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Current Opinion in Pharmacology

Emerging targets in osteoarthritis therapy

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Osteoarthritis (OA) is a destructive joint disease in which the initiation may be attributed to direct injury and mechanical disruption of joint tissues, but the progressive changes are dependent on active cell-mediated processes that can be observed or inferred during the generally long time-course of the disease. Based on clinical observations and experimental studies, it is now recognized a that it is possible for individual patients to exhibit common sets of symptoms and structural abnormalities due to distinct pathophysiological pathways that act independently or in combination. Recent research that has focused on the underlying mechanisms involving biochemical cross talk among the cartilage, synovium, bone, and other joint tissues within a background of poorly characterized genetic factors will be addressed in this review.

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Current Opinion in Pharmacology 2015, **22**:51–63

This review comes from a themed issue on **Musculoskeletal**

Edited by **James A Gallagher** and **R Graham G Russell**

For a complete overview see the Issue and the Editorial

Available online 10th April 2015

http://dx.doi.org/10.1016/j.coph.2015.03.004

Introduction

Osteoarthritis (OA) is the most common joint disorder and is a leading cause of disability in the adult population. The disease manifestations in the joint are well characterized, including progressive loss of articular cartilage, cartilage calcification, osteophyte formation, subchondral bone remodeling, and mild to moderate inflammation of the synovial lining. Many therapeutic clinical trials have been conducted with designs based on subject selection related to the joint location or on whether the disease is primary or secondary to other types of arthritis [1–3]. Most trials, including those addressing targeted therapies, have evaluated patient-reported outcomes of function and pain at later stages of disease when there is radiographic evidence of damage, that is, joint space narrowing and osteophytes. However, symptoms and disease progression do not necessarily correspond in an individual patient and there is significant patient-to-patient variability in the time course of progression. Furthermore, the disease multifactorial process is impacted by aging, genetic predisposition, abnormal biomechanics, obesity, and trauma and influenced by co-morbidities such as cardiovascular disease, metabolic syndrome, and diabetes. Recognition that it may be possible to classify OA patients according to these diverse etiologies could optimize patient cohort selection for trial design [4–7].

Till date, no efficacious structure-modifying agent has been approved by any regulatory agency and available pain therapies are limited in efficacy and have associated toxicities [8]. Although there are promising candidates, there is a paucity of validated diagnostic and prognostic molecular biomarkers that could be used to evaluate efficacy in pre-symptomatic early-stage disease before irreversible joint damage [9,10,11•,12]. Imaging biomarkers are also under intensive study [13]. Given the complexity of OA, a single therapy will not be effective and therefore promising strategies should focus on how to address both symptoms and structural changes [14–17]. This review will focus on emerging strategies based on novel research findings that are undergoing validation and translation in pre-clinical models and have promise for development in proof-of-concept early phase trials and for informing the design of future definitive clinical trials.

Existing therapies and current research goals

Current guidelines consist of OA therapy in the following defined order: first, behavioral interventions; second, simple analgesic such as acetaminophen (paracetamol); third, nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors [18]; fourth, intraarticular injection of hyaluronic acid or corticosteroid; and finally fifth, total joint replacement. Anti-pain drugs include opioids and centrally acting drugs such as duloxetine, which have adverse side effects. Since these current treatment options are lacking efficacy for the majority of patients, there is a great, unmet medical need that has been exacerbated by the recent closure of research programs by pharmaceutical companies wary of investing in identifying complex OA treatments and proving their efficacy in clinical trials [8].

Despite the identification of pro-inflammatory cytokines such as interleukin (IL) 1, which is used *in vitro* to mimic the catabolic responses that occur in OA, as potential targets in pre-clinical animal models, anti-cytokine

therapies that have been successful in other inflammatory and autoimmune diseases affecting joints have not proven to be effective against OA in clinical studies [19,20]. Preclinical studies indicate that MMP-13 is a crucial target for blocking cartilage erosion in OA [21] and that a number of other molecular targets should be amenable to therapy [22–24]. However, therapies that directly inhibit catabolic enzymes or signaling pathways, have inadequate efficacy or unacceptable side effects, even with increased specificity. Thus, many clinical programs addressing such products as OA therapies have been discontinued. This has fostered renewed efforts in the academic community to find novel strategies.

Emerging strategies for structure modification

Current research goals are directed toward understanding the different etiologies in terms of the common and distinct molecular mechanisms that would be amenable for targeted therapies. One classification scheme proposes a continuum of potential phenotypes [4] involving post-traumatic, metabolic, and aging-related (including post-menopausal), changes that are most prominent at young, middle, and advanced ages, respectively, as well as a genetic phenotype, in which different mutations produce susceptibility across an age-associated continuum [25]. Any of these OA phenotypes may be associated with abnormal biomechanics and malalignment as part of a whole-joint organ failure that frequently involves episodes of inflammation [26].

Laboratory studies using cell-based assays, animal models, and human OA joint tissues have identified a number of molecular pathways that are induced by mechanical, inflammatory, and oxidative stresses in the resident cells. In the cartilage, these stresses result in the release of the chondrocytes from growth arrest, loss of homeostasis, and activation of aberrant cellular signal transduction and gene expression [27]. Among the early events is the disruption of the pericellular matrix, associated with abnormal activation of cell surface receptors [28••,29]. The subsequent loss of surface lubrication is associated with proteoglycan loss and collagen erosion, while increased cartilage calcification and tidemark advancement or duplication are associated with vascular penetration from the subchondral bone. Since the damaged collagen network cannot be repaired to its original state, the challenge is to develop therapies that either prevent the destruction in the first place or promote repair to replicate the physiological and functional properties of the original cartilage.

Targeted therapies, however, have been elusive, since manipulation of any of the genes encoding potential targets by knockout or transgenic overexpression in mice can individually have profound effects on OA development [30,31]. For example, mice deficient in the crucial aggrecan-degrading and collagen-degrading genes, *Adamts5* and *Mmp13*, are protected against cartilage damage and other aspects of OA development. The mouse studies do not necessarily correspond with genome wide association studies (GWAS), which have identified genes that harbor OA susceptibility alleles, including *GDF5*, *SMAD3*, *DIO2*, *DIO3*, *RUNX2*, *PTHLH*, *CHST11*, *TP68*, *DOT1L*, *COL11A1*, *VEGF*, and *IGFBP3* [32–35]. Many of these, including GDF5, whose 143383C to T SNP has been validated thus far as the strongest OA-related variant and which is regulated by DNA methylation [36,37], are skeletal developmental genes that could be associated with cartilage calcification, osteophyte formation, and subchondral bone changes in OA [38]. On the other hand, proteomic profiling of OA synovial fluid indicates that a major proportion of the knee OA proteome contains acute phase response, coagulation, and complement proteins generated from the synovium [39]. Gene profiling data will probably enable subsetting of different OA populations into cohorts, but whether a single, one-drug-fits-all strategy will result is highly unlikely. Furthermore, profiling single patients to guide individualized OA therapy is a long-term future goal [12].

Inflammatory, mechanical, and oxidative stress

Inflammation can be observed at the macroscopic level as synovitis and synovial effusion during operative procedures such as arthroscopy or by MRI and is associated with more rapid progression to OA [40–43]. Recent studies, however, highlight a role for chronic low-grade inflammation, termed 'microinflammation', which is often associated with aging and can disrupt homeostasis in joint tissues and drive the degradative responses [44,45,46,47••]. This is an important consideration in OA joints, since mechanical stress may induce similar signaling responses in the absence of overt inflammation.

Oxidative stress, resulting from increased levels of reactive oxygen species (ROS) relative to antioxidants, may act together with inflammatory and/or mechanical stress to accentuate catabolic processes, depending upon the availability of signals and the state of the tissue damage. Mechanical injury, inflammatory cytokines, and matrix fragments, such as fibronectin fragments via integrins can induce ROS, and the age-related decline in the responses of chondrocytes to anabolic growth factors may be attributable to altered cell signaling mediated by increased oxidative stress [48,49]. NF-κB signaling is an integrating mechanism underlying most responses to inflammatory, mechanical, and oxidative stresses [27,50–52]. Components of NF-κB signaling are found prominently among the different gene signatures in experimental OA models [53].

Genomic and proteomic analyses of synovial fluids and joint tissues collected at the time of arthroscopic or joint