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Opinion Article

OPINION ARTICLE

2021: The Year We Rewrite the Osteoarthritis Textbooks?

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Roughly half of us will develop painful osteoarthritis (OA) in at least one joint over our lifetime. Despite this, the study of OA pathogenesis has lagged behind more tractable diseases of the joint such as rheumatoid arthritis, partly because it has, for a long time, been considered an inevitable disease of aging. Its insidious nature, inaccessibility of tissue, and heterogeneity of clinical phenotype presents further problems when attempting to unravel key disease processes. The landscape has changed beyond recognition in the past 20 years through a number of key developments; the identification of specific matrix-degrading enzymes that are responsible for breaking down the articular cartilage; the validation of mouse models of OA induced by surgical destabilization of the joint, in which the temporal control of pathogenesis can be interrogated through careful molecular studies; and large-scale agnostic 'omics' studies such as genome-wide association studies. Much of this has been made possible by enhanced spending by funding bodies, recognizing the huge societal burden of age-related disease and the importance of the patient in driving the research agenda.

Arguably, the cornerstone of OA research is epidemiology. This has taught us much about the natural history of disease, associated risk factors, and above all, the importance of abnormal or excessive mechanical joint loading in OA development. Molecular pathogenesis has needed to be mindful of such findings, thus OA is now widely recognized as a mechanobiological problem. Many mechanosensitive pathways are triggered when articular cartilage and other tissues of the joint are injured; some of these pathways drive inflammatory gene regulation, by a process that we have termed "mechanoflammation,"[1] others drive pathways associated with repair, regeneration, and chondroprotection. Thus, mechanical signals can drive both beneficial and prodegradative pathways in the joint. We presume that the balance is critical to subsequent joint outcome.

To date, most approaches to target discovery have focused on the pathways that drive degradation. These have ranged from exploring the role of inflammatory cytokines in OA pathogenesis and the effect of selective matrix protease inhibitors. While this seemed to be an intuitive route to follow, clinical studies published in recent years do not support this being a productive approach. Since 2009, six randomized controlled trials using anticytokine (targeting IL1 and TNF) monoclonal antibodies in OA have been published. None of these reached the primary study endpoint. This was likewise the case for two randomized controlled studies in hand OA using hydroxychloroquine (reviewed in[2]). A randomized controlled trial assessing the efficacy of anti-IL6 in hand OA has also recently reported negative results.[3] All four drug classes have proven efficacy in other inflammatory joint diseases such as rheumatoid arthritis (anti-TNF, hydroxychloroquine, anti-IL6) and gout (anti-IL1). These results strongly suggest that mechanoflammation in OA is not driven by the same type of immune-mediated inflammatory process that is seen in other inflammatory arthritides.

Agnostic molecular studies in the past 4 years have shed considerable light on which mechanosensitive pathways are most important in human disease. Of the 70 or so putative gene targets identified in genome-wide association studies in OA to date, there is a notable absence of recognizable inflammatory candidate genes, but strongly represented growth factor clusters.[4,5] These include predicted hypomorphic variants in TGFβ family genes including ligands (Tgfb1, Gdf5), latent binding proteins (LTBP1, LTBP3), and signaling molecules (Smad3), all reaching genome-wide significance. The FGF family is also represented with predicted hypomorphic variants in receptor

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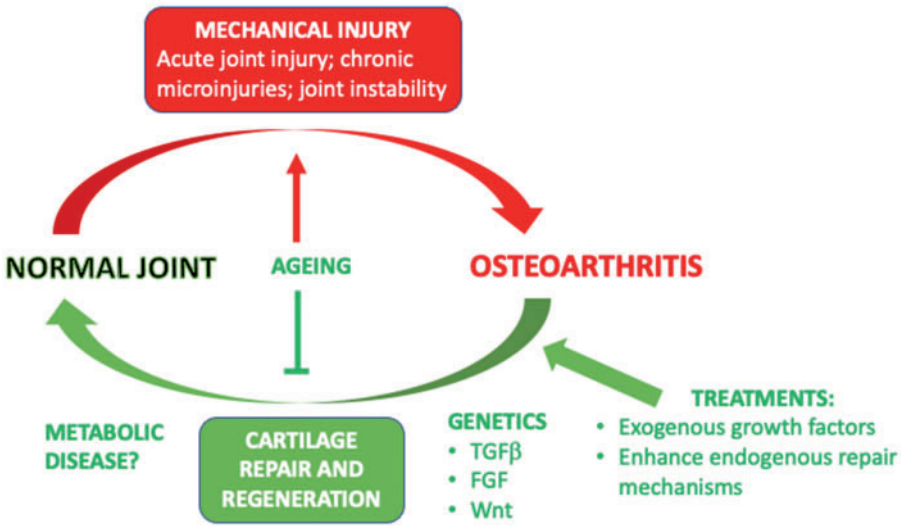

Figure 1. Balance of injury and repair in the OA joint. Aging contributes both to injury through age-related sarcopenia leading to joint instability, and by inhibiting repair possibly by increased senescence and reduced stem cell function. Hypomorphic genetic variants are identified in individuals with OA in TGFβ and FGF pathways. Other factors such as systemic metabolic perturbation may also contribute to reduced repair. Approaches to OA therapy might include increasing bioavailability of endogenous repair factors, promoting stem cell function, or by delivery of exogenous growth factors. The success of these will be dependent on correction of the hostile mechanical environment of the joint.

(FGFR3) and ligand (FGF18). Collectively, these results indicate that loss of reparative capacity within the joint is an important risk factor in the development of disease, and suggest that modifying the repair response may be a tractable therapeutic strategy (Figure 1).

Most textbooks describe articular cartilage as a tissue that has no or limited intrinsic (endogenous) repair capacity. However, a number of published studies contradict this historical paradigm, especially after the hostile mechanical environment of the OA joint has been corrected. Two surgical procedures are designed to off-load the joint mechanically: joint distraction, a procedure in which the osteoarthritic joint is held rigid and under tension for 6–12 weeks by an external metal frame secured into the bone above and below the joint, and high tibial osteotomy, in which a wedge shape of bone is removed from the tibia to correct malalignment of the knee joint (reviewed in[6]). Both procedures have been shown to deliver significant improvements in pain and function, and MRI imaging shows regrowth of a tissue that resembles articular cartilage where the cartilage had previously been lost. Taken together with the genetic risk variants which largely associate with repair pathways, it begs the question whether OA should be reconsidered, primarily, a disease of failed tissue repair. This concept also fits well with the recognition that failed repair occurs in many tissues as a result of aging, the other strong etiological factor in OA development.

So how does this change our view towards target discovery and validation in OA? Recent clinical studies indicate that structural damage in OA can be modified by intra-articular delivery of sprifermin, a truncated FGF18 ligand that acts through FGFR3.[7] This is the first convincing demonstration of structure modification in OA by a pharmacological agent, thus supporting the concept that targeting regeneration of the cartilage is a clinically tractable approach. Despite this apparent success, this study failed to show pain modification in the primary analysis, and this has dampened initial enthusiasm. Pain in preclinical OA is mediated by nerve growth factor (NGF) (reviewed in[8]) and recent phase III studies confirm the clinical efficacy of NGF neutralization in patients.[9,10] Whether improved regenerative strategies will align with symptom improvement in future studies, is unknown. What now seems intuitive is that we should consider mechanical off-loading approaches, perhaps combined with pro-regenerative agents, to maximize reversal of cartilage loss to be able to test this hypothesis. This decade promises to be an exciting one for OA researchers and patients alike!

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