

38th International Sun Valley Workshop
August 3-6, 2008
Translational Research in OA-
From Molecules to Animals to Humans Session
(Session Summary)

Translational research in osteoarthritis - From molecules to animals to humans

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Keywords: Osteoarthritis, Cartilage Degradation, Animal Models, Cytokines, Growth Factors, Metalloproteinases

Osteoarthritis (OA) is a multifactorial disease that is closely associated with aging and is the leading cause of chronic disability in older adults¹. Besides age, the primary risk factors for the development of OA include obesity, joint anatomy (shape and alignment), joint injury, genetics, and female sex (for hand and knee OA)². OA affects the entire joint structure and is characterized by cartilage destruction and loss, degeneration of soft tissues within the joint including the meniscus (knee OA) and ligaments, weakness of the muscles supporting the joint, localized bony hypertrophy including subchondral thickening and osteophyte formation, varying degrees of synovitis, and thickening of the joint capsule. These pathological changes result in joint enlargement and deformity that is often accompanied by pain and loss of function.

Current management of OA is inadequate due to the lack of any treatments proven to affect disease progression. A better understanding of the basic mechanisms responsible for the development of OA is needed in order to discover new therapeutic targets that could be used to slow or halt disease progression. When new agents that have disease modifying potential are discovered they need to be tested in the appropriate animal models and then targeted to the right patients at the right stage of the disease process. This translational research approach to OA was the focus of the session which had the following objectives: 1) Review the basic cellular and molecular mechanisms that lead to the develop-

ment of osteoarthritis, 2) Discuss mechanisms relevant to osteoarthritis discovered through the use of mouse models, and 3) Review the design and early results from a large prospective clinical research study in human osteoarthritis.

Despite the knowledge that OA is a disease of the entire joint and can be considered a form of "joint failure" that results from multiple tissues being affected, much of the research to date has focused on mechanisms relevant to cartilage destruction in OA. A host of cytokines and growth factors are active in cartilage as OA develops stimulating both matrix synthesis and degradation³. These mediators act locally on the articular chondrocytes. Unlike bone, where at least three cell types (osteoblasts, osteocytes, and osteoclasts) regulate bone turnover, the chondrocyte is the only cell type present in articular cartilage and so is responsible for both synthesis and breakdown of the matrix.

There appears to be a change in the phenotype of the chondrocyte as OA develops. This normally quiescent cell rarely, if ever, divides and exists in a low metabolic state in its anaerobic, avascular, aneural environment. The normally slow turnover of the cartilage matrix is reflected by the half-lives of its two major constituents. Type II collagen has a half-life of about 100 years⁴ and aggrecan of about 25 years⁵. As damage to the cartilage matrix occurs (what starts this damage is not always clear and was a question asked repeatedly by the group but probably related to abnormal joint mechanics in many cases) the chondrocytes divide and can progress to a hypertrophic phenotype or at least "hypertrophic-like". This change can be driven by various growth factors and cytokines as well as by fragments of matrix proteins. In the session, we learned how the OA process is driven by aging and reactive oxygen species (Loeser), BMPs, cytokines, and chemokines (Sandell), type II collagen fragments (Fosang), and cell signaling and matrix changes (Chen). Also reviewed were the goals of a large multicenter observational study called the Osteoarthritis Initiative

The author has no conflict of interest.

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Accepted 11 August 2008

(Lester) which seeks to collect the data needed to determine risk factors and to develop improved measures (imaging and biomarkers) for disease progression.

A cartilage centric view of OA was reflected in the presentations of all of the speakers but, aided by the expertise of the audience in areas other than cartilage, a lively discussion was carried on throughout the session centered on trying to understand what are the key factors driving the development of OA, in which tissue(s), and how in the world can this slow but complex process be stopped. Some important questions emerged from the discussion including: Are the changes in bone primary or secondary? Is there a master regulator of joint tissue destruction in OA? Would inhibition of chondrocyte hypertrophy slow or prevent the development of OA and if so how would you do it? Is modulation of cell signaling a viable approach and what signaling proteins should be targeted? Does estrogen play a role in OA in postmenopausal women? Can we detect OA at an early stage and pick out people more likely to progress? What imaging methods could be used and where do we stand with biomarkers?

Clearly, there are still more questions than answers in the OA field. But as evidenced by the outstanding presentations and the enthusiastic participation of the audience during the session, progress is being made. OA is no longer considered a "wear and tear" degenerative disease that is an inevitable consequence of aging. There are many paths by which OA can develop, some of which are likely initiated at birth due to developmental influences on joint shape and mechanics. Our concept of OA is as a disease of the joint as an organ is advancing although we still know more about the changes occurring in cartilage than the other joint tissues. Genetics play a role and contribute up to 50% of the risk of developing OA. OA is also no

longer considered to be a "non-inflammatory" form of arthritis. One needs only to look at the extensive list of inflammatory mediators found in OA joint tissues to realize that inflammation is an important part of the disease process. Although we are probably still years away from having an effective therapy to slow disease progression in OA we are getting closer.

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