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Wnt/Beta-catenin Signaling as one of the Therapeutic Targets in Osteoarthritis

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Introduction

Osteoarthritis (OA) is a progressive degenerative joint disorder, which causes joint pain and stiffness. OA is one of the major health problems worldwide among people aged over 60 years [1]. OA is characterized by the degradation of extracellular matrix (ECM) molecules, which is followed by the degeneration of the articular cartilage. No rational medical therapy is available for OA except for palliative pain control and physiotherapy before the patient undergoes joint replacement surgery. In the healthy adult cartilage, homeostasis in chondrocytes is maintained by fine-tuned gene expressions of transcriptional factors, ECM molecules, and their respective catabolic enzymes for the maintenance of ECM. In the cartilage of a patient with OA, having abnormal mechanical stress, trauma, and inflammation, there is dys regulation of homeostasis, and the degradation of ECM leads to reduced elasticity and loss of tolerance to mechanical stress of the articular cartilage. In this review, we simply describe the role of ECM [2-5]. In OA pathology and Wnt/beta-catenin signaling in general due to the presence of several good reviews and homepage on those molecules. In the second half of this review, we introduce our strategy, drug repositioning strategy, identifying multiple candidate drugs for therapeutic uses in the future.

ECM and Wnt/beta-catenin Signaling in OA

The ECM of the articular cartilage mainly consists of type II collagen (encoded by COL2A1 in human) and agree can (encoded by ACAN in human), which are synthesized in articular chondrocytes. A master transcriptional factor, SRY-box9 (SOX9 in human) is known to enhance gene expressions and the synthesis of ECM. Meanwhile, SOX9 decreases gene expressions of matrix metallo proteinases (MMPs) and a disinterring and metallo protease with thrombo spondin motifs (ADAMTSs), which catabolize ECM in the articular cartilage [6,7].

Wnt/beta-catenin signaling regulates crucial aspects of gene expressions and cell fates during embryogenesis [8,9]. And in aged and damaged adult tissues derived from mesenchymal stem cells (MSCs), e.g. in bone [10], muscle [11,12] and tendon [13]. In Wnt/beta-catenin signaling, when secreted Wnt ligands are absent, beta-catenin is steadily phosphorylated by casein kinase 1(CK1) and glycogen synthase kinase 3 (GSK3) in the degradation complex assembled by Axin1 and adenomatous polyposis coli (APC), and is subsequently degraded through the ubiquitin/proteasome pathway. Wnt ligands suppress the phosphorylation and degradation of beta-catenin. Consequently, beta-catenin is accumulated in the cytoplasm and then translocated into the nucleus to interact with the T-cell factor/lymphoid-enhancing factor (TCF/LEF) and activate expressions of Wnt/beta-catenin-target genes. In human OA, high serum levels of Frizzled-related protein (FRZB) and dick kopf 1 homolog (DKK1), which are secreted antagonists for Wnt ligands, are associated with the reduced risk of hip OA14.

In addition, gene variants of FRZB are risk factors for hip and knee OA [14,15]. An abnormal up regulation of genes encoding key molecules in Wnt/beta-catenin signaling is observed in the articular cartilage of rodent OA models [16,17]. Human OA-derived chondrocytes [18] and the degraded areas of human articular cartilage [19]. Functionally, Wnt/beta-catenin signaling is known to have inhibitory functions for mouse Sox9 proteins in mouse chondrocytes. Physiological binding of beta-catenin to Sox9 induces degradation of both proteins in chondrogenic cell line [20], which further leads to the reduction of Sox9 function and Wnt/beta-catenin signaling. Consistently, the chondrocyte specific beta-catenin inactivation mice have very similar phenotypes compared to those of chondrocyte specific Sox9 over expression transgenic mice [8,20,21]. Activation of Wnt/beta-catenin signaling is also related to the expression of MMP [13] one of collagenase depredating type II collagen, in mouse chondrocytes [22]. Lef1, a transcriptional activator for Wnt/beta-catenin signaling directly binds to Mmp13 promoter and induces its expression, while knock-down of Lef1 down-regulates IL-1b-mediated Mmp13 expressions [23]. Finally, gain of function and loss-of-function for factors of Wnt/beta-catenin signaling in

mouse knee is associated with OA pathology, demonstrating that Wnt/beta-catenin has negative effects for OA [24-27]. Although Wnt/beta-catenin signaling is one of the essential signaling pathways for cell proliferation and differentiation in other organs, including bone tissues of patients with osteoporosis, the down regulation of the signaling in chondrocytes is predicted to be beneficial in OA pathology.

Drug Repositioning Strategy for OA

Drug repositioning strategy, where by a drug already used for a specific disease is applied to another disease, has been gaining increasing attention from both the academia and industry. Especially, drug repositioning strategy has been advanced and modified to find anticancer drugs [28]. The advantage of this strategy is that the identified drugs can be readily applied to clinical practice, because the optimal doses, adverse effects, and contraindications are already established. Drug repositioning enables fast and cost-effective application of identified drugs.

In an effort to search for candidate drugs that can be potentially used for OA, we have targeted Wnt/beta-catenin signaling. Firstly, we started a screening 1,186 FDA-approved drugs, which activate human FRZB promoter in luciferase reporter assay in human chondro sarcoma. In this assay, we found verapamil [29], which

a. Enhances the activation of FRZB promoter,

b. Inhibits Wnt3a-induced Wnt/beta-catenin signaling,

c. Increases Sox9 expressions, (43) suppresses the degradation of ECM molecules in chondrocytes. And (54) has the potential to ameliorate OA in the rat model with destabilized medial meniscus (DMM).

Verapamil is an L-type calcium channel blocker that has long been used for hypertension, angina pectoris, cardiac arrhythmia, and most recently cluster headache. Since seven other calcium channel blockers (nifedipine, thioridazine, diltiazem, loperamide, perhexiline, nicardipine, felodipine) had no effect on Wnt/beta-signaling in human chondrosarcoma, the target of verapamil is not the calcium channel, but possibly Wnt/beta-catenin signaling in chondrocytes. These successful results encourage us to apply the drug repositioning strategyfor identifying a drug that targets another factor of Wnt/beta-catenin signaling. In the second screening, we used lithium chloride (LiCl), an inhibitor of GSK3, to activate Wnt/beta-catenin signaling at the level of intracellular factors, by using Wnt signaling-responsive TOPFLASH reporter. In 2017, we reported a second drug, fluoxetine [30]. Fluoxetine

a. Inhibits both Wnt3a- and LiCl-induced Wnt/beta-catenin signaling,

b. Increases Sox9 expression,

c. Suppresses the degradation of ECM molecules, and (34) ameliorates OA in the rat model with DMM.

In chondrocytes, fluoxetine blocks Wnt/beta-catenin signaling at the beta-catenin level by blocking the assembly of the degradation complex with GSK, CK1, and Axin1. Fluoxetine is an antidepressant drug in belonging to a class of selective serotonin reuptake inhibitors (SSRIs). In contrast to fluoxetine, none of the other SSRIs (paroxetine and fluvoxamine) suppresses Wnt/beta-catenin signaling in human chondrosarcoma, suggesting its possible role not as an SSRI, but as an inhibitor of Wnt/beta-catenin signaling. Altogether, with the drug repositioning strategy, we have identified novel drugs, that can inhibit Wnt/beta-catenin signaling and suppress OA progression in the rat model.

Conclusion

In conclusion, we propose that Wnt/beta-catenin signaling factors could be new therapeutic targets in OA. At present, the use of drugs, which block Wnt/beta-catenin signaling, in human OA cartilage remain in its infancy. However, we believe that studies on the mechanical function of candidate drugs in Wnt/beta-catenin signaling, which are determined by the use of the drug repositioning strategy, lay the foundation for the development of novel approaches for preventing the progression of human OA.

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