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Review Article

The role of Wnt signaling on Tooth Extraction Wound Healing: Narrative review

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ABSTRACT

Compared to an incisional skin or mucosal wound, a tooth extraction wound results in far more soft tissue loss. A blood clot instantly fills the gap left by the extracted tooth. An embryonic type of bone forms during the healing of extraction wounds, and mature bone only later replaces it. Osteocytes in embryonic bone, also known as coarse fibrillar bone or immature bone, differ from those in adult bone in terms of number, size, and irregular arrangement. This immature bone is more radiolucent than mature bone due to the higher cell density and the smaller volume of calcified intercellular material. The Wnt gene family contains genes that encode secreted signaling proteins that have good promise for promoting bone regeneration. However, we still have a limited understanding the interplay of the molecular elements of the Wnt pathway in signal transduction, from ligand detection on the cell surface to transcription of target genes in the nucleus. We discuss the function of Wnt signaling molecules in this review, in tissue repair following tooth extraction and present recent results about these molecules. Conclusions: Wnt signaling activity helps to hasten bone regeneration while bone healing is slowed down by mutations in LRP5/6 or β-catenin.

1. Introduction

When compared to an incisional skin or mucosal wound, a tooth extraction wound results in far more soft tissue loss. Nevertheless, the mending procedure makes use of the same fundamental mechanisms. A blood clot instantly fills the gap left by the extracted tooth. The clot may occasionally become dislodged; if this occurs, an infection may enter and cause a painful inflammation of the socket's bony lining, known as a dry socket. Around 10 days, the socket becomes epithelized as the socket rim's epithelial cells proliferate and move through the clot. The inflammatory reaction occurs within the clot, first engaging neutrophils and subsequently macrophages. The proliferative and synthesizing phase is different from that of soft tissues because the cells encroaching on the clot are not fibroblasts, but rather osteogenic potential cells from the nearby bone marrow. These cells start to make bone once they are within the clot. Intramembranous and endochondral ossification are the two ossification methods used to regenerate bone. As a result of intramembranous ossification, which repairs tooth extraction sockets, accurate clarification of the molecular alterations in various stages of bone healing is necessary to comprehend these occurrences. An embryonic type of bone forms during the healing of extraction wounds, and mature bone only later replaces it. Osteocytes in embryonic bone, also known as coarse fibrillar bone or immature bone, differ from those in adult bone in terms of number, size, and irregular arrangement. This immature bone is more radiolucent than mature bone due to the higher cell density and the smaller volume of calcified intercellular material. This explains why a socket after an extraction incision seems to be empty at a time when it is almost filled with sponge bone and why bony callus cannot be seen in radiographs (Nanci, 2018; Ito et al., 2022; Horibe et al., 2021; Kumar, 2015) (See Fig. 1).

Polypeptide growth factors promote new connective tissue and bone in accordance with our understanding of the molecular mechanisms

Abbreviations: Wnt, Wingless-related integration site; GFs, Growth Factors; Dkk1, Dickkopf-related protein 1); HIF-1α, hypoxia-inducible factor-1α; Lef1, lymphoid enhancer-binding factor 1; Tcf1, The transcription factor T cell factor 1 ; Sfrps, Secreted Frizzled-related proteins; GSK3, Glycogen synthase kinase 3; ALP, Alkaline phosphatase; LiCl, Lithium chloride; BMP, Bone Morphogenetic Protein; MSCs, Mesenchymal stem cells.

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underlying bone regeneration. EGF, FGF, insulin-like growth factor, PDGF, TGF, platelet-rich and poor plasma, are a few growth factors that have been researched thus far. The Wnt (Wingless-related integration site) gene family contains genes that encode secreted signaling proteins that have good promise for promoting bone regeneration (Nanci, 2018; Kumar, 2015).

Small secreted glycoproteins known as Wnt molecules control a wide range of extracellular functions, including bone regeneration, stemness, patterning, growth, and cancer. The Wnt signaling system is extremely intricate and has undergone little change throughout evolution. The Wnt pathway is an intricate complex of targets and chemical mediators. Mammals have so far been found to have 19 different Wnt, 10 frizzled receptors (FZD). The canonical pathway, recognized as the β-catenin pathway, and the β-catenin independent pathway, also recognized as the non-canonical pathway, make up the Wnt signaling apparatus. The canonical Wnt signaling encourages the cytoplasmic production of the protein b-catenin, which is necessary to ensure metabolic balance and fetal maturity. The noncanonical pathway will affect tissue patterning, among other things, by influencing cell polarity and mobility. However, we still have a limited understanding how the Wnt pathway's molecular components mechanism to transduce the signal, the detection of ligands from the transcription of target genes in the nucleus to the cell surface (Pereira et al., 2009; Jridi et al., 2020).

In this narrative review, we examine the role of Wnt signaling molecules in tissue repair following tooth extraction and recent results about these molecules.

2. Methods

A review of the relevant scientific literature of Wnt Signaling on Tooth Extraction Wound Healing was carried out on Google Scholar and PubMed. Articles that discussed or looked into the effects were found in the search results, Wnt Signaling have on Tooth Extraction Wound Healing. The cited papers from the journals were additionally assessed for relevance and included if they matched the criteria. One of the requirements for admission was having access to the whole document (Table 1).

Table 1
Research Methods and Selection Criteria.

	Research Methods
A	PubMed and Google Scholar were used to search the literature for investigations on Wnt signaling and bone healing. The combinations served as search strategies. ("name of Wnt Signaling" + "Tooth Extraction Wound Healing") of the terms: "Wnt signaling", "β-catenin", "HIF-1",, combined with "Tooth Extraction Wound Healing", "soft tissue healing", " bone healing or repair". According to the criteria for inclusion, the papers were evaluated between January 1 of 2000 and September 30, 2023, in English.
B	- English; January 1, 2000–September 30, 2023 publication span. The publications included reviews, book chapters, original research papers, in vitro experiments, in vivo animal or human studies, and clinical trials. - Articles lacking complete texts, case studies, papers with irrelevant or worthless data, and non-English articles were removed.

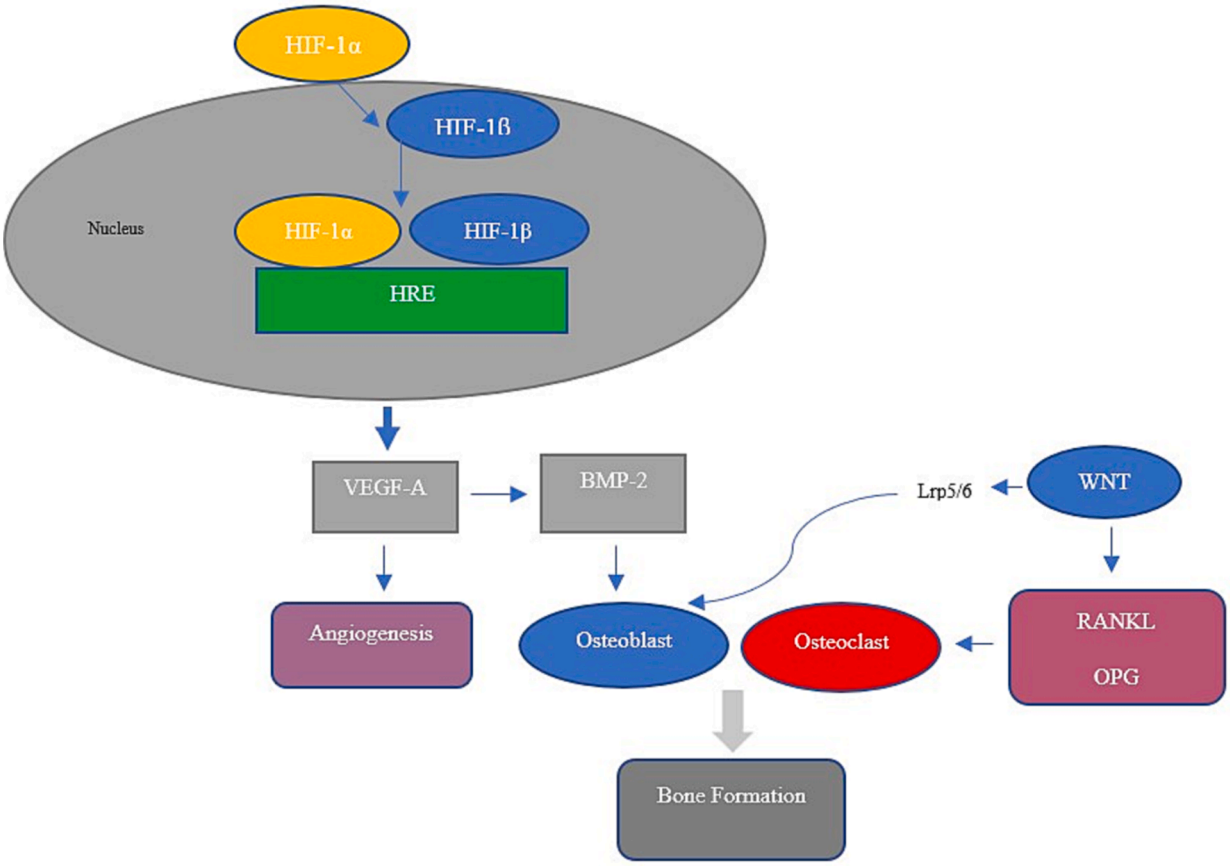

Fig. 1. HIF-1 directly controls the genes involved in the healing process, increases the expression of VEGF-A, a key component of angiogenesis, and promotes BMP-2 production. Osteoclasts (red) are hematopoietic cells play a role in bone resorption. One of the main roles of Wnt signaling in osteoblasts is to reduce RANKL and boost OPG synthesis, which prevents the creation of osteoclasts. When Wnt attaches to the Lrp5/6 and Frizzled receptor complex, Wnt/b-catenin signaling is then activated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.1. Roles of Wnt signals in inflammatory stage

Following tissue damage in inflammatory stage, platelets aggregate at the site of the wound to create a clot that attracts cells to repair the damage and acts as an archive for growth factors (GFs) that stop pathogens from invading. According to the study, β-catenin-dependent Wnt signaling inhibits platelet aggregation; nevertheless, it is still unclear how Wnt signaling directly affects platelet control during the initial stages of in vivo wound healing (Midwood et al., 2004; Nurden et al., 2008; Steele et al., 2009).

Neutrophils, monocytes, and lymphocytes penetrate the area of wounds within hours of injury in an effort to release cytokines and GFs after phagocytosing cell debris. This is the beginning of the inflammatory response. The inflammatory reaction is essential for battling an infection, but in chronic inflammation, it is generally thought to be harmful to both the healing of soft tissue and the regeneration of hard tissue (Martin and Leibovich, 2005; Newton et al., 2004).

What roles Wnt signaling plays in the inflammatory response is unknown. Oxygen tension is one possible reason. When exposed to hypoxia, embryonic stem cells create hypoxia-inducible factor-1α (HIF-1α), which controls the expression of Wnt genes in lymphoid enhancer-binding factor 1(Lef1) and the transcription factor T cell factor 1 (Tcf1). Changes in HIF-1α activity could be the direct cause of the activation of the Wnt pathway after injury (Mazumdar et al., 2010).

HIF-1 is divided into 2 subunits, HIF-1α and HIF-1β, and is only functional as a heterodimer. The essential transcription factor known as HIF-1 controls adaptive responses to hypoxia. Oxygen-dependent hydroxylases that target crucial proline and asparaginyl residues control HIF-1′s stability and functionality. HIF-1α protein levels rise exponentially as oxygen concentrations drop. As a result of the decrease of PHDs and FIH as well as the lower oxygen cofactor presence in hypoxic circumstances, HIF-1α degradation is constrained. The phosphorylation of stabilized HIF-1 then causes it to become active, enabling dimerization of HIF-1. Together with transcriptional coactivators p300 and CBP, The *cis*-acting hypoxia regulatory element in the promoter region of HIF-1 genes is where the active transcription factor attaches after moving there from the cytoplasm to the nucleus (Elson et al., 2000; Kelly, 2003; Li, 2007; Hong et al., 2014; Lisy and Peet, 2008; Coleman and Ratcliffe, 2009; Semenza, 2011).

2.2. Roles of Wnt signals in proliferative stage

The proliferative phase forms within days or months of an injury, and it is during this time that the distinction between repair and regeneration is most pronounced. Granulation tissue, which is produced by highly proliferative fibroblasts and new blood vessels at the wound site during the repair process and produces fibronectin, collagen III, glycosaminoglycans, glycoprotein and proteoglycans, accumulates at the site of the injury. While cell migration seems to be supported by this matrix, it is only temporary. Granulation tissue is replaced by a matrix rich in collagen type III, which gives the wound site tensile strength. The extracellular matrix's hyaluronan content is significantly higher throughout the regeneration program, and researchers hypothesize that this may limit or lessen the amount of collagen that overactive fibroblasts deposit at the wound site. Researchers have provided evidence to support this notion, demonstrating that hyaluronan removal causes fibrotic scarring and that Wnt3a induces hyaluronan production (Carre et al., 2010; Larson et al., 2010).

MSCs are differentiated into osteoblastic by WNT3A ligand both through the canonical Wnt pathway and the noncanonical Wnt/Protein kinase C pathway. Additionally it might stop mature and immature osteoblastic cells from going through the methods of programmed cell death (Tu et al., 2007; Jullien et al., 2012).

2.3. Roles of Wnt signals in maturation stage

Bone repair is a dynamic, intricate process that is closely regulated by a number of cellular signaling pathways and a number of substances that are expressed in concentration dependent manner. The most crucial signaling channels involved in bone regeneration is the Wnt pathway. This pathway, which is expressed in the primary osteoblast, osteoclast, and osteocyte cell types in bone tissue, has been demonstrated to influence skeletal metabolism. Additionally, it has been demonstrated that early bone regeneration at the fracture site upregulates the Wnt pathway (Xu et al., 2014; Khoswanto, 2020).

Numerous Wnt ligands are expressed more frequently throughout the repair process during bone healing. Connexin 43 and c-myc are two additional Wnt pathway target proteins that are activated. According to these findings, Wnt signaling controls the bone proliferation during the repair process (Chen et al., 2007; Zhong et al., 2006).

Wnt signaling in bone formation has been extensively studied, either by utilizing genetically modified mouse models or researching human disorders that damage the skeleton. Additionally, multiple cell types, including osteoblasts, osteoclasts, and osteocytes, may interact during this Wnt-mediated bone production process, frequently communicating with one another. Given the complexity of the system and the close proximity of these many cells within the bone tissue, it is still unclear which cells are responsible for the formation and reacting to the various Wnt stimuli (Nanci, 2018; Xu et al., 2014).

Wnt signaling is necessary for maintaining bone mass throughout life. In active osteoblasts, the Wnt signaling pathway is still important, and it appears to be crucial in osteoclast regulation development. Deletion of β-catenin in osteoblasts led to decreased bone mass and a discernible increase in osteoclastogenesis, in contrast to similar conditions, continuous activation of β-catenin markedly boosted bone deposition with a decrease in osteoclast production (Glass et al., 2005; Regard et al., 2012).

Numerous investigations have demonstrated that β-catenin is activated at fracture sites. Throughout the process, the β-catenin protein is extensively expressed in bone injury repair, as demonstrated by Chen et al. (2007) They discovered during the initial stages of wound healing, β-catenin regulates osteoblasts develop from mesenchymal cells through differentiation using loss and gain of function methods. Early bone repair is hampered by either an increase or a decrease in β-catenin. β-catenin encourages the differentiation of osteoblasts into the bone and increases bone repair in the latter phases when cells have committed to becoming osteoblasts (Chen et al., 2007; Leucht et al., 2008; Macsai et al., 2012).

Although Wnt signaling plays significant functions in osteoblasts, it also directly affects osteoclasts. Osteoclast differentiation is prevented by Wnt/b-catenin signaling because it reduces RANKL signaling. β-catenin heterozygous mice had increased osteoclast differentiation, however β-catenin in osteoclast precursors is stabilized, can reduces osteoclast differentiation. In osteoblasts, at least three genes are expressed, including Opg, RANKL and M−CSF to control osteoclast differentiation. By means of interactions with RANK, a receptor expressed on the surface of osteoclast precursors, RANKL, which is expressed on the surface of osteoblasts, encourages the maturation of osteoclasts. Opg is a secreted RANKL receptor that blocks the RANKL-RANK connection to prevent osteoclastogenesis. Expression of RANKL or Opg can both be regulated by Wnt signaling (Khoswanto, 2020; Modarresi et al., 2009; Wei et al., 2011; Holmen et al., 2004).

The activity of the Wnt signaling pathway is closely controlled by secreted antagonists, which is Dickkopf-related protein 1 (Dkk1) also essential for bone healing. Dkk1 interferes with the Wnt signaling pathway by forming a complex with Low-density lipoprotein receptor-related protein 5 (Lrp5) and Low-density lipoprotein receptor-related protein 6 (Lrp6). Mice with the Dkk1 gene deletion had more bone mass without altering the rate of bone resorption. Dkk1 adenoviral expression successfully inhibited osteoprogenitor cell differentiation

and stopped bone growth at the site of damage. Additionally, Dkk1 therapy increased the number of undifferentiated tissues that resembled mesenchymal tissues and decreased chondrogenic differentiation at fracture sites. Only when administered on the first day following surgery, rather than four days later, Dkk1 antibodies significantly enhance fracture repair. Dkk1 inhibition promoted healing and produced mechanically stronger bone at the wound site (Komatsu et al., 2010; Morvan et al., 2006; Li et al., 2011; Ross and Pawlina, 2016).

Another Wnt antagonist that is secreted, called Sost is only expressed in osteocytes, and when it is overexpressed in bone, it lowers the number of osteoblasts and bone production. Sost inhibits the development of the Wnt-LRP complex by attaching to the extracellular of LRP5/LRP6. BMD and bone growth were all enhanced in Sost knockout mice. Additionally, these animals have greater abnormalities in bone healing as a result of increased osteoblast counts and trabecularized spicule thickness. In vivo research has demonstrated that systemic treatment of Sost antibodies dramatically improved bone growth at the site of bone injuries in mice, rats, and cynomolgus monkeys, among other animal models (Winkler et al., 2003; McGee-Lawrence et al., 2013; Li et al., 2011; Sarahrudi et al., 2012).

Secreted Frizzled-related proteins (Sfrps) are Wnt pathway antagonists that bind Wnt ligands and are crucial for bone formation. Sfrp1 directly opposes canonical Wnt signaling by interacting with Fzd or Wnts. The enhancement of β-catenin expression, sfrp expression rises in Wnt-dependent early bone development. Increased bone volume and mineral have been seen in the trabecular of Sfrp1-deficient animals, but not in the cortical area. Sfrps expression has significantly decreased 4 days after bone injuries, according on a microarray expression analysis. When sfrp1 function is lost in vivo, early bone union is encouraged by a direct switch of progenitor cells towards the osteoblast lineage. At day 14 following bone injuries, the sfrp1/- mice displayed a marked reduction in the cartilage callus and an increase in intramembranous bone. Additionally, compared to wild-type mice, these mice showed earlier bone remodeling over the course of fracture repair process (Kawano and Kypta, 2003; Bodine et al., 2004).

Another significant intracellular negative regulator of the pathway bone remodelling is Gsk3b. With the aid of GSK-3 inhibitors, the role of GSK-3 during bone healing has been studied. Lithium chloride (LiCl), a well-known GSK-3 inhibitor, can increase Wnt signaling and quicken fracture healing. However, this impact only materialized after mesenchymal cells committed to becoming osteoblasts late in the process of healing. Undifferentiated mesenchymal cells gather during early lithium treatment prior to the bone injuries (Phiel and Klein, 2001).

3. Discussion

When an alveolar bone suffers an injury, a series of actions are initiated, the first of which is to stop the bleeding. An attempt is then made to isolate the wounded tissues from the other part of the body in order to preserve homeostasis. Within minutes of tissue injury, there is a vascular response that is mostly a result of the hypoxic state that happens in tissues without a circulatory supply. One of the first molecular reactions to injury seems to be the stimulation of b-catenin-dependent Wnt signaling. Typically, this activation occurs quickly and is mostly localized to the damaged area (Whyte et al., 2012).

Based on the discovery that system inhibitors boost the expression of genes associated with inflammation, β-catenin-dependent Wnt signaling may prevent or restrict the inflammatory response. The discovery that the resorbing phenotype seen in a mouse model of arthritis, osteoarthritis' bone forming might take its place by increasing Wnt signaling through inhibition of Dkk1 has led to a more direct connection. The finding that osteolytic lesions are connected to unrestrained Dkk1 activity lends more credence to the idea that a decrease in Wnt signaling results in bone loss. However, it is important to note these Wnt signaling consequences are primarily due to a proosteogenic influence rather than because Wnt signaling directly affects inflammatory mediators (Kim et al., 2010; Baker-LePain et al., 2011; Tian et al., 2003).

During osteoblast differentiation, mesenchymal cells in the Wnt and BMP pathway interact. BMP-2 suppresses Alkaline phosphatase (ALP), but the Wnt system directly regulates the upregulation of ALP induction in mesenchymal cells. For example, BMP-2 can stimulate osteogenic cell differentiation, whereas β-catenin has no effect or inhibits the mechanism. The coordinated role of SMAD1/4 and β-catenin in mesenchymal cell differentiation gene expression. It has been demonstrated that the loss of the BMP receptor type 1a gene osteoblastic cells prevents the expression of several metabolic Wnt genes in the cortex and results in an overexpressed Wnt7b gene, which effectively corrects the deficiency in periosteum growth (Fischer et al., 2002; Bain et al., 2003; Avery, 2013; He et al., 2017; Song et al., 2021; Rim et al., 2022).

Bone resorption and bone growth must be balanced and can be controlled by osteoclasts and osteoblasts through endocrine and autocrine mechanisms, and they are crucial in regulating bone metabolism. The canonical Wnt signaling pathway influences the growth and differentiation of MSCs, osteoblast, and osteoclasts, contributing to bone healing and have a crucial role in maintaining bone homeostasis (Liu et al., 2022).

During bone remodelling, Wnt signaling interacts with inflammatory signaling mechanisms. The significance of TNF is proven to activate the endogenous regulator Dkk-1 osteoblast differentiation by inhibiting the activity of Wnt signaling. TNF overexpression in mice results in joint degeneration deterioration that goes unaccompanied by adequate bone healing. Nevertheless, neutralizing Dkk-1 and anti-Dkk-1 antibodies prevented joint deterioration in TNF transgenic mice and caused the growth of bone, indicating dynamic bone repair. In other words, it's the body's delicate balance between bone formation and bone resorption that keeps there interference between the Wnt signaling and the process of inflammation brought on by TNF (Heiland et al., 2010; Diarra et al., 2007).

4. Conclusions and future outlook

Wnt signaling contributes to the acceleration of bone regeneration, while mutations in β-catenin or LRP5/6 slow down bone healing. Additionally, inhibiting the Wnt signaling pathway's negative regulators, such as GSK-3 and Sost, can enhance bone growth. The Wnt signaling system has emerged as a viable target for the creation of novel medicines that increase bone formation. This could be an interesting target for bone healing after tooth extraction and guided bone regeneration in the future.

Authors' contributions

CK developed the research concepts and designed the study. CK and IRK revise and edit the manuscripts.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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