SOXC Transcription Factors in Arthritis Diagnosis and Treatment

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Osteoarthritis (OA) and rheumatoid arthritis (RA) are two common disorders that disrupt the quality of life of millions of people. Sex-determining region Y-related (SRY) high-mobility group (HMG) box C, SOXC, is a superfamily of transcription factors that have been recently shown to be involved in various physiological and pathological processes. These include embryonic development, cell differentiation, fate determination, and autoimmune diseases, as well as carcinogenesis and tumor progression. The SOXC superfamily includes SOX4, SOX11, and SOX12, all have a similar DNA-binding domain, i.e., HMG.

SOX4 SOX11 therapeutic targets rheumatoid arthritis

1. Introduction

Osteoarthritis (OA) and rheumatoid arthritis (RA) are two forms of arthritis with a similar clinical phonotype, causing joint pain, stiffness, and probably disability, but occurring for different reasons and differing in pathophysiological mechanisms and in treatment strategies. These two common disorders affect more than 220 million people in the world. Osteoarthritis, the most common type, is a degenerative joint disease, characterized by the progressive deterioration of the articular cartilage or of the entire joint (the articular cartilage and the joint lining), the ligaments, and the subchondral bone. In addition, although inflammatory conditions can be associated with OA, basically, it is not an inflammatory disease. On the other hand, RA is a chronic systemic autoimmune inflammatory disorder characterized by the infiltration of inflammatory cells at the synovial lining resulting in hyperplasia and the destruction of cartilage and bone tissues (reviewed by Pap and Korb-Pap [1]). Typically, RA starts in the peripheral joints and progresses to damage the proximal joints if left without treatment. In the meantime, prolonged joint inflammation can destroy the joints and cause bone erosion and a loss of cartilage.

To date, there is no cure for OA or RA, and the available therapeutic protocols are able to partially reduce the pain, relieve the symptoms, improve quality of live and increase survival. However, an understanding of the involved signaling biomolecules and their targets and inhibitors is advantageous in designing new therapeutic arthritis drug or drug combinations. A little over 30 years ago, the gene of the male sex-determining region of the Y chromosome (SRY) was discovered, which later facilitated the discovery of the whole family of essential regulatory gene-encoding transcription factors (TFs) that control cell fate in many processes [2][3]. To date, 20 SRY-like box (*SOX*) genes have been reported in the mammalian genomes, which encode eight groups of SOX TFs, named from A to H. However, during the past decade, studies have found links between the dysregulation of sex-determining region Y-related (SRY) high-mobility group (HMG) box C (SOXC) levels and the progression of arthritis disorders. SOXC

is a superfamily of TFs that have been recently shown by several studies to be involved in the onset and pathogenesis of arthritis. Interestingly, the great majority of these studies have been conducted during the last 5 years [4][5][6][7][8][9][10][11][12][13][14][15][16][17]. The *SOXC* gene family encodes SOX4, SOX11, and SOX12 TFs that contain a conserved high mobility group (HMG)-box domain by which SOXC proteins are able to bind to minor grooves in the DNA. SOXC TF binding to DNA can lead to alterations in the chromatin architecture associated with changes in the downstream genes at both transcriptional and functional levels.

2. SOXC Transcription Factors under In Vivo Inflammatory Conditions Associated with Arthritis

At local inflammatory sites in humans, a specific type of CD4+ T cell was found to enhance ectopic lymphoid-like structure (ELS) formation through the production of the chemokine CXCL13 and other mediators [17]. These ectopic structures were proved to play crucial roles in the body's response to infections and during cancer and autoimmune diseases [18]. For instance, ELSs' immune activity was reported to be correlated with a better prognosis of cancer [19] and to stimulate the autoimmune response, i.e., via autoantibody production [20][21]. The function of the ectopic ELSs was reported to be maintained by fibroblast-like synoviocytes (FLSs), nonimmune cells located at the synovial tissues and strongly participating in the pathogenesis of RA. Related to that, in synovial CD4+ T cells from patients with RA, SOX4 was found to be significantly upregulated when compared with patients' blood CD4+ T cells, which was further correlated with CXCL13 production and ELS formation in RA synovium [17].

In healthy tissues, FLSs populate at the synovial lining of the joints and maintain the synovial fluid homeostasis through producing cartilage-protecting proteins and enhancing joint lubrication. However, in arthritic inflammatory conditions, FLSs are epigenetically changed and transformed into a main source of catabolic enzymes and inflammatory cytokines that promote the degeneration of joints [22].

3. SOXC Transcription Factors as Potential Diagnostic Biomarkers of Arthritis

Developmental biology studies support the idea that SOX4 and SOX11 are essential in promoting articular and bone formation [13][23]. However, according to both the preclinical and the clinical studies, the progression of arthritis diseases was found to be associated with dysregulated levels of SOX4 and SOX11 TFs, which indicates that both could be used as diagnostic biomarkers of arthritis; however, there is still little data available regarding the role of SOX11 in RA. The upstream signaling molecules are advanced glycation end products (AGEs), tumor necrosis factor alpha (TNF), secreted modular calcium-binding protein 2 (SMOC2), tumor necrosis factor (TNF-β), the long non coding (Lnc-PATR1), and the miRNAs miR-31-5p and miR-373-3p. However, the downstream target molecules include disintegrin-like and metallopeptidase with thrombospondin types 4 and 5 motif (ADAMTS4 and 5, respectively), the transcription factor RELA, the motor protein myosin1c (MYO1C), the protein kinase (ERK), the mechanical target of rapamycin kinase (mTORC1), Lnc MCM3AP-AS1, and miR149-5p.

3.1. SOX4 as a Potential Diagnostic Biomarker of Osteoarthritis

The progression of OA disorder was recently documented in several studies to be associated with upregulated levels of SOX4 (summarized in **Table 1**). In this regard, higher levels of SOX4 were seen in both OA models of chondrocytes and in OA patients [7]. In addition, SOX4 was elevated in inflamed arthritis patients' synovium compared to non-inflamed synovium and then was considered to be an early diagnostic biomarker during OA pathogenesis [5].

3.2. SOX4 as a Potential Diagnostic Biomarker of Rheumatoid Arthritis

As indicated above, RA is basically chronic inflammatory disease, in which a high level of SOX4 seems to be required for the progression of inflammatory conditions at a local site. This has been evidenced by the fact that SOX4 is upregulated in both RA patients and RA mouse models [10][11][17][24][25].

3.3. SOX11 Is Dysregulated during Osteoarthritis

Unlike SOX4, which is upregulated in almost all of the studies investigating its role in arthritis disease, SOX11 is downregulated in some studies and upregulated in others during osteoarthritis progression. For instance, SOX11 was reported to be upregulated in both patients with OA and IL-1β-treated chondrocytes, which was associated with osteoarthritis progression via the induction of TNF-α [12].

4. Signaling Mechanisms Involved in SOXC TFs Promoting Arthritis

Mechanistically, SOX4 promoting arthritis has been documented to occur through regulating several signaling pathways. (1) As a critical mediator of the TNF-induced transformation of FLS, SOX4 interacts with RELA (NF-κB signaling molecule) to regulate the expression of TNF downstream genes and thus maintains the transformation of FLS and inflammatory pathology in arthritis [10][26]. (2) SOX4 is regulated by the ROS/TGF-β signal to enhance OA pathogenesis and FLS senescence [5]. (3) SOX4 is involved in osteoarthritis onset by increasing the levels of two major aggrecanase-degrading articular cartilage enzymes, Adamts4 and Adamts5, through binding to their gene promoters [8]. The degradation of the cartilage extracellular matrix (ECM) is one of the main features associated with arthritis. The degradation of aggrecans in the ECM of aggrecan was found to regulated by these two enzymes. Thus, SOX4 appears to regulate the level of these enzymes and then promote arthritis. (4) SOX4 is upregulated in synovial CD4+ T cells and contributes to the production of CXCL13 and the formation of ELSs at the inflammatory sites in RA patients [17]. (5) SOX4 activated the long noncoding MCM3AP-AS1, aggravated OA progression via targeting the miR-149-5p/Notch1 axis and then modulated autophagy and ECM degradation [7].

5. SOX4 as a Therapeutic Target of Arthritis

Targeting the SOXC proteins or the mechanisms that stabilize them during arthritis through the systemic delivery of inhibitors has been suggested as an option to be explored [25][27][28]. However, as explained above, although it is dysregulated during OA and RA, the currently available data do not provide a conclusive overview about the role of SOX11 in arthritis. Whether it is involved in arthritis progression or needed for joint maintenance and the proper functioning of cartilage and bone cells is not yet clear. On the other hand, SOX12 appears to have no role in arthritis disease nor in skeletal system development [29]. However, SOX4 has been suggested by several recent studies as a therapeutic target of OA and RA [4][8][11][17][24]. Therefore, targeting SOX4 and other signaling molecules could improve the current therapeutic strategies in arthritic disorders.

6. Upstream Molecules That Can Target SOX4 to Treat Arthritis

Through direct and indirect binding to SOX4 TF, several upstream factors and signaling molecules have been recently reported to target SOX4 during arthritis, such as ROS)/TGF, TNF, SMOC2, AGEs, Lnc PART1, and the miRNA, miR-31 (**Figure 1**).

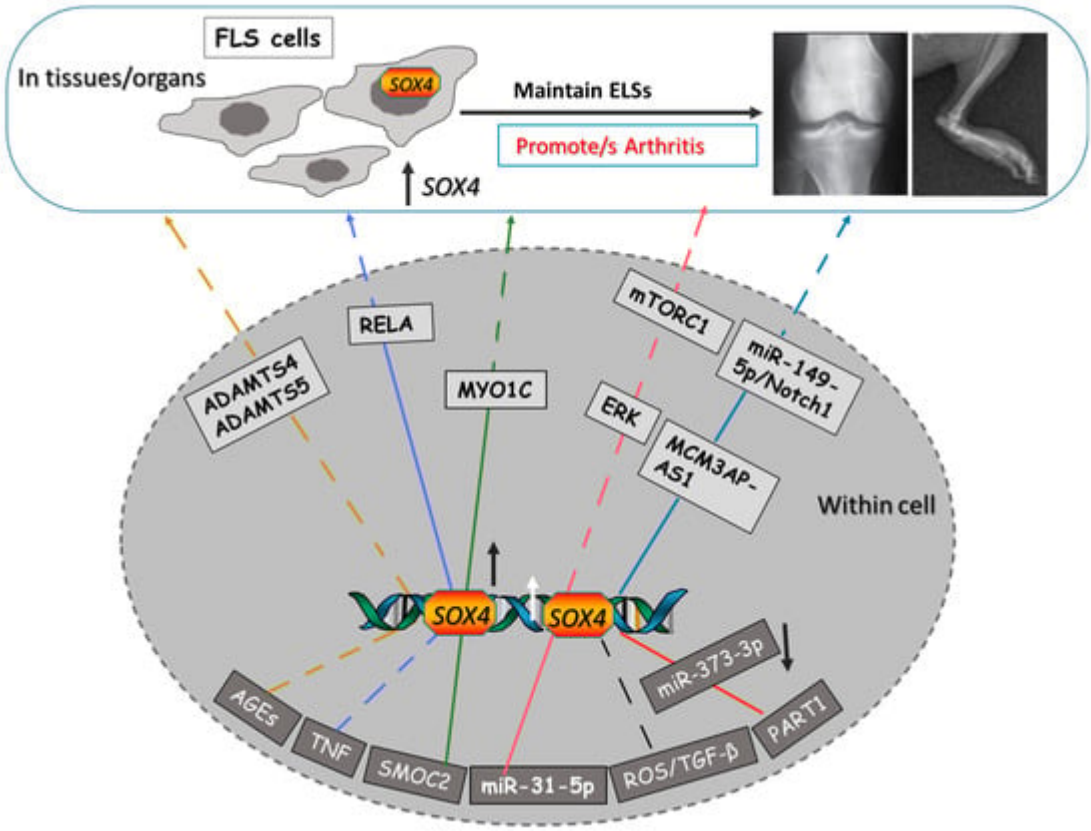

Figure 1. Representative diagram of the involved upstream and downstream molecules in SOX4 regulating arthritis progression. SOX4 upstream molecules within the grey background; indirect targeting, dashed lines; direct binding, continuous lines. The same signaling pathways are shown by the same colors. The upstream signaling molecules

shown are advanced glycation end products (AGEs), tumor necrosis factor alpha (TNF), secreted modular calcium-binding protein 2 (SMOC2), tumor necrosis factor (TNF-β), long non coding PART1 (Lnc-PART1), and the miRNAs miR-31-5p and miR-373-3p. However, the indicated downstream target molecules include disintegrin-like metallopeptidase with thrombospondin type 4 and 5 motifs (ADAMTS4 and 5, respectively), the transcription factor RELA, the motor protein myosin1c (MYO1C), the protein kinase ERK, the mechanical target of rapamycin kinase (mTORC1), Lnc MCM3AP-AS1, and miR149-5p.

On the other hand, the endogenous secreted modular calcium-binding protein 2 (SMOC2) has been recently recognized as a key molecule to control the aggressive behavior in FLSs during arthritis. Mechanistically, SMOC2 exerts this function via SOX4-mediating transcriptional regulation leading to increased levels of upregulated motor protein myosin1c (MYO1C) and hence causing cytoskeleton remodeling and enhancing synovial migration and invasion during RA [25].

In human chondrocytes, the inflammation and degradation of the cartilage-specific proteoglycan core protein and the onset and development of OA was reported to be regulated by advanced glycation end products (AGEs). Mechanistically, in a dose-dependent manner, AGE-induced chondrocyte injury was found to upregulate the levels of both SOX4 and phosphorylated p38. In the meantime, treatment with the p38 inhibitor reduced AGE-induced SOX4 expression, indicating that the upregulation of SOX4 that resulted from AGE treatment is mediated by p38 [6]. However, two miRNAs were found to target SOX4, miR-31-5p and miR-373-3p. Lower levels of miR-31-5p and higher levels of SOX4 were seen in OA chondrocytes models and in OA patients. Mechanistic experiments indicated that miR-31-5p negatively regulates SOX4 expression by direct interaction with its 3'-untranslated region. In the meantime, the upregulation of miR-31-5p suppressed mTORC1 in an ERK-dependent way via the inhibition of SOX4 [9].

7. Transcriptional Activity of SOX4 in Arthritis

Based on recent data, SOX4 was found to autoregulate its own expression besides regulating its family-member SOX11. As recently interpretated by Jones and colleagues [10], the autoregulation or regulation of own expression is a common mechanism seen in several developmentally important TFs to protect their abundance and activity from being repressed by other factors [30]. Regulating the expression of SOX11 by SOX4 was reported to occur through binding to a regulatory region in the 3′ UTR, which suggests that SOX4 is a crucial factor in the regulation of inflammatory responses [10]. Related to this, the single nucleotide polymorphism (SNP) in the 3′ UTR was found to be responsible for susceptibility to another common skeletal system disease osteoporosis, suggesting that the 3′ UTR region is involved in regulating *SOX4* gene expression during inflammatory diseases [31]. SOX4 polymorphisms were also shown to contribute to variations in low mineral mass density in humans [32]. In this regard, prospective mechanistic studies are needed to explore the function of SOX4 during OA and RA in relation to its structural analysis.

8. SOX4 and Its Implications in Osteoporosis

Osteoporosis, a metabolic bone disease affecting millions of the world's population, is characterized by a lower bone mineral density, bone fragility, and a loss of bone mass. It commonly occurs during the postmenopausal period in women and in the elderly population due to the increase of bone remodeling and the imbalance between bone osteoclastic and osteoblastic activity. An impaired osteoblast associated with decreased bone formation in SOX4 +/− mice suggested an important role for SOX4 in the formation and the resorption of bone [33]. Similarly, in osteoblast progenitor cells the SOX4 level was higher, while SOX4 deficiency in osteoblasts reduced the proliferation rate of progenitor cells and delayed the differentiation of osteoblasts [34]. Moreover, based on a systematic PubMed database search, SOX4 has been suggested to be among a set of five genes which should be further validated for their predictive, diagnostic, and clinical value in osteoporosis [35].

9. SOX4 Involvement in Other Autoimmune Disorders

As a downstream target of TNF-α [36], SOX4 was found to play a crucial role in regulating the immune response. In line with this, a direct role for SOX4 was shown in upregulating the expression of the CD39 enzyme in the tTreg cells of human peripheral blood. In addition, upregulating SOX4 in Treg significantly increased the CD39 level, while SOX4 knockout Treg showed the opposing effect [37]. Interestingly, a high level of CD39 in CD4+ T cells was seen in the synovial fluid isolated from patients with juvenile arthritis [38].

On the other hand, primary Sjögren's syndrome (pSS) is an autoimmune condition in which a pathogenic type of T helper cells (CCR9+) is upregulated in patients and contributes to the immunopathology of pSS [39][40]. In synchronization with its upregulation of inflammatory diseases, the transcriptomic analysis of circulating CCR9+ cells showed higher levels of SOX4 in CCR9+ cells when compared with the other Th cells [41]. In addition, SOX4 was suggested to promote the production of high IFN-γ by CCR9+ Th cells, confirming the role of SOX4 in enhancing autoimmune disease progression, since aberrant IFN-γ expression is one of the factors that is associated with autoimmune inflammatory diseases [42].

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