

Short Commentary

Defective Signal Transduction in Osteoarthritic Chondrocytes and Synovial Fibroblasts Should Become a Target for Drug Intervention

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Although it has been known for some time that pro-inflammatory cytokines are an essential driver of synovial joint inflammation in osteoarthritis (OA), drugs [e.g. Anakinra, Tocilizumab, Tofacitinib, Adalimumab] that target the signal transduction pathways activated by these cytokines including, Interleukin-1 β (IL-1 β), IL-6 and tumor necrosis Factor- α (TNF- α) are routinely employed in the medical therapy of rheumatoid arthritis (RA) [1], but NOT OA. Why is that? Several possible explanations arise from a perusal of the relevant medical literature in the PubMed database. For example, it is well known that genetic and mechanical stressors are integral to the development and progression of OA pathology but the type of inflammation inherent in cartilage destruction in OA was originally classified as “non-classical.” [1]. But is this the case? I think not.

In fact, a majority of the basic and clinical evidence indicates that synovitis is an integral aspect of OA pushing the progression of OA to synovial joint failure [2]. For example, the salient finding that activated T-cells can be found in the synovial tissue of patients diagnosed with OA is persuasive evidence that immune cell-mediated inflammation is a contributor to OA progression [2]. In addition, molecules such as nitric oxide, prostaglandin E₂, and inflammatory neuropeptides can influence the progression of OA is evidence that inflammatory episodes drive the synovial joint in OA to joint failure [1].

What of the cellular signaling pathways that produce elevated levels of pro-apoptosis molecules [3] matrix metalloproteinases (MMPs)

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and the ADAM/ADAMTS families [4,5] as well as pro-inflammatory cytokines [e.g. IL-1 β , IL-6, TNF- α] [1]? All of these cytokine-mediated activities are germane to the progression of OA [1]. Thus, the signaling pathways, mainly, the Stress-Activated Protein Kinase/Mitogen Activated Protein Kinase (SAPK/MAPK), Janus Kinase/Signal Transducers and Activators of Transcription (JAK-STAT) appear to be altered (i.e. deregulated) in the state of progressive OA and relevant drugs for other medical indications such as RA have already been developed and US-FDA approved. Why haven't some (or all) of these drug agents been rigorously tested in OA clinical trials to determine their efficacy?

One particular issue is, indeed, irksome. Most, if not all of the disease-modifying OA drug (DMODs) development strategies have focused on pain pathways, and other biological or phenotypic-stabilizing components of articular cartilage such as directly inhibiting the sulfated-proteoglycan-degrading enzyme, aggrecanase, other enzymes such as cathepsin K or anabolic components of cartilage physiology, including fibroblast growth factor-18 (FGF18). Thus, DMOD development appears to be most focused on using various therapies that retard the dissolution of cartilage during the OA process. However, more recently, various stem-cell therapies and/or other cell-based therapies such as might be achieved by the intra-articular administration of platelet-rich plasma and bone marrow aspirate have been employed, but as yet are relatively unproven therapies for OA [6].

In 2019 I pointed out that a formulation of strontium ranelate (SrR) [1] had been used for treating knee OA and was shown to retard the loss of cartilage as measured by a delay in joint space narrowing. In fact, a review of systemic drugs for OA by Apostu et al. [7] indicated that SrR and others, including, collagen hydrolysate and hyaluronic acid have yielded positive results in OA clinical trials.

At the molecular level, recent pre-clinical studies showed that SrR aided in cartilage “healing” via the Wnt/ β -catenin pathway [8], an indication that, at least, some research teams have recognized the role of signal transduction in promoting cartilage regeneration by intervening in a metabolic pathway that supports the health of articular chondrocytes. The importance of regulating the Wnt/ β -catenin pathway with respect to cartilage and skeletal long bone development is well-known. However, recent advances have also traced the role of Wnt/ β -catenin activity to T-cells as well [9,10]. Of note, Taniguchi et al. [11] showed that the high-mobility group box (HMGB) member, HMGB2, regulated chondrocyte hypertrophy by mediating Runt-related transcription factor 2 expression and Wnt/ β -catenin signaling. Moreover, the results of these studies suggested that the loss of the interaction between HMGB2 and β -catenin in the superficial zone of articular cartilage may be the cause of gene alterations including those gene expressional events that regulate cell death and initiate OA-like pathogenesis. Thus, a further understanding of the control of the HMGB2/Wnt interaction is likely to be an important consideration when future studies focus down on how the failure of the HMGB2/Wnt interaction can result in articular cartilage surface fibrillation commonly a signature event in the early to middle stages of OA.

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