytes. As a result, it seems that the osteoarthritic cartilage tries to "return" to a functional status of cellular development, which has already been deployed during the stage of the enchondral ossification of the bones. It is rather unfortunate that this "return" is insufficient and cannot restore the already existing osteoarthritic lesions.

The role of inflammation in the development of OA is another controversial issue. Osteoarthritis "per se" is not considered to be a typical inflammatory joint disease for two very specific reasons: i. the lack of neutrophils in the joint fluid, and ii. the lack of signs of systemic inflammation. There is much dispute regarding the role of inflammation of the synovium in the pathophysiology of OA. Nevertheless, there are signs of both synovitis (infiltration of the synovium by activated B- and T-lymphocytes) and hyper-expression of pre-inflammatory mediators, proving that inflammation of the synovium may play a potentially important role in the development of OA. Several inflammatory molecules (IL-1, IL-6, IL-7, IL-17, IL-18, aggreganases, IL-1 RI, TNF-α, Nitric Oxide, MMP-1, MMP-3, MMP-8, MMP-13, PGE_2, COX-2) are involved in the whole procedure. Their action can be either autonomous or in combination with others and they are usually controlled by specific transcriptional inflammatory factors (NF–$\kappa\beta$, C/EBP, AP-1). Several of these factors are catabolic. Others (e.g. BMPs, TGF-β) are anabolic, leading to the formation of osteophytes. The final result is the destruction of ECM, the cloning of chondrocytes, the hypertrophy of chondrocytes, the calcification of cartilage and the development of micro-fractures. All these lead to the destruction of cartilage.

Nitric oxide (NO) in particular seems to play a very crucial role in the pathophysiology of OA. Nitric oxide is produced by chondrocytes. The fact that NO inhibits the production of proteoglycans and the synthesis of collagen and enhances the synthesis of metalloproteinases, the apoptosis of chondrocytes and the inflammatory response of the chondrocyte, rendered this molecule as the ideal target in the quest against OA. However, it has recently been discovered that the role of NO in the pathophysiology of OA is double: not only enhances its development, but it inhibits it as well. Therefore there are many crucial questions regarding its action which still remain to be answered.

The potential association between the development of OA and the homeostasis of the adipose tissue is another recent development in the scientific quest to understand what exactly causes OA. Adipose tissue is no longer considered to be just a place of the human body where "energy" is stored. On the contrary, several proteins such as the adipokines (adiponectin, resistin, leptin) and the cytokines are produced in the adipose tissue, rendering the latter an active partner and part of the endocrine system. Adipokines in particular seem to play a very important role in the homeostasis of the chondrocyte as well. Leptin for instance controls the differentiation of chondrocytes during the process of endochondral ossification, controls the activity of MMP-13 on chondrocytes and is expressed more intensively in the presence of advanced OA. It seems that adipokines not only are involved in the accumulation of body mass and fat, but they are dynamically controlling the metabolism of the articular cartilage and the turnover of the ECM in osteoarthritic cartilage as well. This is probably the reason why the reduction of fat only and not weight in overweighed patients with osteoarthritis, significantly relieved them from their symptoms. This is probably also the reason why statins (HMG-CoA reductase inhibitors) have also an inti-inflammatory action by inhibiting the action of MMPs and pro-inflammatory cytokines, even though their protective role against OA is still under scrutiny. And finally, this also the reason why, there seems to be a connection between leptin, osteoporosis and OA.

Another controversial issue regarding the pathophysiology of OA is whether anabolism and catabolism co-exist in OA and "which one begins first". The connection between the increased production of proteinases (e.g. MMP-1, MMP-3, MMP-8, MMP-13 and aggreganases) and the destruction of the articular cartilage is well established. The local depletion of proteoglycans and the destruction of the collagen fibers initially occurs on the surface of the articular cartilage. As a result, the more the destruction of the articular cartilage progress, the more water ECM contains and the more ECM loses its resistance to shear forces. Anabolism on the other hand occurs at the lower layers of the articular cartilage, in an effort to repair the accumulated damage. This is mainly achieved through the increased production of collagen type II fibers. This "regenerative" effort of the articular cartilage is also proved by the increased concentration of several anabolic factors in the osteoarthritic cartilage such as BMP-2, inhibin bA/activin and factors of the TGF-β family. It seems that anabolism co-exists with

catabolism in osteoarthritic cartilage. There is evidence that catabolism is probably the first to be initiated. Although anabolism follows, it is incapable of repairing the accumulated articular damages caused by OA.

Genetics

The genetic predisposition to the development of OA has always been under consideration and investigation. It is true that all patients with the same anthropometric characteristics (age, height, weight and race) do not suffer from OA. It is also true that women are more often affected from OA than men. The only factor which may be the causative factor of these peculiarities is genetics, hence the involvement of genes in the development of OA has recently been "re-visited", and new data shed light to this ambiguous issue.

There has recently been enough evidence that genetic predisposition may play a certain role in the development of OA with an early onset. Twins-based epidemiological studies have showed that genetic predisposition may influence the suffering from OA in over 70% for certain joints. Polymorphism and mutations have recently been discovered in biological molecules which may "predefine" susceptibility to the development of OA (Vitamin D receptor, estrogen receptor α, IL-I gene cluster, bone morphogenetic protein-2, CD36 and cyclooxygenase 2) and in genes responsible for the production of extracellular matrix (COL2AI, COL9AI, AGCI, CILP and ADAMI2). Several of these "pathological" genes, seem to play a very important role in the initial development of both the extracellular matrix and other parts of the musculoskeletal system, contributing to the manifestation of several dysplasias of the articular cartilage. In a recent Genome-wide association study, it has been discovered that the existence of certain polymorphisms of a single nucleotide in parts of the genes responsible for the production of HLA II and III is associated with the development of knee OA in a statistically significant manner. The impaired expression of genes regulating cholesterol efflux in human chondrocytes has also been associated with the development of OA. It is also very interesting that the expression of several genes is different between men and women, hence explaining the different incidence of OA between sexes.

It seems that when patients with genetic predisposition to the development of chondral lesions come across with mechanical instability or other environmental factors, the development of OA is almost unavoidable.

Conclusion

The pathophysiology of osteoarthritis is extremely complicated and multi-factorial. The until recently believed theory that OA is just a degenerative disease which is initiated due to ageing or due to a simple deviation from the proper mechanical axis of loading is not considered to offer adequate answers to several crucial questions. The increased incidence of OA in elderly people and in

women in particular is not just a coincidence. Genetic predisposition may explain the development of OA in only just a few of the patients who share common phenotypic characteristics. Only when we fully understand all the pathogenetic mechanisms which are involved in the development of OA, we will be able to better and earlier intervene in favour of all patients who are suffering or will be suffering from osteoarthritis.

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