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EDITORIAL

Disease-modifying agents in osteoarthritis: where are we now and what does the future hold?

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Osteoarthritis (OA) remains one of the most common chronic health conditions and a leading cause of pain and disability among adults.[1] The Global Burden of Disease report estimates that over 500 million individuals are affected by OA worldwide,[2] with global prevalence having increased by 113% since 1990.[3] By 2030, OA is predicted to be the single greatest cause of disability globally, with one-third of the global population estimated to be affected.[4]

Despite the immense burden that OA already brings to the global population, the general treatment paradigm has remained largely unchanged. This comprises symptomatic treatment of the disease, combining non-pharmacological management (patient education, weight loss, activity modification, and physiotherapy) and pharmacological management (predominantly confined to analgesic and anti-inflammatory agents). Surgical intervention with joint arthroplasty may be required for end-stage disease.[5]

Although a vast array of research into disease-modifying osteoarthritic drugs (DMOADs) has been carried out with a range of potential pharmacological targets identified, none have yet gained regulatory approval. These agents are defined by their ability to alter the underlying pathophysiological mechanisms of OA in order to inhibit structural disease progression, while providing symptomatic relief.[6] The US Food and Drug Administration (FDA) and the European Medicines Agency draft guidance states that in order for a DMOAD to be approved, there must be clear demonstration of slowing of knee or hip joint space width on radiographs with relevant symptomatic benefit.[6,7] A range of these potential DMOADs remain at varying stages of investigation and development, and have traditionally centred around potentiating or inhibiting pathways related to three predominating disease-driving OA 'endotypes': cartilage-driven, inflammation-driven, or bone-driven.[8] Given the range and growing complexity of potential agents and targets for disease modification in OA, the authors recommend that agents are categorized and considered from the main endotypes in which they act. Such agents include bone morphogenetic proteins (BMPs),[9,10] Wingless-like signalling inhibitors,[11-13] proteinase inhibitors,[14-17] growth factors,[18-20] and anabolic bone remodelling agents.[21-23] More recently, there has been increasing interest in novel agents and themes, including specific plant extracts,[24] the action of non-coding RNAs (ncRNAs),[25,26] the influence of the gut microbiome,[27,28] and gene-environment interactions,[29-31] which could be harnessed in the OA disease process.

Emerging approaches and future therapies: although encouraging results have been observed from preclinical studies of several potential DMOADS including those mentioned above, currently large-scale clinical trials of such agents have proven unconvincing in achieving meaningful improvements in OA-related symptoms, despite several showing substantial structural improvements. Consequently, attention has recently turned to gene-environment-disease interactions of OA and the molecules that may modify such interactions.

Recent studies of the effects of ncRNAs in the OA disease process have revealed these molecules to be important mediators of joint inflammation,[32] chondrocyte apoptosis,[33] and extracellular matrix (ECM) degeneration. Until recently, these ncRNA peptide chains were thought to be 'translation noise', of no functional consequence, however more recently these molecules have been

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shown to have important effects on gene expression and molecular pathway modulation. A recent study by Zhou et al[25] showed that one such long non-coding RNA, H19, significantly reduced OA-related inflammation in a mouse model, mediated through potentiation of IL-38 and IL-36R. Separately, Luobu et al[26] showed the potential importance of the circular RNA 'S-phase cyclin A-associated protein in the endoplasmic reticulum' (circSCAPER) in OA-associated inflammation. Their in vitro study of human chondrocytes revealed that circSCAPER promoted interleukin-1 beta (IL-1β) associated cartilage degradation through chondrocyte proliferation arrest, apoptosis enhancement, and ECM degradation. Knockdown of circSCAPER reduced chondrocyte degradation.[26] Further study of these and other ncRNAs as potential DMOADs may provide insightful data.

As our knowledge of the pathogenesis of OA expands, so does our awareness of the number of common pathways and interactions between OA, other diseases, environmental influences, and the microbiome. The association between OA and metabolic syndrome is now well established, but also emerging is the shared genetic basis between OA and conditions such as obesity and major depressive disorder.[30,31,34] Furthermore, our knowledge of the interplay between the gut microbiome, the environment, and OA is rapidly evolving. The collection of trillions of microbial organisms that reside in the gastrointestinal tract has been shown to play a key role in host metabolism, the immune system, and inflammatory response.[27] Recent evidence has shown the involvement of the gut microbiome in OA progression.[35,36] The ability for exercise to directly modulate the microbiome and its relationship to the severity of OA is also being evaluated.[29] Furthermore, the effect of probiotic supplementation in modulating disease progression of OA has been evaluated in a mouse model of OA, which showed significant reduction in cartilage degeneration in the probiotic supplemented cohort.[36] The beneficial effects of probiotics in OA have also been shown in a recent large double-blind randomized controlled trial, where probiotic treatment with lactobacillus casei Shirota in patients with knee OA showed significant improvements in OA-related knee function (Western Ontario and McMaster Universities osteoarthritis index)[37] and pain compared with placebo.[28]

A notable component of the bone-driven OA endotype is mediated through the subchondral bone plate.[38] This endotype is characterized by hypomineralization of subchondral bone, osteophyte generation, development of microfractures & cysts, and subchondral plate sclerosis.[39,40] Subchondral plate remodelling and attrition may precede and mediate cartilage degeneration in OA.[41] The repurposing of established regulation-approved bone remodelling agents employed in the treatment of other bone diseases for use in bone-driven OA also shows potential. Recombinant parathyroid hormone (PTH) (Teriparatide), which is an established FDA-approved therapy for osteoporosis,[42] has shown promise in preclinical studies. Systemic injection of higher-dose PTH reduced OA progression by preserving subchondral bone and reducing cartilage degradation,[22,23] and more recently intra-articular injection showed similar OA-attenuating effects with much lower doses.[21]

Recently, new molecules have emerged as potential pharmacological agents within the inflammation-driven model of OA. The protein Peli1, which has an emerging role in IL-1R regulation and a host of other interactions in macrophage-associated inflammation, has been shown to have a substantial pro-inflammatory role in OA-associated cartilage degradation.[43] Recent in vitro and in vivo models demonstrating knockdown of Peli1 showed reduced expression of IL-6, tumour necrosis factor alpha, and matrix metalloproteinase-3, and resulted in attenuated chondrocyte-related degradation.[43] Similarly, Dihydrocaffeic acid (DHCA), the main bioactive component in the plant Gynura bicolor, has shown both anti-oxidative and anti-inflammatory properties[44]. More recently, DHCA demonstrated chondroprotective effects in vitro and in a destabilised medial meniscus OA mouse model, through downregulation of the inflammatory mediators nitric oxide synthase and IL-6.[24]

To conclude, advances in our understanding of the pathogenesis of OA have enabled the identification of an increasing array of potential pharmacological targets and novel disease-modifying agents for OA. However, despite encouraging preclinical data and some clinical evidence for benefit, none have yet reached the threshold of symptomatic improvements required for regulatory approval. Recent interest in novel molecular targets and agents, including ncRNAs, manipulation of gene expression, and modulation of the gut microbiome, could provide valuable avenues for further study in this rapidly evolving field.

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