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New developments in osteoarthritis and cartilage biology

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Osteoarthritis (OA) is a degenerative joint disease and the most common form of arthritis. Characterised by articular cartilage loss, subchondral bone thickening and osteophyte formation, the OA joint afflicts much pain and disability. Whilst OA has been associated with many contributing factors, its underpinning molecular mechanisms are, nevertheless, not fully understood. Clinical management of OA is largely palliative and there is an ever growing need for an effective disease modifying treatment. This review discusses some of the recent progress in OA therapies in the different joint tissues affected by OA pathology.

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Introduction

With our ever ageing population comes a significant increase in the incidence of musculoskeletal disease and an acute need for effective therapeutic interventions. Osteoarthritis (OA) is a degenerative joint disease and the most common form of arthritis with 33% of people aged 45 years and over seeking treatment for OA in the UK. It is therefore a massive world-wide healthcare and financial burden. Characterised by articular cartilage (AC) loss, subchondral bone thickening and osteophyte formation, the OA joint afflicts much pain and disability [1].

Whilst OA has been associated with many contributing factors including ageing, obesity, trauma, genetics, amongst others, its underpinning molecular mechanisms are, nevertheless, not fully understood; indeed it is even still a matter of debate as to which is the precipitating pathology. Now regarded as a disease of the whole joint, clinical management of OA is largely palliative with the use of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and steroid injections. In some individuals, only prostheses can offer long-term aid.

Clinical trials to date have included glucosamine sulfate, chondroitin sulfate, sodium hyaluronan, doxycycline, and matrix metalloproteinases (MMP) inhibitors; all of which have varying levels of efficacy and none of which have successfully and reproducibly prevented OA disease development or progression. As such, there is an ever growing need for an effective disease modifying treatment. Whilst our understanding of the aetiopathology of OA is dramatically advancing, few advances have been made in the pharmacological intervention of disease progression. This review discusses some of the most recent progress in OA therapies in the different joint tissues affected by OA pathology that were not already discussed by the recent review published in this journal in 2015 [2••].

Targeting AC maintenance

AC degradation is one of the main hallmarks of OA development and to date, research has largely sought to identify those factors that target the AC to produce its disease-defining deterioration. However, the lack of blood vessels and the high ratio of extracellular matrix to cell area make this tissue difficult to target for repair; indeed pharmaceutical interventions are usually reliant on blood circulation of compounds through the body and to the cells through the matrix. An elegant and comprehensive review in this journal has recently summarised the most recent advances in finding new targets for reducing AC degradation, including cartilage degradation, autophagy, circadian clock, mechanical, inflammatory, oxidative stress, innate immunity, chondrocyte hypertrophy, pain [2••]. In addition to those mentioned by Goldring and Berenbaum [2••], further targets have recently been examined and are discussed herein.

Oxidative stress is emerging as a main contributor to OA severity. Recently, pathways centred around Heme Oxygenase 1 (HO-1), a major anti-oxidant, have been shown to play a major role in the oxidative stress response in chondrocytes. Indeed, Bach-1 (BTB and CNC homology) is a negative regulator of HO-1, and its deletion in mouse chondrocytes *in vivo* was shown to protect from OA development, via the promotion of HO-1 and autophagy [3•]. In addition, Nrf2 (nuclear factor (erythroid-derived 2)-like 2) is a promotor of HO-1 expression, and its

deficiency in mice lead to more severe OA development [4]. This effect was reduced with a histone deacetylase inhibitor (trichostatin A) following Nrf2 activation and HO-1 expression. Sulfuraphane was used a potent activator of Nrf2, inducing HO-1 expression, and decreased cartilage degradation in a murine post-traumatic model of OA [5]. These studies support HO-1 as a potent new target for cartilage degradation in OA.

TGFα (Transforming Growth Factor-α) is a member of the epidermal growth factor (EGF) family and has been shown to be increased by 4 fold in the AC of OA rats [6]. It was subsequently found that TGFα can reduce chondrocyte anabolism while increasing catabolic processes and thus was proposed to be a potential target for therapy for AC degradation in OA development [7••]. Recently, Appleton *et al.* (2015) used pharmacological tools, namely AG1478, to inhibit TGFα *in vivo* in a rat OA model [8]. AG1478 was able to reduce cartilage degradation and OA severity, as well as increasing the levels of CPII (C-propeptide of collagen type II) in the serum while decreasing C2C (collagen type II breakdown product) levels, markers of cartilage anabolism and catabolism respectively. This study is one of the first to show pharmacologic efficacy in blocking post-traumatic OA development *in vivo*.

AC matrix degradation products have been shown to promote further joint degeneration. Indeed, fragments of collagen type II, aggrecan and fibronectin can induce further degradation through upregulation of MMP activity [9–11]. However, a complex interaction between specific fragments and concentration and mechanical stress may result in anabolic responses as well [12]. The signalling involved in these responses seems to be similar between cell types: indeed, Lees *et al.* [13] recently described the effect of an aggrecan 32-mer fragment derived from ADAMTS (A Disintegrin And Metalloproteinase with Thrombospondin Motifs)and MMP cleavage of aggrecan on chondrocytes, synovial fibroblasts and macrophages [13]. Treatment with this aggrecan 32-mer fragment resulted in pro-catabolic, anti-anabolic and pro-inflammatory activities, which were all abrogated in the absence of MyD88 (myeloid differentiation primary response gene 88), and was achieved via Toll-Like Receptor 2-dependent activation of the signalling pathway NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells). This same pathway was also shown to be responsible for Fibronectin fragment catabolic responses from chondrocytes, suggesting potential targets for slowing the progressive degeneration of the AC in OA [14].

Although very informative, these studies have been performed in animal models, and thus further trials into human tissues and patients will be required to truly understand the potential of these targets for therapy.

Targeting the subchondral bone

Subchondral bone pathologies in OA joints, although often considered secondary, are one of the earliest detectable changes and are now considered to be a potential trigger for subsequent OA progression [15,16]. These pathologies include sclerosis leading to joint space narrowing, with associated hypomineralisation and inferior bone quality due to abnormal local bone remodelling. It is therefore unsurprising that pharmacological interventions for the subchondral bone in OA have focussed on targeting regulation of osteoclast/osteoblast activity and as such, the bone remodelling process.

Inhibition of osteoclast activity

Bisphosphonates are potent inhibitors of osteoclast activity, and are widely used in clinical practice to prevent the bone loss associated with conditions such as Paget's disease, metastatic bone disease and osteoporosis [17]. The use of bisphosphonates as means of OA therapies has been well investigated over the past decade with varying efficacy, and as such, more recent pharmacological studies have focussed upon the timing at which treatment with anti-resorptive agents should be used for disease modification [18••]. Pamidronate disodium (PAM) is a bisphosphate which completely prevents OA pathology in rabbits undergoing early anterior cruciate ligament transection (ACLT)-induced OA when administered short-term post ACLT. Similarly, long-term PAM administration reverses OA pathology in this model. This is therefore suggestive that PAM can significantly inhibit and even reverse early OA subchondral bone pathology, thought to be through OPG:RANKL (Osteoprotegerin — Receptor Activator of NFkB Ligand) mediated regulation of osteoclastogenesis [19]. Similarly, the pre-emptive use of another bisphosphonate, Alendronate, in a rat model for severe OA prevents OA bone pathologies including reduced subchondral bone loss and reduced osteophyte formation when compared to non-alendronate treated rats. Alendronate treatment also reduced AC degeneration, suggesting that osteoclastic activity drives AC degeneration [20]. Similar chondroprotective effects of the bisphosphonates clodronate and zoledronic acid have been reported on bovine chondrocyte cultures and ACLT in rabbits, respectively [21,22].

Whilst animal studies are informative, clinical trials are required to investigate the true therapeutic value of bisphosphonates in human OA. In the past two years there have been four clinical trials detailing the effects of bisphosphonates on human OA, with varying results. Nishii *et al.* found that 2 years alendronate treatment in patients with symptomatic hip OA revealed clinical efficacy for decreasing pain. Despite this, no differences were observed in OA disease pathology, as determined by radiographic measurements of Kellgren-Lawrence score, joint space narrowing and centre-edge angle [23]. Similar advantages for bisphosphonate use in improving pain