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# Nuclear receptors as potential drug targets in osteoarthritis

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Osteoarthritis is amongst the major causes of disability worldwide, but no medications that can slow or stop progression of this disorder have been identified. Recent evidence suggests roles for a variety of members of the nuclear receptor family of ligand-activated transcription factors in various forms of osteoarthritis. Since nuclear receptors are amongst the major classes of drug targets, these studies suggest that modulators of nuclear receptor activity might provide novel strategies to treat osteoarthritis. This review focuses on recent advances in our understanding of the role of nuclear receptors in osteoarthritis onset and progression, as well as their therapeutic implications. Future studies should continue to examine the possible roles of additional nuclear receptors in the pathophysiology of different types of osteoarthritis.

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## Introduction

Osteoarthritis (OA) is one of the major causes of disability and loss of independence worldwide, with rapidly rising incidence [1]. In addition to causing enormous individual suffering, OA is a huge burden on health care systems and economies due to loss of productivity. Strikingly, while the importance of lifestyle changes (e.g. exercise, weight management) in managing OA symptoms and progression is becoming increasingly clear, there are still no pharmacological approaches that can stop, slow, or reverse disease progression. One reason for this lack of pharmacological treatments is that we are only just beginning to understand the complexity of the factors that initiate and drive OA. Indeed, our view of OA has changed drastically over the last few decades [2,3]. One of the major paradigm shifts is that we recognize that OA is not one disease or one phenotype, but can be driven by multiple risk factors including age, sex, genetics, injury, and metabolic conditions (including obesity and metabolic syndrome) [4]. It is likely that all these phenotypes are driven by different molecular pathways, providing a possible explanation for why studies examining modulators of specific pathways were not successful in trials that did not stratify according to OA phenotypes. Another paradigm shift is that our view of OA has evolved from a cartilage-centric perspective to one that recognizes the importance of all joint tissues (e.g. synovium, subchondral bone, cartilage, ligaments, meniscus, muscle, among others) in joint homeostasis and pathology [5]. Therefore, strategies exclusively aimed at maintaining cartilage matrix and structure will likely not be able to address OA in the long term.

This changing view of OA, along with the development of high throughput technologies in genomics, proteomics, and most recently metabolomics, has allowed us to identify novel molecular players in OA initiation and progression, some of them OA phenotype-specific. Amongst these players, the family of nuclear receptors (NR) has received quite a bit of attention. Nuclear receptors are ligand-activated transcription factors; binding of their ligand (in general, small lipophilic molecules) induces their function as transcriptional activators or, in some instances, repressors [6]. In humans, there are 48 different nuclear receptors that can be subgrouped into several subfamilies. These include receptors for well-known hormones such as glucocorticoids, thyroid hormone, estrogen, and vitamin D. Other NRs are 'orphan' receptors for which the respective ligand(s) has not been identified. Some NRs can form homodimers, but many rely on heterodimer formation with one of the three Retinoid X Receptor (RXR) proteins, which are NRs themselves. Because of space limitations, we refer to several recent reviews on NRs for details of their biology [6–8].

Several features make members of the NR superfamily attractive as potential drug targets for OA [7]. A study by Collins-Racie *et al.* showed more than 30 NRs to be expressed in human articular cartilage, and more than 20 of these to be differentially expressed in OA versus

**Table 1**

**Effect of current nuclear receptor pharmacological modulators on OA.**

| Pharmacological ligand | Mechanism of action | Effects on OA | OA clinical trials | References |
|---|---|---|---|---|
| Vitamin D | Activation of vitamin D receptors | Effect in human clinical studies inconclusive. | Completed | [10–12] |
| Glucocorticoids | Activation of glucocorticoid receptors | Minimal evidence for beneficial pain and functional outcomes in humans. | Completed | [15–17] |
| Selective GR agonists and modulators (SEGRAMs) Compound A | Selective activation of glucocorticoid receptors | Anti-inflammatory properties, without induction of leptin or Ob-R expression in *in vitro* studies. | Not initiated | [19••] |
| Estrogen therapy | Activation of estrogen receptors | Effect in human clinical studies inconclusive. | Completed | Reviewed in [24••] |
| Selective estrogen receptor modulators (SERMs) Levormeloxifen Raloxifene Bazedoxifene | Tissue specific activation or inhibition of estrogen receptors | Protective effect in joint tissues; decreased pain outcomes in OA. | In progress | Reviewed in [24••] |
| Thiazolidinediones Pioglitazone Rosiglitazone | Activation of PPARγ | Protective effects in *in vivo* animal models of OA. | Not initiated | [31–34] |
| GW3965 | Activation of LXRα and LXRβ | Decreases proteoglycan degradation and PGE2 production *in vitro*; decreases joint paint in rat OA model. | Not initiated | [26] |

healthy cartilage [8]. In addition, many NRs are involved in the regulation of metabolism and/or inflammation, which we now understand to be key processes controlling OA progression. Moreover, a large number of specific natural and synthetic agonists and antagonists for many NRs are available and well characterized pharmacologically, making them attractive targets from a therapeutic perspective. Here, we will discuss recent findings on how NRs control OA progression as well as potential therapeutic implications (summarized in Table 1).

## Roles of nuclear receptors in osteoarthritis

### Classical nuclear hormone receptors

Many classical nuclear hormone receptors play key roles in skeletal development, homeostasis and disease. Surprisingly, for some of them (including the thyroid hormone and vitamin D receptors), very little is known about a potential role in OA. Based on the established effects of their ligands on cartilage and other joint tissues, roles of these receptors in OA is likely, but these have not been explored in detail. Further evidence for a role of thyroid hormone signaling in OA comes from the recent association of polymorphisms in the *DIO2* gene, which encodes a key enzyme in thyroid hormone metabolism, and OA [9]. As for Vitamin D, the evidence for protective effects of the hormone on OA is controversial, and the relative contribution of joint-specific versus systemic effects is unclear [10–12]. Detailed studies including targeted ablation of the genes encoding these NRs in adult joint tissues of mice will be required to elucidate their roles in OA and their suitability as drug targets.

Glucocorticoid (GC)/corticosteroid injections into the joint have long been used as a treatment of OA, based on the potent anti-inflammatory actions of these hormones. However, recent studies question whether GC injections provide symptomatic relief for patients [13–17]. The target cells for these actions are not completely known; while our previous microarray studies have shown that GCs suppress expression of many pro-inflammatory genes in chondrocytes directly [18], other target cells including synovial cells, osteoblasts and/or osteoclasts are likely involved. One study has shown more specific activities of a Selective GR Agonist/Modulator (SEGRAM) on synovial cells, suggesting that further refinement of ligands could increase the value of these compounds [19••]. Moreover, it is not known whether these effects are mediated by the glucocorticoid receptor or other, non-canonical mediators of GC signaling. Thus, while corticosteroid injections will likely remain an important part of OA treatments for the time being, their disease-modifying abilities are not clear currently.

Females show higher rates of OA in the human population, especially after menopause, suggesting a role of estrogens and, by extension, estrogen receptors (ERs) in this disease. Although reports on OA-associated polymorphisms in the gene encoding ERα await validation in larger cohorts [20–23], both clinical and preclinical studies suggest that estrogens and in particular selective estrogen receptor modulators (SERMs) could offer both symptomatic and structural benefits in OA [24••,25]. By contrast, very little is known about roles of related NRs, such as progesterone and androgen receptors, in OA.

## RXR partners

As mentioned above, many NRs including several orphan receptors function as obligate heterodimers with RXRα,