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The Role of Bone Morphogenetic Protein-2 On Bone Formation In Mesenchymal Stem Cells and Its Current Application

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Abstract

An important growth factor found in bone remodelling and repair regulation is bone morphogenetic protein-2 (BMP-2). It plays a significant role in the osteogenic differentiation of mesenchymal stem cells (MSCs), which are multipotent stromal cells capable of differentiating into various cell types, including osteoblasts. The therapeutic application of BMP-2 in tooth regeneration has shown promising results, particularly in orthopedic and dental fields. The purpose of this research is to determine how BMP-2 influences MSCs' osteogenic differentiation and to investigate its possible therapeutic uses in regenerative medicine and bone tissue engineering. The results showed that BMP-2 greatly improves MSCs' osteogenic differentiation. The mineralization of MSCs treated with BMP-2 was shown to be greater than that of control cells on in vitro studies. Animal models on in vivo investigations showed that BMP-2 enhances bone repair and increases bone growth. Patients with critical-sized bone defects have been shown to benefit from BMP-2's ability to enhance bone regeneration in clinical studies. As a powerful osteogenesis inducer in MSCs, BMP-2 is an important component of bone engineering. Significant therapeutic implications arise from its capacity to improve bone growth and repair, especially in relation to the treatment of bone defects. Future research should focus on optimizing BMP-2 delivery methods and exploring its synergistic effects with other osteogenic factors to maximize its therapeutic potential.

Keywords: Bone morphogenetic protein; mesenchymal stem cells; osteoblast; osteogenesis; bone remodeling

1. Introduction

In vertebrates, bone serves as a mineralized connective tissue that enables movement, supports body weight, protects internal organs from external forces, and maintains mineral homeostasis. During embryonic and early postnatal development, as well as during puberty, bone mass rises substantially. Human bone mass reaches its maximum around age 20 and remains constant throughout life. Fractures occur when the mass of the skeleton or a single bone suddenly decreases, highlighting how crucial it is to maintain bone mass.[1] Bone disease can arise from an imbalance in the process of bone remodeling, which occurs continually throughout life.[2]

In the process of maintaining bone homeostasis, cells called osteoblasts and osteoclasts work together to keep bone strong and healthy. Bone resorption is facilitated by osteoclasts, whereas bone formation is facilitated by osteoblasts. To keep bone mass constant, it is essential to regulate the influx, maturation, and specialisation of these cells.[1, 2] Resorption and formation are steady under physiological circumstances. When the equilibrium is disrupted, bone architecture and function become aberrant, leading to metabolic bone illnesses such as osteoporosis, osteomalacia, and periodontal infections, which hinder fracture repair.[3]

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Numerous cytokines, hormones, and signaling pathways are implicated in bone remodeling. The molecular mechanisms underlying cellular communication between osteoblasts and osteoclasts represent a fundamental aspect of bone cell biology.[3] An important part of bone metabolism and growth secreted from osteoblats is bone morphogenetic proteins (BMPs).[4, 5] Additionally, BMPs are involved in the processes of apoptosis, chondrogenesis, adipogenesis, and nervous system maintenance.[6]

As an activator for osteoblast and haematopoietic differentiation in addition to bone production, bone morphogenetic protein-2 (BMP-2) the most powerful osteoinduction potential among BMP subtypes.[4, 7] As a multifunctional growth factor, BMP-2 was discovered in the 1965 by Marshall Uris and be a necessary chemical for adult animals bone growth.[6, 8]

In research on bone graft transplantation, the release of BMP-2 by mesenchymal cells is essential for starting the healing of fractures, bone, and chondrogenic growth.[9] BMP-2 might serve as a base for tissue engineering in bone construction.[5] This narrative review seeks to evaluate the function of BMP-2 in preserving bone homeostasis.

2. Literature review

2.1. The Process of Bone Remodelling

Bone possesses significant regeneration capabilities, and during fracture reconstruction, ontogenetic processes of skeletal development continue in healing injured skeletal. Numerous growth hormones, different cells, and extracellular matrix interact dynamically to regulate this regenerative process, which includes both anabolic and catabolic activities. A hematoma forms once inflammatory cells invade the injured tissue after fracture. Following this, mesenchymal stem cells primarily sourced from the periosteum, serves as precursors to chondrocyte and osteoblast. Activated osteoblasts replace the soft callus matrix with a mineralised, irregularly woven bone matrix, while osteoclasts reabsorb it during endochondral ossification. Finally, vascularization and many cycles of bone resorption and production make up the final step of restoration, which restores the structure, durability, and function of the bone.[1]

Osteocytes and bone lining cells are in charge of the exact coupling of bone production and resorption, which is regulated by local variables and systemic hormones, and is necessary for the management of proper physiological bone remodelling.[10] Bone multicellular units (BMUs) are organised into specialised units that include precursor cells, osteoblast lineage cells (osteoblasts, osteocytes, and bone-lining cells), and osteoclasts, which are cells that resorb bone.[11] Mesenchymal stem cells within the bone marrow stroma transform into osteoblasts, which are essential for both the production and mineralization of bone matrix. During osteoclastogenesis, monocyte/macrophage lineage progenitors fuse to become osteoclasts, which are huge, multinucleated gigantic cells.[11]

After several successive steps are combined, the process of bone remodelling may begin. Quiescence, activation, resorption, reversal, and formation are the four successive steps that make up the remodelling cycle.[10, 11] (Figure 1)

Activation occurs prior to resorption, which is followed by reversal, with mineralization being the final step.[11] When bone surfaces are no longer dormant, they are prepared for remodelling, a process known as activation. The procedure begins with the surface of the bone being colonised by mononuclear osteoclast precursors, which are then differentiated and fused into competent osteoclasts. The cytoskeleton of active osteoclasts is subsequently rearranged when they cling to the bone matrix. They create a sealing zone around the resorption site and take on a polarised shape.[10]

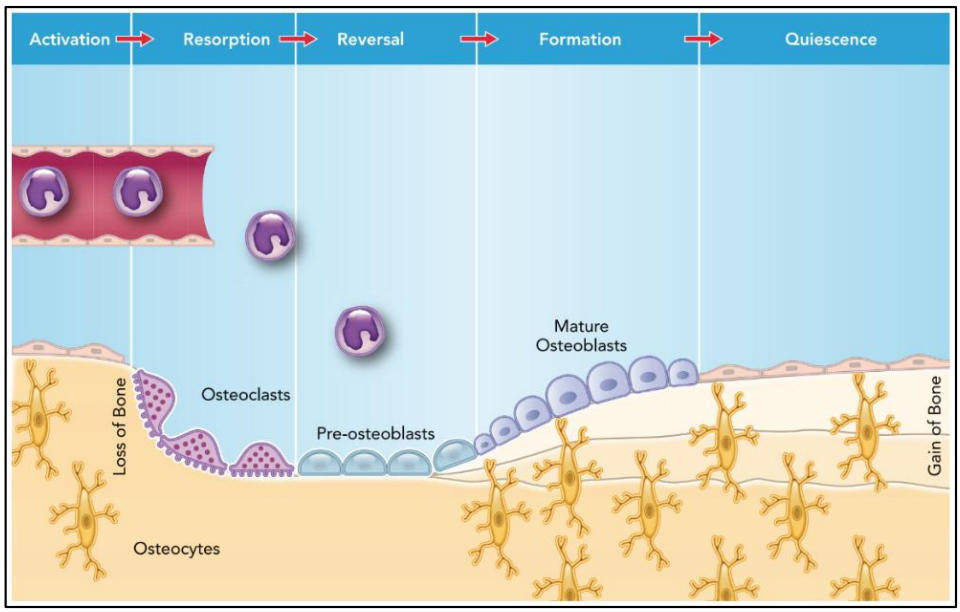

Figure 1. Physiological bone remodelling.[11]

In response to osteocyte or endocrine activation signals, osteoblasts bring in osteoclast precursors to the remodelling area during the resorption phase. Together, osteoclasts break down the bone matrix by removing its organic and mineral components. Scalloped erosion, also known as Howship's or resorption lacuna, is the distinctive feature of a resorbing surface. During the resorption phase, it usually lasts as long as the osteoclast itself, which is about 8 to 10 days. [10, 11]

The reversal phase, which lasts 7–14 days, marks a shift from destruction to repair as almost all osteoclasts disappear. Osteoclastic cells are completely replaced by osteoblastic cells during the formation phase. The final differentiation of osteoblasts marks the end of bone remodelling. The surface environment of the resting bone is preserved until the remodelling process that follows begins.[10, 11]

The creation and resorption of bone are two ongoing processes. The resorption of old or damaged bone is an integral part of the bone remodelling process. Osteoclasts are derived from haematopoietic precursors. On the other hand, mesenchymal stem cells give rise to osteoblasts, which are in charge of making and mineralizing new bone matrix. At all ages, proper bone microarchitecture, mass, and function depend on a delicate balance between osteoclasts and osteoblasts (Figure 2).[12, 13]

The primary roles of osteoblasts in bone production and osteoclastogenesis regulation are well-documented. During the process of osteogenesis, bone morphogenetic protein (BMP) aims at osteoblast precursors, bone marrow cells, and pluripotent mesenchymal cell lines. Committed pre-osteoblasts are the end product of a series of differentiation steps in which pluripotent stem cells show a decrease in proliferation capacity. After differentiating into mature osteoblasts, pre-osteoblasts deposit mineralization-inducing components necessary for bone matrix development. Finally, mineralizing osteoblasts undergo terminal differentiation to become osteocytes, and the recently released bone matrix embeds them.[13]

Terminally developed osteoclasts are big multinucleated cells with the unique capacity to resorb bone. [1, 13] When cells are exposed to macrophage colony-stimulating factor (M-CSF), they multiply. Surface receptor activator of nuclear factor kB (RANK) is expressed by precursor cells, whereas osteoblasts and stromal cells from the bone marrow create the ligand RANKL. When ligands attach to receptors, they signal precursor cells to undergo osteoclast lineage differentiation. Because RANK is present on the surface of terminally differentiated osteoclasts, this contact is necessary for osteoclast development and promotes osteoclast activity. In order to decrease

osteoclastogenesis, osteoprotegerin (OPG) acts as a soluble decoy receptor by competing with RANKL for binding to RANK. Osteoclast production and activity depend on the balance between RANKL and OPG.[1, 13]

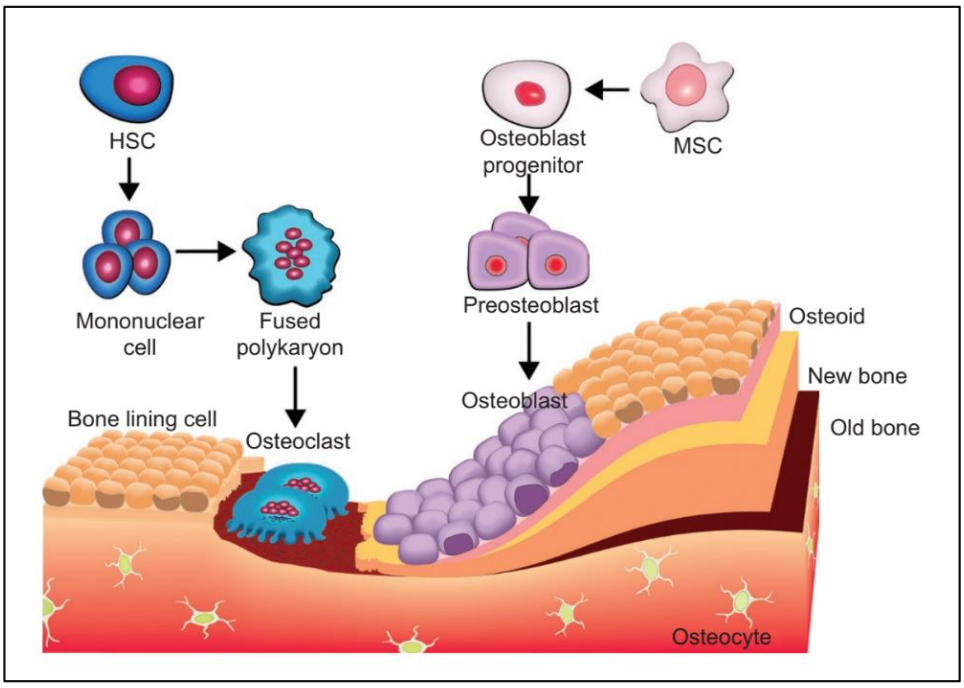

Figure 2. Diagram showing osteoblast and osteoclasts in bone formation.[13]

2.2. BMP-2 Signaling Osteogenesis in Mesenchymal Stem Cell (MSCs)

Inducing the transformation of mesenchymal cells into cartilage and bone tissues is the role of BMP-2, a 396-amino acid polypeptide growth factor. A tissue-engineered bone construct compatible with the growing craniofacial skeleton may use BMP-2 as its starting point.[5] It has been shown that some cell types, such as embryonic stem cells, haematopoietic stem cells, and mesenchymal stem cells (MSCs), have the ability to regenerate damaged tissues. Because of their anti-inflammatory and high differentiation capacity, MSCs generated from bone marrow are the best option for tissue engineering.[14] During osteoclast-mediated bone resorption, the bone matrix or serum releases BMP-2, which is the principal factor responsible for the development of MSCs into osteoblasts.[6]

Proteins released by osteoblasts that are involved in osteogenesis are crucial in the process of bone creation.[4] Cell proliferation, maturation and deposition of the extracellular matrix, and matrix mineralization are the three usual developmental steps of osteogenic differentiation.[13] During these phases, a number of proteins are expressed. Active proliferation of preosteoblasts is seen during the first phase, which is also when collagen, fibronectin, and the TGF-β1 receptor are expressed. As a result, alkaline phosphatase (ALPL) and collagen type 1 alpha chain (COL1A1) expression levels rise and proliferation is downregulated. The expression of many osteoblastic markers, such as osteopontin (OPN), osteocalcin (OC), integrin-binding sialoprotein (IBSP), ALPL, and COL1A1, finally completes matrix formation. IBSP controls the development of hydroxyapatite crystals, while OPN encourages mineralisation and bone growth. Osterix (OSX) and runt-related transcription factor 2 (RUNX2) are essential regulators in the process.[15]

By encouraging mesenchymal stem cell (MSC) migration and differentiation into the osteogenic phenotype, bone morphogenic protein-2 (BMP-2) is crucial in adult bone remodelling and homeostasis.[14] There are four distinct phases that bone morphogenetic protein (BMP) goes through when it is subjected to osteogenic induction: the propensity, differentiation, bone production, and remodelling phases.[5] When BMP-2 binds to certain receptors,

such as complexes of BMP type I and BMP type II serine/threonine kinase receptors on target cells, it activates signalling pathways in osteoblasts. These pathways include both canonical and non-canonical pathways, and they are mediated by Smad.[6, 15] By directly associating with the type I receptor, BMP-2 activates it via its interaction with the type II receptor.[12]

The conformation of BMP receptors determines the signalling channels by which BMP-2 affects osteoblast developmental stages.[12] Type Ia activin receptors, type Ib BMP receptors, and type Ia BMP receptors are all bound to by BMP-2. On most cell surfaces, you will see BMPRIa, although BMPRIb is not as common. To facilitate oligomerisation with BMPRII, BMP-2 either preferentially connects with preexisting BMPRII-BMPRIa/b complexes or interacts with BMPRIa particularly at its beta4beta5 loop. Additionally, when BMP-2 is present, BMPRII may oligomerize with BMPRIa/b, resulting in the pairing of type I and type II receptors and the activation of separate signalling pathways (Figure 3).[6, 8]

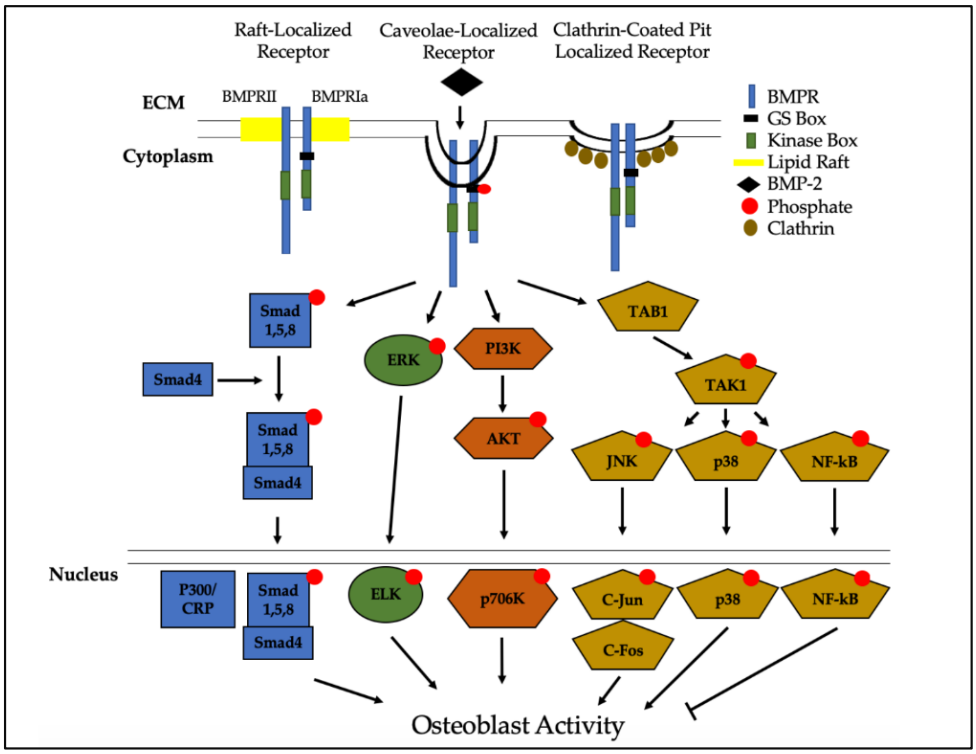

Figure 3. Signaling pathways by Bone Morphogenic Protein 2 (BMP-2).[6]

The activation of Smad and Non-Smad signalling pathways occurs upon binding of BMP-2 to BMPRs. When BMPRIa and BMPRIb phosphorylate downstream proteins, namely Smad1/5/8 (R-Smads), the Smad pathway is activated [6, 16, 17] One of the main functions of R-Smads (Smad 1/5/8) is to act as a transducer for BMP receptors. They interact with many transcription factors, such as Osx and RUNX2, to control the transcription of target genes after activation, when they translocate to the nucleus and bind Smad4. [6, 15, 17, 18]

2.3. Application of BMP-2 in Bone Regeneration

Because of its capacity to provoke MSC migration and differentiation towards the osteogenic phenotype, BMP-2 has found use in bone repair and regeneration treatment.[14] There is a need to address important concerns before BMP 2 is widely used as an adjuvant in craniofacial surgery, despite its promising results as an osteo-inductive agent in clinical settings. Dental offices were able to begin using recombinant human BMP-2 (rhBMP-2) for maxillary sinus grafting and bone-grafting operations linked to extraction sockets in 2007, thanks to approval from

the US Food and Drug Administration. In dental applications, a collagen sponge or synthetic bone-grafting materials such β-tricalcium phosphate are used to inject rhBMP-2 into a defect. The effects of rhBMP-2 on alveolar bone regeneration have been shown in many clinical and preclinical research (Figure4) [19]. These studies have focused on periodontal regeneration, bone augmentation techniques, and bone restoration in peri-implantitis abnormalities.

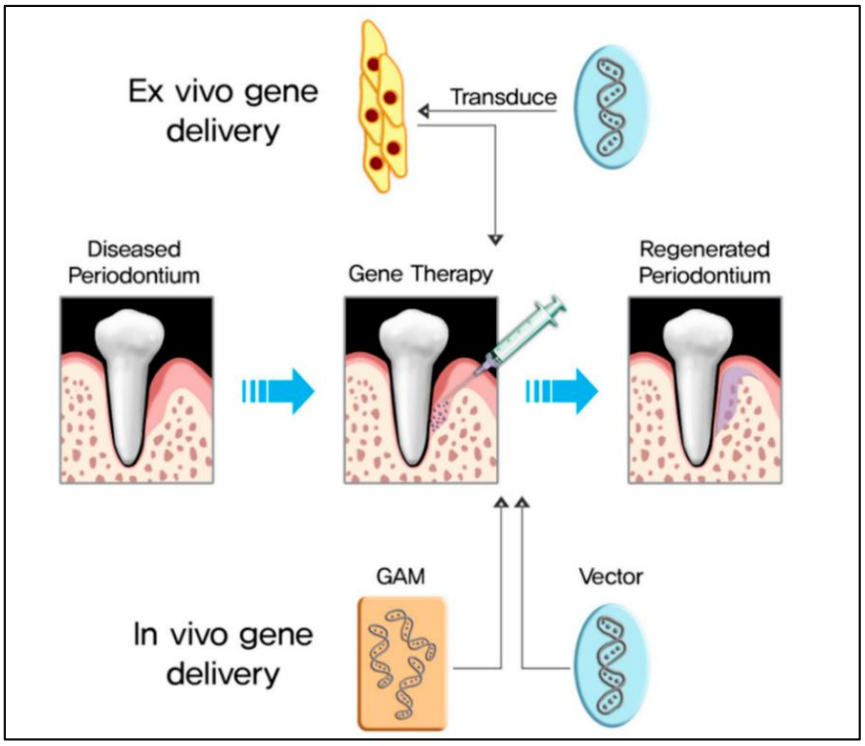

Figure 4. Gene therapy-based regeneration method for periodontal tissue reconstruction [19]

The side effects linked with dose levels are the main worry in rhBMP-2 treatment. The short half-lives (minutes to hours) and high clearance rates of protein growth factors are a common constraint among them. Imperfections are treated with a high initial dosage of rhBMP-2 in order to maintain an effective in vivo concentration throughout the healing process. In addition, the carrier system and host circumstances may affect the necessary dosages. According to prior research, the concentration of rhBMP-2 varied between 0.75 and 2.0 mg/mL. Adverse effects, such as large swelling, seroma formation, cystic bone lesion formation, and cancer development, are linked to rhBMP-2 when administered at a level over what is considered normal. Potential bone overgrowth, interactions with exposed dura, cancer risk, immunogenicity, local toxicity, effects on distant organs, systemic toxicity, and reproductive toxicity were among the concerns raised by Poynton and Lane about the use of rhBMP-2.

Concerns of rhBMP-2 therapy mostly revolve on dose-related adverse effects. Protein growth factors exhibit limitations due to their brief half-lives, ranging from minutes to hours, and their swift clearance rates. A large initial dose of rhBMP-2 is used to correct imperfections so that an effective in vivo concentration may be maintained throughout the healing process. Also, the doses that are required could change depending on the host conditions and the carrier system. Previous studies found that rhBMP-2 concentrations ranged from 0.75 to 2.0 mg/mL. When supplied at a level above what is considered normal, rhBMP-2 is associated with adverse consequences such as significant swelling, seroma formation, cystic bone lesion formation, and cancer development. Poynton and Lane voiced concerns with the use of rhBMP-2, including the possibility of bone overgrowth, interactions with exposed

dura, potential for malignancy, immunogenicity, local toxicity, effects on distant organs, systemic toxicity, and reproductive toxicity.[19]

3. Discussion

Bone remodelling and regeneration are carefully controlled processes that include the creation and resorption of bone. Bone health is dependent on these activities. A large body of research points to bone morphogenetic proteins (BMPs) in the processes of osteoblast development and bone production.[1] MSCs derived from bone marrow or umbilical cord are more capable of osteogenic development when exposed to BMP-2, as shown by Marupanthorn et al. When transplanted into muscles, BMP-2 may stimulate the creation of ectopic cartilage and bone, as reported by Samara et al. [20]. The differentiation of osteoblasts, chondrocyte proliferation and differentiation are all controlled by BMP signalling.[21] In their study, Li et al. found that in comparison to the negative control group, the group with overexpressed BMP-2 had a far better capacity for osteogenic differentiation.[22] After maxillofacial cyst enucleation, Hwang et al. show that rhBMP-2 helps patients create more bone.[23] The repair of critical-sized defects in the mandible and calvaria has been shown to be accomplished by bone morphogenetic proteins (BMPs). The Food and Drug Administration has also given the green light to the use of recombinant human BMP-2 (rhBMP-2) in regenerative treatments, such as spinal fusion, alveolar ridge augmentation, and sinus floor augmentation.[14]

The BMP-2 protein functions as a paracrine or autocrine factor, synthesized by cells and engaging with receptors on osteoblasts and osteoclasts. When BMP-2 enters the circulation or bone matrix, proteases continue digesting it.[6] Bone morphogenetic protein 2 (BMP-2) activates two pathways—one canonical (Smad-dependent) and the other non-canonical (Smad-independent)—on MSCs, kicking off osteogenic development. In order for MSCs to differentiate into osteoblasts, activation must occur, since it causes the phosphorylation of Smad1/5/8 and the upregulation of osteogenic transcription factors.[6] This study's findings align with previous research demonstrating BMP-2's capacity to enhance bone formation. For example, research has shown that BMP-2 greatly increases the expression of osteogenic markers in MSCs, including alkaline phosphatase (ALP), osteopontin (OPN), and osteocalcin (OCN). Based on these results, BMP-2 is a promising agent for use in regenerative medicine and bone tissue engineering due to its strong osteogenic properties.

In the field of dentistry, BMP-2 has shown encouraging results in improving bone healing and regeneration. Its proven use in periodontal regeneration and dental implant treatments is extensive. Dental implants may be made more stable and integrated with the help of BMP-2, which stimulates bone development in the area. As an additional benefit, BMP-2 has shown promise as a substitute for conventional bone grafts in periodontal treatment by stimulating bone and periodontal tissue regeneration.[24]

The use of BMP-2 in therapeutic settings, however, is not devoid of difficulties. Unpredictability in MSC response to BMP-2, impacted by variables including donor variability and culture circumstances, is a major obstacle to its reliable therapeutic use. Because of its high price tag and the risk of side effects including inflammation and ectopic bone growth, BMP-2 must be dosed and administered with extreme caution.

Improving and perfecting BMP-2 delivery techniques to make it more effective and safer should be the goal of future studies. Achieving continuous and localized BMP-2 administration using strategies like gene therapy techniques and controlled-release systems has the potential to improve therapeutic results while minimizing unwanted effects.[19] The osteogenic potential and regenerative dentistry uses of BMP-2 might be further enhanced by investigating its synergistic effects with other growth factors and signalling molecules.

4. Conclusion

The production and maintenance of healthy bone depend on Bone Morphogenetic Protein-2 (BMP-2). The process of bone regeneration is significantly enhanced by the differentiation of mesenchymal stem cells (MSCs) into osteoblasts. While BMP-2 shows great promise for dental applications, it is not without its drawbacks, including high prices and the possibility of adverse effects. To improve its distribution and lessen these problems,

further research is required. In the grand scheme of things, BMP-2 is a key player in developing new options for bone and tooth repair.

Conflict of Interest

The literature review does not contain any conflict of interest.

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