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Review Paper

Exploring the Role of Wnt Signaling Pathway in Orthopedic Health and Disease: Mini-review

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ABSTRACT

The intricate orchestration of cell types and developmental processes in multicellular organisms hinges upon signaling pathways, such as Wnt, which play a pivotal role in embryonic development and adult tissue homeostasis. Over the past four decades, significant efforts have been made to elucidate the complexities of the Wnt signaling pathway and its diverse physiological functions. Wnt signaling has emerged as a crucial regulator in orthopedic contexts, particularly in fracture healing and osteoarthritis. This review delves into the intricate involvement of the Wnt pathway in these orthopedic conditions and explores its impact on bone formation, chondrogenesis, and joint pathologies. Moreover, it examines the therapeutic potential of targeting Wnt signaling in the treatment of osteoporosis, highlighting the promising avenues opened by advancements in understanding rare bone disorders, such as sclerosteosis and van Buchem disease. By elucidating the multifaceted roles of Wnt signaling in orthopedic health and disease, this review offers insights into potential therapeutic strategies to enhance fracture healing, mitigate osteoarthritis progression, and address bone-related disorders.

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Introduction

The evolution from unicellular to multicellular organisms signaled the dawn of intricate life forms. With multicellularity, orchestrating the creation and arrangement of diverse cell types during development ensures their sustained presence throughout an organism's lifespan. The Wnt pathway is one of the earliest signaling pathways to govern these vital physiological mechanisms [1, 2]. The Wnt signaling pathway operates as a communication cascade between cells, triggered by the presence of lipid-modified proteins from the Wnt family secreted by one cell. At its core, this pathway involves a Wnt ligand emitted by a secreting cell, which interacts with specific receptors on the surface of a receiving cell along with intracellular signal transducers. Once the ligand is recognized and the signal relayed inside the cell, activation of the pathway ensues, eliciting various cellular responses such as increased mitotic activity, determination of cell types, or establishment of cell polarity. These responses coordinate crucial developmental processes in organisms. Beyond development, Wnt signaling regulates tissue equilibrium and facilitates regeneration in adulthood [3, 4]. Over the 40 years since the initial discovery of the first Wnt gene, extensive research has revealed various components of the Wnt signaling pathway and elucidated their functions in many physiological contexts spanning the animal kingdom [5]. Additionally, researchers have explored the involvement of the Wnt signaling pathway in orthopedics, uncovering its relevance in certain orthopedic conditions. Further investigation of its role in this field is required [6, 7].

Components of the Wnt signaling pathway at the molecular level

Wnt proteins stem from various Wnt genes, among which Wnt1 is the pioneering member, initially discovered more than 30 years ago in murine models [8]. Mammalian genomes contain up to 19 distinct Wnt genes [8]. Genes within the Wnt family encode secreted growth factor proteins rich in cysteine, playing pivotal roles as signaling molecules [9]. Wnt proteins are transported into the extracellular space aided by Wntless proteins. Following secretion, they bind cell surface receptors on target cells [10]. Wnt proteins exhibiting these traits were classified as canonical, while those lacking these characteristics were categorized as non-canonical [11]. Canonical Wnts have been demonstrated to elevate cellular levels of the transcriptional coactivator β-catenin, thereby showcasing their transformative potential [12]. In contrast, non-canonical Wnt ligands activate alternative signaling pathways independently of β-catenin. These pathways involve different molecular mechanisms, such as releasing intracellular calcium and activating protein kinase C or c-Jun N-terminal kinase. The regulatory mechanisms governing the canonical Wnt/β-catenin pathway ensure that β-catenin levels remain low under non-activated conditions, preventing its accumulation and subsequent activation of downstream gene transcription. This tight regulation is essential for maintaining cellular homeostasis and preventing inappropriate pathway activation, which can lead to various diseases [13]. Under normal conditions, cytoplasmic β-catenin levels remain low without Wnt signaling. Activation of the Wnt/β-catenin pathway occurs when a Wnt ligand binds to a receptor from the Frizzled family, which is accompanied by the recruitment of co-receptor low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6). This ligand-receptor interaction triggers a cascade of intracellular signaling events that stabilize β-catenin. This prevents its degradation and allows it to accumulate in the cytoplasm where it can translocate to the nucleus and influence gene transcription. Activation of the Wnt/β-catenin pathway is crucial for various cellular processes, including cell proliferation, differentiation, and tissue homeostasis [13]. Given its critical role in development and tissue maintenance, it is unsurprising that a diverse array of modifiers regulates the β-catenin pathway activity. These regulators ensure that the pathway functions appropriately across different stages of cellular processes, such as cell proliferation, differentiation, and tissue homeostasis. Through this extensive network of controls, the β-catenin pathway can be precisely tuned to meet the organism's needs while preventing aberrant activation that could lead to diseases such as cancer or developmental disorders. These effectors can exert either promoting or antagonistic effects at different stages of the signaling cascade, highlighting the complexity of their regulation. This intricate control ensures that the pathway functions properly in various cellular processes, such as cell proliferation, differentiation, and tissue homeostasis while preventing aberrant activation that could lead to diseases like cancer. The diverse range of regulatory proteins underscores the pathway's dynamic and context-dependent nature. Usually, the canonical Wnt/β-catenin pathway is recognized for its osteoanabolic effects, as evidenced by the considerable osteoporotic bone characteristics observed in humans and mice with deficiencies in one or more elements of this signaling pathway [14-17].

The role of the Wnt signaling pathway in bone fracture repair

Bone tissue possesses the unique ability for scarless self-repair following injury. Nonetheless, the complex process of effective fracture healing depends on precise interactions between diverse cell types and signaling molecules. Any disturbance to this tightly orchestrated process can result in delayed healing or non-union formation [18]. Orthopedic patients may experience fracture healing complications at a reported rate of 5%–20% [19, 20]. Impaired bone healing can arise from various factors, including inadequate mechanical stabilization, infections, compromised blood supply, concurrent medical conditions, advanced age, hormonal imbalances, nutritional deficiencies, medication regimens, and genetic variations [21-23]. This pathway is essential for several critical functions, including embryonic bone development, maintenance of bone homeostasis, mechanotransduction in bone tissue, and bone regeneration. It orchestrates key processes that govern bone formation and growth during development while ensuring bone integrity throughout life. Furthermore, they are vital in sensing mechanical forces and facilitating bone repair and regeneration. Given its widespread influence on skeletal health, understanding this pathway offers valuable insights into potential therapeutic approaches for treating bone disorders and promoting the healing of bone injuries [24-27].

Osteoarthritis and Wnt

Osteoarthritis (OA) is the most widespread joint ailment, marked by deterioration of articular cartilage, irregular bone restructuring, and formation of osteophytes, culminating in chronic pain and limitations in joint function. Radiographic indications of OA are prevalent in most individuals by the age of 65 years, with approximately 80% of those aged >75 years experiencing its effects [28]. Numerous studies have documented the incidence of OA; however, the pathogenesis remains unclear. Degeneration of articular cartilage is a primary driver of pathological alterations in OA. Cartilage, being avascular, lacking nerves and lymphatics, and possessing viscoelastic properties, primarily bears loads and facilitates smooth joint movement [29]. Chondrocytes, the exclusive cell type found in adult articular cartilage, respond to structural changes, including alterations in collagen synthesis and degradation of the extracellular matrix [30, 31]. The primary components of articular cartilage are collagens, primarily type II collagen and aggrecan. Type II collagen provides structural support, contributing to the cartilage's tensile strength, while aggrecan, a large proteoglycan, is responsible for retaining water and maintaining the cartilage's compressive properties. Together, these molecules play a crucial role in maintaining articular cartilage's mechanical integrity and elasticity, which is essential for joint function [32, 33]. The degeneration of articular cartilage is thought to arise from an imbalance between synthesis and metabolic activity [34-37]. The influence of Wnt proteins on OA is evident through their effects on various bone-related processes, including bone formation, endochondral ossification, bone growth, repair, and joint development. These pathways regulate cellular mechanisms that maintain the integrity and function of bones and joints. Disruptions in Wnt signaling can contribute to the pathogenesis of OA by affecting these crucial processes. Understanding the role of Wnt in OA provides valuable insights into potential therapeutic targets aimed at modulating these pathways to slow disease progression and promote joint health [38]. Bone growth encompasses a complex sequence of chondrocytes events, including proliferation, migration, condensation, and adhesion [38, 39]. Wnt3a promotes chondrocyte hypertrophy and differentiation by activating the canonical Wnt signaling pathway. This activation plays a pivotal role in regulating cartilage development and maturation, suggesting that Wnt3a is a key player in cartilage biology and may have implications for understanding cartilage-related diseases and potential therapeutic strategies [40, 41]. Wnt5a activates the Wnt/β-catenin pathway, resulting in increased release of inflammatory mediators. This activation exacerbates cartilage damage, enhances inflammatory responses, and accelerates OA progression. These results suggest that Wnt5a significantly amplifies the inflammatory processes that drive OA pathogenesis, highlighting its potential as a therapeutic target for mitigating disease progression [42-45]. Wnt proteins, including Wnt7b and Wnt receptors, such as LRP and Wnt antagonists, are crucial in activating Wnt signaling pathways and regulating osteocyte maturation and bone growth. These molecules orchestrate key processes in bone development by modulating the differentiation and function of osteocytes, influencing bone formation, remodeling, and homeostasis. The dynamic interplay between Wnt proteins, their receptors, and antagonists is essential for maintaining bone health and may offer therapeutic targets for bone-related disorders [44, 45]. A previous study established a strong relationship between Wnt7b and inflammation in the articular cartilage, bone, and synovial tissues derived from patients with OA and RA. This connection underscores the potential role of Wnt7b in driving inflammatory processes in these tissues, offering insights into its possible involvement in the pathophysiology of both OA and RA [46-49]. Numerous investiga-

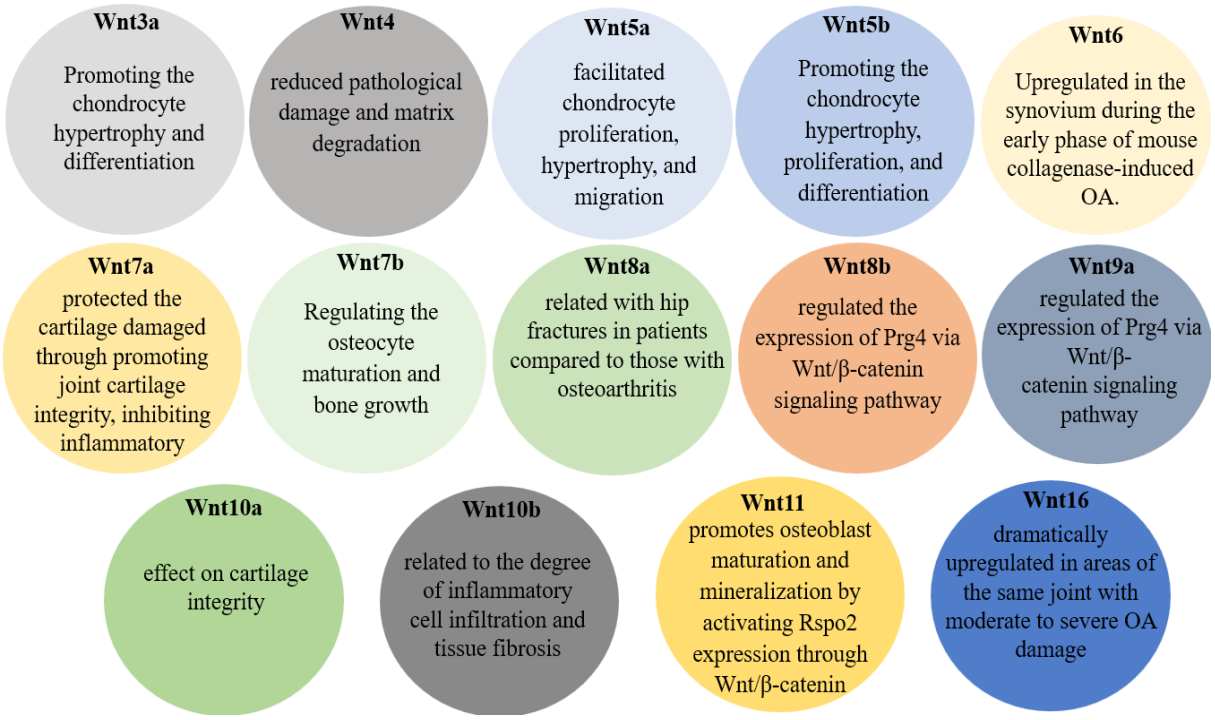

Figure 1. Role of Wnt members in OA
OA: Osteoarthritis.

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tions have suggested that most Wnt molecules can trigger both Wnt cascade and non-cascade pathways, consequently contributing to cartilage deterioration. However, Wnt16 is known to activate Wnt signaling and counteract the progression of cartilage degradation by regulating excessive Wnt activation [50-52]. It has been demonstrated that Wnt16 shows limited activation of β-catenin. Additionally, the study highlighted that increasing Wnt16 levels could slow disease progression by modulating the Wnt/β-catenin pathway in temporomandibular OA. This suggests that enhancing Wnt16 expression may provide a therapeutic approach for managing OA by influencing the key signaling mechanisms involved in its pathogenesis [53]. A substantial body of research investigating the role of Wnt molecules and their effects on OA has significantly advanced our understanding of Wnt biology. This growing body of knowledge has illuminated the complex mechanisms through which Wnt signaling contributes to OA pathogenesis, offering potential new avenues for therapeutic intervention to modulate these pathways to mitigate disease progression [54]. While numerous studies have emphasized the pivotal role of Wnt signaling in bone and joint formation, a considerable body of research has also suggested the potential benefits of inhibiting Wnt signaling and the associated pathways in managing OA. Thus, it is essential to regulate the biological activity of Wnt-related pathways in a balanced manner, given the complexity of these signaling networks in OA (Figure 1).

Rotator cuff tears (RCT) and Wnt

The RCT are prevalent musculotendinous injuries that often result in functional impairment and persistent pain in a significant proportion of affected individuals [55, 56]. Secondary muscle degeneration, characterized by phenomena, such as fatty infiltration, plays a crucial role in RCT [57]. Although surgical repair is the standard approach for treating ruptured rotator cuff tendons, it is often insufficient to prevent or reduce fatty infiltration in the surrounding skeletal muscle. This limitation suggests that while tendon repair may restore mechanical function, additional strategies may be necessary to address the underlying muscle degeneration and prevent further adipose tissue accumulation within the muscle [58, 59]. Progressive fatty degeneration of skeletal muscles substantially reduces elasticity and contractile strength, increasing the likelihood of tendon retear after surgical repair. This decline in muscle function compromises the stability and effectiveness of the repaired tendon, emphasizing the need for interventions that address tendon injury and prevent or reverse muscle degeneration to enhance long-term recovery outcomes [60, 61]. In large RCT, both the quantity of fibroadipogenic progenitors (FAPs) and their capacity for adipogenic differentiation tend to increase [62]. Moreover, previous studies have indicated that inhibitors of the platelet-derived growth factor receptor α (PDGFRα) pathway, such as imatinib, retinoic receptor agonists like

adapalene, and β-3 agonists, such as amibegron, can effectively inhibit the adipogenic differentiation of FAPs and alleviate fatty infiltration in cases of RCT [63, 64]. It is widely recognized that the AKT signaling pathway and Wnt5a/glycogen synthase kinase-3 beta (GSK3/β)-catenin pathway are critically involved in adipogenesis in FAPs. These pathways play a fundamental role in regulating the differentiation of FAPs into adipocytes, influencing various cellular processes, such as proliferation, differentiation, and the balance between adipogenesis and other mesenchymal lineage commitments. The intricate interactions between these signaling networks underscore their importance in maintaining tissue homeostasis and their potential as therapeutic targets for conditions related to adipose tissue accumulation or loss [65, 66]. The distinct roles of these pathways in FAPs following RCT remain an area of interest for further investigation. It is crucial to note that excessive fatty infiltration in muscle tissue tends to be less common and generally less severe following other tendon injuries, such as Achilles tendon tears. This contrast highlights the unique pathophysiological responses triggered by different types of tendon injuries. It suggests that the mechanisms involved in fatty infiltration may vary depending on the specific tendon and injury context [67, 68]. The observed disparity in fatty infiltration patterns between the rotator cuff and gastrocnemius muscle following tendon tears suggests that there may be distinct differences in FAPs between these two muscle groups. Further investigation into these potential differences could offer valuable insights into the mechanisms underlying fatty infiltration after tendon injuries [69-71]. According to research results, early treadmill exercise induces elevated levels of neuropeptide Y (NPY) at the site of rotator cuff healing, which could potentially suppress the expression of Wnt3a/β-catenin, thereby extending the duration of the healing process [72].

Osteoporosis and the role of the Wnt signaling pathway

Osteoporosis, a common bone disorder, is characterized by a significant reduction in bone mass, mineral density, and overall bone strength, leading to an elevated risk of fracture. This compromises the structural integrity of bones, making them more fragile and prone to breaking even under minimal stress or injury [73]. Wnt signaling plays a crucial role in bone development, regulating osteoblast differentiation, maturation, and maintaining normal bone homeostasis. Its activation can have dual effects in treating bone diseases, promoting bone formation under certain conditions while potentially exacerbating pathological bone remodeling in others. This duality underscores the complexity of Wnt signaling and highlights the need for precise modulation to optimize therapeutic outcomes [73, 74]. β-catenin knockdown leads to a significant increase in osteoclast numbers, driving enhanced bone resorption and substantially reducing bone mass. This process plays a critical role in the pathogenesis of osteoporosis, as the imbalance between bone resorption and formation ultimately compromises skeletal integrity [75]. Bone resorption inhibitors include bisphosphonates, estrogen, calcitonin, selective estrogen receptor modulators, and Wnt pathway inhibitors. Among these, dickkopf-1 (Dkk-1) is a key antagonist of the Wnt signaling pathway and plays a significant role in bone development and remodeling. Its mechanism involves the inhibition of Wnt signaling through competitive binding to the β-helix domain of LRP5/6 co-receptors, which prevents the activation of downstream signaling cascades. This modulation ultimately influences the transcription of Wnt target genes, impacting bone homeostasis by regulating the balance between bone formation and resorption [76, 77]. Additionally, patients experiencing disuse bone loss due to prolonged bed rest showed significantly elevated serum levels of Dkk-1 and diminished β-catenin expression. These changes are associated with reduced bone formation and increased bone resorption, highlighting the critical role of Wnt signaling dysregulation in the pathophysiology of bone loss under such conditions [78]. These studies highlight that increased Dkk-1 levels can inhibit osteoblast function and disrupt bone formation. Therefore, targeting Dkk-1 expression in bone tissue is a promising therapeutic approach for osteoporosis, aiming to restore the balance between bone resorption and formation, thereby enhancing bone health [79, 80].

Sclerosteosis and Van Buchem disease and Wnt

Skeletal dysplasia is a broad group of genetic disorders resulting from defects in critical pathways and genes involved in bone growth, differentiation, and mineralization. These disorders are characterized by abnormalities in several essential signaling pathways that play pivotal roles in bone biology. Key implicated pathways include Wnt signaling, NOTCH signaling, fibroblast growth factor signaling, and Hedgehog signaling. These pathways regulate various cellular processes, such as osteoblast differentiation, cell cycle regulation, and maintaining the balance between bone formation and resorption. Disruptions in any of these pathways can lead to a wide range of disorders with clinical manifestations that vary depending on the specific genes involved and the severity of the dysfunction [81-83]. Sclerosteosis and van Buchem disease are autosomal recessive skeletal dysplasia characterized by a deficiency in sclerostin protein, leading

to progressive skeletal overgrowth [84]. Sclerosteosis predominantly manifests among the progeny of Dutch colonists who arrived in South Africa during the seventeenth century. Van Buchem disease predominantly occurs in the Dutch population residing in the Netherlands [85, 86]. The skeletal features observed in both sclerosteosis and van Buchem disease share similarities, such as heightened skull thickening, jawbones, long bones, and ribs [84, 87, 88]. Although mature osteoblasts produce sclerostin to some extent, osteocytes are the primary source of sclerostin [89]. The Wnt/β-catenin signaling pathway activates osteogenic differentiation and supports bone formation [90]. Sclerostin, a potent inhibitor of the Wnt pathway, modulates osteogenic differentiation of precursor cells and impacts bone formation [91]. In contrast, suppression of the Wnt pathway results in upregulation of receptor activator of nuclear factor-κB ligand (RANKL) and dysregulation of osteoprotegerin (OPG), ultimately leading to the promotion of osteoclastogenesis [38]. Investigations into rare bone disorders, such as sclerosteosis and van Buchem disease, have revealed the critical role of sclerostin in maintaining bone homeostasis [92]. In cases of sclerostin deficiency, osteocytes lose their ability to regulate new bone deposition by osteoblasts, akin to a snake without fangs [93]. Since both conditions arise from genetic mutations resulting in osteocytic sclerostin deficiency, directing therapeutic interventions toward the osteocyte could represent a promising approach for treating these diseases.

Conclusion

In conclusion, the Wnt signaling pathway is a pivotal regulator of numerous facets of musculoskeletal biology, influencing everything from development and homeostasis to pathological conditions, such as osteoarthritis, fracture healing, rotator cuff tears, and osteoporosis. This review highlights the complex interactions between Wnt signaling and critical cellular processes that govern bone and joint health, emphasizing its essential role in maintaining musculoskeletal integrity. Understanding these mechanisms offers valuable insights into potential therapeutic strategies for treating musculoskeletal disorders and enhancing tissue repair and regeneration.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and supervision: Morteza Nakhaei Amroodi, and Pouria Tabrizian; Methodology: Mojtaba BaniAsadi, and Saeedreza Amiri; Resources and data curation: Saeedreza Amiri, and Mansour Krimi; Visualization: Mansour Krimi, and Pouria Tabrizian; Project administration: Morteza Nakhaei Amroodi; Validation and formal analysis: Khatere Mokhtari, and Mojtaba BaniAsadi; Investigation, and writing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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