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Osteoarthritis (C Lozada, Section Editor)

Wnt Signaling in Osteoarthritis: a 2017 Update

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Opinion statement

Osteoarthritis is a progressive degenerative disease of the joints in which the articular cartilage within the joints deteriorates with associated juxta-articular bone formation. While the etiology of OA is still under investigation, preclinical studies have determined that the Wnt/β-catenin signaling and bone morphogenic signaling pathways are important for the formation and repair of the joint tissues, and the effects are on both the phenotype and function of the joint tissue cells. In addition, individuals with polymorphisms in the gene, FRZB, that codes for the wnt signaling protein secreted frizzled related protein 3 (sFRP3) have higher risk of developing OA. A number of proof-of-concept preclinical studies have been performed on inhibitors of the Wnt signaling pathway, and have altered the disease progression. Proof of concept studies assessing the regenerative capacity of mesenchymal stem cells as treatments for painful knee OA have reported both encouraging and discouraging results. Therefore, the identification of the molecular pathways that are responsible for joint formation and repair has led to the development of new novel interventions for the treatment of OA that are now entering clinical trials. The ability to slow or reverse the progression of osteoarthritis may soon be within our reach.

Introduction

Osteoarthritis (OA) is a progressive degenerative condition with effects on cartilage and bone; it is the most common chronic joint disease [1]. OA patients suffer from pain, decreased function, swelling, and lack of mobility in the affected joints. Risk factors for OA include obesity, history of joint trauma, aging, collagen mutations, and acetabular dysplasia. The therapeutic options for OA are currently limited to pain control and joint replacement surgery, but it is becoming increasingly important to find effective treatments as the occurrence of the disease accelerates with an increasingly obese and aging population [1, 2]. Research on the Wnt signaling pathway has provided improved understanding of OA development in the molecular level [3]. The Wnt pathway is a highly conserved signal transduction cascade with a central role in cartilage development and tissue homeostasis, and animal studies targeting the Wnt signaling pathway have shown the first promising results towards developing an OA treatment [4]. Rodents with OA exhibit different levels of Wnt proteins and Wnt gene expression than the controls, and modulation of the Wnt pathway induced OA in healthy animal models [4, 5]. These studies have elucidated the regulatory role of Wnt signaling in OA and prompted further research and clinical testing on drugs targeting components of the pathway. If researchers can determine the proper targets and successfully modulate the Wnt pathway, this may lead to potential therapies for OA. This paper highlights the major developments and potential emerging treatments with the focus on Wnt signaling pathway in OA during the last 5 years.

Research and development

A number of preclinical studies have investigated the presence of gene expression and the activity of the proteins synthesized from these genes in both normal and osteoarthritis joints. One group studied the expression of genes in cells harvested from regions of the synovial membrane from 12 patients with knee OA that appeared normal or were inflamed [12]. Eight hundred ninety-six genes which were differentially expressed in the two regions and some of the pathways involved were associated with cartilage metabolism, Wnt signaling, inflammation, and angiogenesis. In contrast to the unregulated Wnt-5a and low-density lipoprotein receptor-related protein 5 genes, the FZD2 gene and the gene for Dkk-3 were both downregulated [12].

Another paper investigated the association of common single-nucleotide polymorphisms (SNP) related to the Wnt pathway in knee and hip OA. Nine potential Wnt pathway-related genes (WNT1, WNT10A, WNT16, DVL2, FZD5, BCL9, SFRP1, TCF7L1, and SFRP4) were studied. Six hundred eighty control subjects and 606 patients having joint replacement surgery were analyzed for 78 SNPs. Once the statistically significantly associated SNPs were identified and genotyped in another cohort of OA patients and control subjects, they found some which showed association in the first cohort did not have the association confirmed in the replication study. In combined analysis, the odds ratio (OR) was 3.13 (1.34–7.28; $P = 0.009$), suggesting some SNPs related to the Wnt signaling pathway may affect genetic predisposition to OA in these joints [13].

Another group of researchers specifically studied the transcriptomes of cartilage from end-stage hip OA patients and normal subjects [14]. They provided the first whole-genome gene expression comparison between cartilage from human hip OA and control subjects (neck of femur—NOF). The team inspected nine femoral head cartilage samples from female OA donors and ten

cartilage samples from female NOF fracture donors; they confirmed the two samples to be significantly different through macroscopic scoring. Between the two sample groups, the researchres identified 71 canonical pathways in which there were 998 differentially expressed genes. Their differential gene expression dataset strongly resembled the results of similarly defined studies researching comparable tissue and potentially revealed differences between individual genes within hip and knee OA even though both types of OA involve common molecular pathways.

Studies looking at the role of specific proteins within the Wnt/β-catenin signaling pathway to determine the role they play in the pathogenesis of OA have also been done. Peng X et al. investigated the Wnt/β-catenin signaling using mesenchymal progenitor stem cells (MPCs) [15]. After MPCs were collected from femoral condyle OA patients, they were either stained using toluidine blue (TB) or immunostained using anti-collagen II or anti-aggrecan antibodies, trying to determine their chondrogenic differentiation capabilities. These OA-derived MPCs demonstrated lowered differentiation capabilities along with enhanced Wnt/β-catenin activity. In addition, in normal MPCs, inhibiting the Wnt/β-catenin signaling pathway increased proliferation and differentiation, whereas activating the pathway using rWnt3a protein led to decreases in the proliferation and differentiation. These data suggest Wnt/β-catenin signaling regulates p53 expression, and preventing the expression of the p53 gene increases the differentiation and proliferation of MPCs.

Van den Bosch MH et al. studied specific Wnt proteins expressed in the synovium and their potency to induce OA in 12-week-old male mice [16]. Wnt5a, Wnt8a, Wnt16, and WISP1 were used, with adenoviral vectors to get them to be overexpressed in the synovium, and then assessed if this overexpression led to OA pathology by histology. They found that overexpression of Wnt8a and Wnt16, but not Wnt5a, in the synovium activated canonical Wnt signaling in cartilage, which resulted in an increase in protease activity and cartilage damage. Using Dickkopf-1 to block canonical Wnt signaling decreased cartilage damage elicited with Wnt pathway signaling, yet no cartilage lesions were induced by the non-canonical signaling using Wnt5a. In addition, overexpression of a downstream canonical Wnt signaling protein, WISP1, also led to increased cartilage damage.

Papathanasiou I et al. [17] provided data regarding the role of BMP2 through canonical Wnt/β-catenin signaling to regulate hypertrophy of chondrocytes and various matrix metalloproteinase in OA. As they noted, during OA development, differentiation of normal terminal chondrocytes in the growth plate is also seen, and possibly pointing to Wnt and BMP (bone morphogenetic proteins) having a role in OA pathogenesis. LRP-5, BMPR-IA, BMP-2, BMP-4, and LEF-1 messenger RNA (mRNA) and protein expressions were upregulated in OA human articular chondrocytes compared to normals. Using BMP2 to treat cultured chondrocytes led to increasing β-catenin nuclear translocation and expression of LRP-5. Silencing of LRP-5 decreased nuclear β-catenin protein, MMP, and collagen X levels and increased phospho-β-catenin protein levels in chondrocytes treated with BMP-2. These data suggest Wnt/β-catenin signaling activation induced by BMP-2 and through LRP-5 potentially contributes to hypertrophy of chondrocytes and degradation of cartilage in OA.

Glycogen synthase kinase-3β (Gsk3β) has been shown to promote degradation of β-catenin to downregulate transduction of the canonical Wnt signal.

Miclea RL et al. investigated the role Gsk3β plays in cartilage preservation [18]. They used GIN (a selective Gsk3β inhibitor) and showed that this led to decreased chondrocyte proliferation and expression of cartilage biomarkers which later showed degradation of cartilage matrix and an increase in apoptosis, with resorption of the metatarsal joint of these E17.5 fetal mice with prolonged use.

Microarray analysis confirmed these changes, showing that expression of typical chondrocyte markers was decreased and increases in expression of cartilage matrix degradation proteinases. Additionally, intra-articular (IA) GIN injection into knee joints of rats led to nuclear β-catenin accumulation in chondrocytes in 72 h. Surface fibrillation, reduced glycosaminoglycan expression, and chondrocyte hypocellularity were seen 6 weeks later after three intra-articular GIN injections. These findings suggest that Gsk3β potentially preserves the chondrocytic phenotype by downregulating β-catenin and upregulation may induce in vivo OA-like features.

Abed E et al. looked into R-spondins, which act as Wnt agonists, investigating role of Rspo-1 and Rspo-2 in OA osteoblasts [19]. Rspo-1 expression was similar in OA and normal control osteoblasts; however, Rspo-2 production and expression were decreased in OA osteoblasts, potentially secondary to increased transforming growth factor β1. Reduced, as compared to normal osteoblasts, addition of recombinant human Rspo-2 corrected Wnt-3a-dependent TOPflash TCF/LEF luciferase reporter activity. In addition, adding Rspo-2 to OA osteoblasts led to correcting Wnt-3a-dependent β-catenin levels. Mineralization of OA osteoblasts was increased with Wnt-3a alone, and increases were further seen with Rspo-2. Reduced Wnt/β-catenin signaling and abnormal mineralization may also be due to reduced Rspo-2 levels in OA osteoblasts. Rspo-2, a secreted soluble protein, may be a potential new target for therapies for OA.

Fernandez et al. studied the potential for bone marrow-derived MSCs in articular cartilage repair by comparing these with chondrocytes from OA joints [20]. After subjecting both cell types to similar tissue engineering strategies, and 3 weeks of in vitro chondrogenic differentiation, similar levels of fibrocartilage-specific type I collagen mRNA and protein and hyaline cartilage-specific type II collagen were seen in both groups. However, in the OA chondrocyte extracellular matrix, aggrecan, the dominant proteoglycan in hyaline cartilage, was more. In addition, OA chondrocytes expressed increased mRNA levels of other hyaline extracellular matrix components. These results suggest a potential role for OA chondrocytes to be used in the treatment of OA.

Emerging therapies

Current therapy for OA is limited to symptom relief, mostly pain control with opioids, non-steroidal anti-inflammatory drugs, all with serious potential side effects, or hyaluronic acid derivates, which provide limited efficacy, all of which leads to joint replacement for many patients. However, in the last 5 years, extensive research on the pathogenesis of OA has provided potential therapeutic targets for the disease control (Table 1). Many potential targets and their inhibitors or agonists are already in clinical trials to better define their safety when used in an attempt to slow or stop OA progression and reduce joint pain [2].

Table 1. Clinical trials of MSC-based OA treatments

Patients/indications	Cell source	Dose/cells	Study methods	Outcome	Reference
4 patients with moderate to severe knee OA	Autologous bone marrow	(8–9) × 10^6	30 mL of bone marrow were taken from each patient and cultured for MSC growth. Cells were cultured and then injected in one knee of each patient.	The walking time before pain improved for 3 patients and remained unchanged for 1. The number of stairs they could climb and the pain on visual analog scale improved for all of them.	Davatchi et al. (2011) [6]
12 patients with knee OA	Autologous		infra-patellar fat pad	1.89 × 10^6	Stem cell
injections combined with arthroscopic debridement were administered to patients. Stem cells were prepared with approximately 3.0 mL of platelet-rich plasma (PRP) and injected in the selected knees of patients in the study group.	Although the		preoperative mean Lysholm, Tegner activity scale, and VAS scores of the study group were significantly poorer than those of the control group, the clinical results at the last follow-up visit were similar and not significantly different between the two groups.	Koh et al. (2012) [7]	
56 patients with unicompartmental knee OA	Autologous bone marrow	1.5 × 10^7	The cell-recipient group received intra-articular injection of cultured MSCs with hyaluronic acid 3 weeks after surgery and the control group only received hyaluronic acid.	The effect of treatment showed an added improvement of 7.65 (95% confidence interval [CI], 3.04 to 12.26; $P = 0.001$) for IKDC scores, 7.61 (95% CI, 1.44 to 13.79; $P = 0.016$) for Lysholm scores, and 0.64 (95% CI, 0.10 to 1.19; $P = 0.021$) for Tegner scores.	Wong et al. (2013) [8]

Table 1. (Continued)

Patients/indications	Cell source	Dose/cells	Study methods	Outcome	Reference
				Magnetic resonance imaging scans performed 1 year after surgical intervention showed significantly better MOCART scores for the cell-recipient group. The age-adjusted mean difference in MOCART score was 19.6 (95% CI, 10.5 to 28.6; $P < 0.001$).	
12 patients with chronic knee pain	Autologous bone marrow	4×10^7	Patients were treated with MSCs by intra-articular injection. Articular cartilage quality was assessed by quantitative magnetic resonance imaging T2 mapping.	Patients exhibited rapid and progressive improvement of algofunctional indices that approached 65 to 78% by 1 year. Measurements of cartilage quality by T2 relaxation demonstrated a highly significant decrease of poor cartilage areas (on average, 27%), with improvement of cartilage quality in 11 of the 12 patients.	Orozco et al. (2013) [9]
18 patients with knee OA	Autologous adipose	$(1–10) \times 10^7$	The phase I study consisted of 3 dose-escalation cohorts: the low-dose (1.0×10^7 cells), mid-dose (5.0×10^7), and high-dose (1.0×10^8)	The WOMAC score improved at 6 months after injection in the high-dose group. The size of cartilage defect decreased while the volume of cartilage	Jo et al. (2014) [10]

Table 1. (Continued)

Patients/indications	Cell source	Dose/cells	Study methods	Outcome	Reference
			groups with 3 patients each. The phase II included 9 patients receiving the high dose. The primary outcomes were the safety and the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) at 6 months. Secondary outcomes included clinical, radiological, arthroscopic, and histological evaluations.	increased in the medial femoral and tibial condyles of the high-dose group. Arthroscopy showed that the size of cartilage defect decreased in the medial femoral and medial tibial condyles of the high-dose group. Histology demonstrated thick, hyaline-like cartilage regeneration.	
55 patients with partial medial meniscectomy	Allogeneic bone marrow	5×10^7	A single superolateral knee injection was given within 7 to 10 days after the meniscectomy. Patients were randomized to 1 of 3 treatment groups: group A, in which patients received an injection of 50×10^6 allogeneic mesenchymal stem cells; group B, 150×10^6 allogeneic mesenchymal stem cells; and the control group, a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control.	There was significantly increased meniscal volume (defined a priori as a 15% threshold) determined by quantitative MRI in 24% of patients in group A and 6% in group B at 12 months post meniscectomy ($P = 0.022$). No patients in the control group met the 15% threshold for increased meniscal volume. Patients with osteoarthritic changes who received mesenchymal stem cells experienced a	Vangsness et al. (2014) [11]

Table 1. (Continued)

Patients/indications	Cell source	Dose/cells	Study methods	Outcome	Reference
				significant reduction in pain compared with those who received the control, on the basis of visual analog scale assessments.	

Funck-Brentano T et al. examined how inhibiting the Wnt/β-catenin in mouse OA of the knee models could affect cartilage [21]. They used meniscectomized transgenic and Topgal mice overexpressing Dkk-1 under the control of the 2.3-kb Col1a1 promoter (Col1a1-Dkk-1–Tg mice) as their OA model. In Topgal mice, Wnt pathway was activated in osteocytes in the subchondral bone as well as in osteophytes and synovium at weeks 6 and 4, respectively. Dkk-1expression was increased in control mouse chondrocytes but less in meniscectomized mouse knees. The OA score was decreased in meniscectomized Col1a1-Dkk-1-Tg mice compared with wild type, and in addition, subchondral bone fraction and osteophyte volumes were also decreased. Cartilage explants from Col1a1-Dkk-1-Tg mice showed proteoglycan loss and increased aggrecan C-terminal neoepitope (NITEGE) expression. In osteoblasts from Col1a1-Dkk-1-Tg mice, the expression of vascular endothelial growth factor (VEGF) was decreased, which led to decreased expression of mRNA for matrix metalloproteinases in chondrocytes. The results suggested that Wnt activation in OA affects the entire joint, not only the cartilage but also the bone. Inhibition of this pathway selectively in bone by Dkk-1 potentially can decrease OA severity by the way of inhibition of VEGF.

In another study, Weng LH et al. found increased expression of Dkk-1 in OA joints and OA severity and cartilage degradation marker correlation [22]. They used Dkk1 anti-sense oligonucleotide (Dkk1-AS) in animal models to see if attenuation of Dkk1 expression influenced OA development and found that this led to significant reduction in OA severity with Dkk1-AS treatment leading to a decrease in apoptosis of chondrocytes and osteoblasts, suggesting a potential path for development of therapies of OA.

Bouaziz W et al. looked into the role of sclerostin, a Wnt inhibitor that is produced by osteocytes and has a role in bone formation regulation, in a joint instability model using wild-type (WT) and SOST-knock out (KO) mice [23]. They found sclerostin expression in calcified cartilage of WT mice with OA and in SOST-KO mice, despite high bone volume, cartilage was found to be preserved. SOST-KO mice with destabilization of the medial meniscus had high OA scores, with increased expression of aggrecanases and type X collagen. In in vitro studies of primary chondrocytes, the addition of sclerostin, by inhibiting the canonical Wnt pathway, decreased Wnt3a-increased expression of a disintegrin and metalloproteinase with thrombospondin motifs, matrix

metalloproteinases, and type X collagen. In addition to these, sclerostin inhibited Wnt-phosphorylated c-Jun N-terminal kinase (JNK) with sclerostin treatment inhibiting both Wnt canonical and non-canonical JNK pathways in chondrocytes. These suggest that sclerostin potentially plays an important part for the maintenance of the integrity of cartilage in OA. Additionally, in another study, a changed level of Rho GTPases, recently found to modulate β-catenin nuclear translocation and control the transcription of β-catenin/TCF, was found and this may be useful as a new marker for OA development and may be a potential target for drug development [24].

Previous studies had suggested tetrandrine (Tet) may have an effect on OA through Wnt/β-catenin signaling [25, 26]. Zhou X et al. studied the protective effect of the Tet in OA, in vitro and in vivo [27]. Both in vitro and in vivo, increased expression of matrix metalloproteinase and 훽-catenin genes was noted with significant decreases in tissue inhibitor of metalloproteinase-1. Tet was able to reverse these changes, leading to decreased degradation of cartilage in vivo, assessed using macroscopic and histological observations, suggesting a potentially useful role for Tet in the therapy of OA.

Takamatsu A et al. looked for FDA-approved drugs which are known to induce FRZB (the gene which transcribes secreted frizzled-related protein-3 (sFRP3) which inhibits Wnt signaling) and decrease Wnt/b-catenin signaling [28]. Verapamil led to increased FRZB expression and suppression of signaling in the Wnt/훽-catenin pathway in chondrocytes from OA patients. Also, expression along with nuclear translocation of 훽-catenin was decreased in OA chondrocytes treated with verapamil, which also suppressed Wnt-responsive AXIN2 and MMP3 and increased gene expressions of chondrogenic markers of ACAN encoding aggrecan, COL2A1 encoding collagen type II a1, and SOX9. In a rat model, IA injection of verapamil showed inhibition of OA progression and nuclear localizations of 훽-catenin.

Conclusions

Wnt pathway has been consistently demonstrated to have a regulatory role in OA. Numerous studies targeting different steps along the Wnt/훽-catenin pathway have had varying success in animal models of OA and related cartilage degradation. These study results reveal that this pathway may be effective for the therapy of OA. However, additional studies are warranted to better understand osteoarthritic gene regulation, to determine the precise target to modulate within the complex pathway, and to expand current research into clinical trials. Increased knowledge regarding the origin and regulation of OA will help to identify novel targets for therapeutic intervention that may include Wnt modulation.

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Compliance with Ethical Standards

Conflict of Interest

Dr. Lane reports being a consultant for Samumed, outside the submitted work.
Dr. Yazici reports acting as Chief Medical Officer for Samumed, during the conduct of the study, and grants from Celgene, grants from BMS, and consulting for Novartis, outside the submitted work.
Dr. Baer and Dr. Corr have nothing to disclose.

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