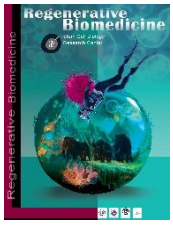

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Review Article

Harnessing BMPs for Bone Regeneration: Mechanisms, Biomaterials, and Clinical Applications

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Abstract

Bone tissue engineering is a rapidly advancing interdisciplinary domain dedicated to the regeneration of skeletal defects through the combined use of stem cells, bioactive growth factors, and engineered scaffolds. Among the growth factors employed, BMPs, members of the TGF-β superfamily, have emerged as critical mediators of osteogenesis. These proteins drive the differentiation of mesenchymal stem cells and activate key signaling cascades such as Smad, MAPK, and Wnt, which collectively facilitate bone formation. However, translating BMP-based therapies into clinical practice involves overcoming major challenges, including precise dose regulation, spatiotemporal delivery, high production costs, and the risk of adverse effects like ectopic ossification. Recent advances in scaffold engineering, particularly the development of smart biomaterials, offer promising strategies for achieving controlled and targeted BMP delivery. This review comprehensively discusses the molecular mechanisms and biological functions of BMPs, evaluates their integration with scaffold technologies, and examines current clinical applications, limitations, and future directions in the context of bone tissue engineering.

Keywords: Bone tissue engineering, Bone morphogenetic proteins, BMPs, Biomaterial scaffold, Osteogenesis

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Introduction

Tissue Engineering is an interdisciplinary field that combines biology, materials science, and engineering to design and construct scaffolds aimed at replacing, repairing, or enhancing the function of damaged or lost tissues in the body. This field has seen significant growth in recent decades, offering various solutions for the treatment of bone, cardiac, liver, neural, and other injuries (1). Among these, bone regeneration stands as one of the most challenging areas of tissue engineering due to the fact that bone is a dynamic, living tissue that, in addition to its structural role, also participates in calcium homeostasis, hematopoiesis, and metabolism (2).

In the design of biological systems for tissue regeneration, the presence of growth factors is essential, in addition to biomaterial scaffolds and stem cells. These factors act as biochemical messengers, guiding cellular differentiation, proliferation, and migration pathways (3). Of the hundreds of identified growth factors, Bone Morphogenetic Proteins (BMPs) are one of the most significant and effective groups for inducing osteogenesis (4). BMPs are a group of secreted proteins that were first discovered by Urist in 1965, who demonstrated that demineralized bone powder could induce new bone formation in non-bony areas (5). It was later determined that this property was due to the presence of BMPs. BMPs are a part of the larger Transforming Growth Factor-β (TGF-β) family and play a critical role in inducing osteogenesis, differentiating mesenchymal stem cells (MSCs), and tissue regeneration (6, 7). BMPs have a unique biological ability to induce osteogenesis (8).

BMP-2 and BMP-7 are two well-known members that have wide applications in bone regeneration and have been approved for use in certain FDA-approved pharmaceutical products (9). These factors can guide stem cells at the injury site towards osteogenesis without the need for external cell supplementation (10). Their functionality is also dependent on the presence of a suitable biomaterial scaffold and a proper microenvironment. Despite the widespread use of BMPs in tissue engineering, challenges such as correct dosing, controlled release, high cost, and potential side effects (such as ectopic bone formation) remain (10, 11). Furthermore, advancements such as nanotechnology, gene therapy, and smart scaffolds could help address these issues (12). Therefore, a comprehensive and systematic review of the various aspects of BMPs—ranging from biological to technological—can significantly aid in the design of more effective bone regeneration strategies. This review article aims to investigate the following aspects:

1) Molecular Biology and Signaling Pathways of BMPs
2) Role of BMPs in Cellular Differentiation and Induction of Bone Formation
3) Applications in Tissue Engineering Scaffolds
4) Clinical and Preclinical Studies
5) Challenges and Limitations
6)Emerging Technologies for Optimizing BMP Performance

BMPs structure, molecular properties and signaling pathways

BMPs are a subset of the TGF-β family, characterized by a biologically active domain with a conserved structure. BMPs are initially

synthesized as inactive precursors, which include a signal domain, a propeptide, and an active region. After cleavage by proteases, the active fragment is released as a dimer (homo or hetero) in the extracellular space. This dimeric structure is essential for biological activity and is stabilized by disulfide bonds between the monomers (13, 14). The BMP family consists of over 20 different isoforms, which are structurally precursors that transform into active dimeric proteins upon translation (15). BMP-2, BMP-4, and BMP-7 are the most significant members of this family, known for their substantial effects on osteogenesis and differentiation of MSCs (16).

BMPs exert their function by binding to two types of transmembrane serine/threonine kinase receptors: Type I receptors such as Activin receptor-like kinase 2 (ALK2), Activin receptor-like kinase 3 (ALK3), Activin receptor-like kinase 6 (ALK6), and Type II receptors such as BMP receptor Type II (BMPR-II), Activin Receptor Type II (ActR-II), and Activin Receptor Type IIB (ActR-IIB). BMP initially binds to Type II receptors, leading to the activation of the Type I receptor complex, which results in the phosphorylation of downstream signaling proteins (17). Proteins like Endoglin and Betaglycan act as co-receptors for BMPs and play a crucial role in modulating the intensity and type of cellular response. These co-receptors can either enhance or inhibit BMP activity under certain conditions (18).

Smad) signaling pathway is one of the primary pathways involved in BMP action, functioning through the phosphorylation of Smad1, Smad5, and Smad8. This pathway plays a key role in the differentiation of stem cells into osteoblasts, regulation of osteogenic gene expression, and tissue regeneration. Upon BMP binding to the Type I and II receptor complex, the Type I receptor is activated, leading to the direct phosphorylation of Smad1, Smad5, and Smad8 (12). These phosphorylated Smads then bind to Smad4 (a Co-Smad), forming a complex that translocates to the cell nucleus, where it activates or suppresses the expression of target genes. Key genes activated by this pathway include Runt-related transcription factor 2 (RUNX2) (a key factor in osteogenesis), Osterix (SP7), and Collagen type I alpha 1 chain (Col1a1), all of which are involved in osteoblast differentiation and extracellular bone matrix formation (19, 20).

In tissue engineering, BMP-induced activation of the Smad pathway in MSCs leads to differentiation into osteoblasts. Studies have shown that loading BMPs onto biological scaffolds activates this pathway and enhances osteogenesis in vivo (21). In addition to the classic Smad pathway, BMPs can also activate non-Smad signaling pathways, known as "non-canonical" pathways. These include Mitogen-Activated Protein Kinase (MAPK), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/Akt), and interactions with the Wingless/β-catenin (Wnt/β-catenin) pathway, all of which play significant roles in regulating cell survival, proliferation, migration, and differentiation (22). BMPs can activate the MAPK pathway via Type I receptors. This pathway includes three main branches:

p38 MAPK (increases osteoblast differentiation and expression of genes like Runx2)

Extracellular signal-Regulated Kinases (ERK1/2) (primarily involved in cell proliferation, and in some cases negatively interacts with Smads)
c-Jun N-terminal kinase (JNK) (activated under oxidative stress, with a dual role in cell survival) (23) (Fig. 1).

The PI3K/Akt pathway is especially important for the survival and resistance of stem cells. BMPs activate this pathway via receptor binding and interaction with other factors like Insulin-like growth factor (IGF), which leads to the phosphorylation of Akt. Akt, in turn, enhances cell survival and osteogenic differentiation by inhibiting proteins like Bad and GSK3β (24). The Wnt pathway, crucial for cell growth and differentiation, interacts with BMP signaling in a complex manner. In many stem cells, simultaneous activation of both the Wnt and BMP pathways enhances osteogenesis. Wnt synergizes with BMP by inhibiting Smad6, which is a negative regulator of BMP Smads (25). In the design of smart scaffolds for bone regeneration, the simultaneous use of factors that activate the MAPK, PI3K, and Wnt pathways alongside BMP can significantly enhance osteoinduction. Additionally, the spatial and temporal control of these pathways is a key to the success of therapeutic outcomes in clinical settings (11, 26). BMP signaling pathways are tightly regulated by a set of negative regulators that prevent overstimulation or inappropriate cellular responses by either inhibiting BMP receptor binding or blocking downstream pathways. These regulators can be divided into two main categories: extracellular inhibitors and intracellular inhibitors (27).

Extracellular Inhibitors

Noggin is one of the most well-known BMP inhibitors, which prevents BMP-2, BMP-4, and BMP-7 from interacting with cell surface receptors by binding directly to them. Noggin plays an inhibitory role in embryonic development, neuronal differentiation, and the regulation of osteogenesis (28). Chordin also inhibits BMP signaling by binding to BMPs and sequestering them away from receptors, through interactions with proteins such as Twisted gastrulation. Chordin is primarily involved in embryonic development and body patterning, but it has also gained importance in tissue engineering (29). Gremlin is an inhibitor involved in both kidney development and the regulation of bone remodeling in adults. This protein is particularly upregulated in pathological conditions like fibrosis and tumorigenesis, exacerbating BMP pathway inhibition (30).

Intracellular Inhibitors

Smad6 and Smad7 (I-Smads), known as inhibitory Smads, prevent the phosphorylation and signal transduction of activated BMP receptors or Smads by binding to them. Notably, Smad6 specifically targets the BMP pathway, inhibiting it in a targeted manner. Some non-canonical pathways, such as ERK, can negatively affect Smads and prevent their translocation to the nucleus, representing a cross-talk mechanism between pathways (27, 31) .

In the design of biological scaffolds, the use of BMP inhibitors in specific regions can prevent unwanted ossification in soft tissues. Additionally, controlling the expression of Noggin or Smad6 in biological environments helps achieve more precise and controlled bone regeneration (6).

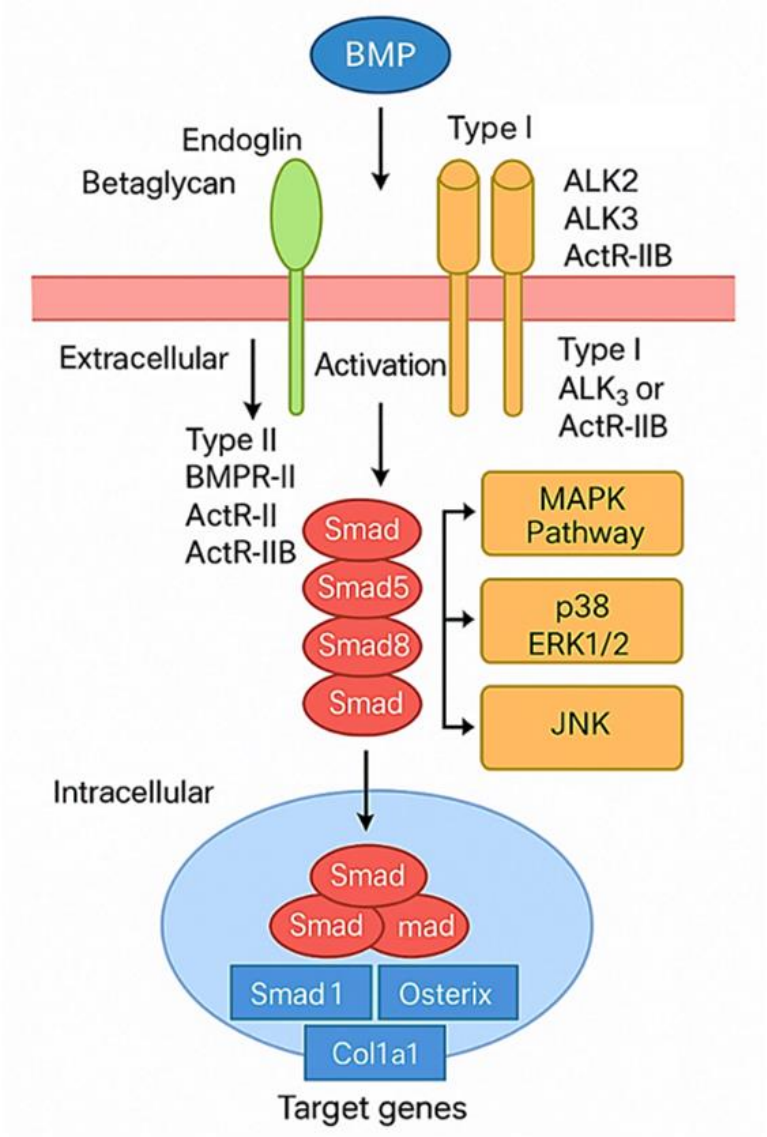

Figure 1. The image depicts a diagram of the BMP (Bone Morphogenetic Protein) pathway and its mechanism of action within the cell. BMP is a morphogenetic growth factor that plays a crucial role in development, cellular differentiation, and cell-cell communication. BMP: Bone Morphogenetic Protein, ALK2: Activin-like Kinase 2, ALK3: Activin-like Kinase 3, ActR-IIB: Activin Receptor Type IIB, BMPR-II: Bone Morphogenetic Protein Receptor Type II, ActR-II: Activin Receptor Type II, Smad: Small Mothers Against Decapentaplegic, MAPK: Mitogen-Activated Protein Kinase, ERK1/2: Extracellular Signal-Regulated Kinase ½, JNK: c-Jun N-terminal Kinase, Col1a1: Collagen Type I Alpha 1.

Application of BMPs in the Design of Bioactive Scaffolds for Bone Tissue Engineering

Bone tissue engineering, as a modern approach to repairing bone defects, is based on three essential pillars: stem cells, growth factors, and biomimetic scaffolds. Among these, scaffolds play a fundamental role as the physical and biochemical substrate for supporting cellular proliferation, differentiation, and organization (32). On the other hand, growth factors, particularly BMPs, have garnered significant attention in

scaffold design due to their unique ability to induce osteogenesis. The aim of advanced scaffold design is to create structures that not only possess suitable physical and mechanical properties but also have the capability for controlled and targeted BMP release (33). Effective scaffolds must be able to deliver and release BMPs efficiently and stably at the site of the bone defect. In Table 1, BMP-carrying biological scaffolds are categorized based on the type of constituent material (10).

Key features of such scaffolds include:

1) High biocompatibility: The scaffold should not induce cytotoxicity or immune responses.

2) Controlled biodegradability: It should degrade in sync with the formation of new bone, providing space for the regenerating tissue (34).

3) Interconnected porosity: The scaffold must have a porous structure with pore sizes between 100–300 μm to facilitate cell migration, nutrient exchange, and vascular infiltration (35).

4) Mechanical compatibility: The scaffold should have sufficient strength to withstand mechanical loads and mimic the extracellular matrix (ECM) of bone.

5) Effective BMP loading and release: It must be capable of loading BMPs without deactivation and release them steadily at physiological doses (36).

6) Biological stability: The scaffold should protect BMPs against enzymatic and physiological degradation and release them at the appropriate time (6).

To design BMP delivery strategies in scaffolds, various methods should be considered, including simple physical release, controlled release using biodegradable polymers, BMP-loaded nanoparticles and microspheres, covalent BMP bonding, and multifunctional scaffolds (10, 37).

Simple physical release: In this method, BMPs are adsorbed or loaded onto the surface or bulk of the scaffold. Although it is the simplest approach, it often results in a burst release, leading to a rapid decrease in BMP concentration over time. This method is suitable for short-term applications or when a low dose suffices but is often inadequate for many clinical scenarios (38).Controlled release via biodegradable polymers: Polymers such as Poly (lactic-co-glycolic acid) (PLGA), chitosan, and gelatin can enable sustained BMP release by controlling degradation rates. When combined with ceramics like Beta-Tricalcium Phosphate (β-TCP), these scaffolds provide a bone-like environment and protect BMPs from premature degradation. This method has shown excellent results in animal models by stimulating endogenous bone formation (39).

Use of BMP-loaded nanoparticles and microspheres: Polymeric or inorganic nanoparticles like PLGA and calcium phosphate (CaP) can encapsulate BMPs and release them at controlled rates depending on physiological conditions. This approach offers enhanced stability, protection against enzymatic degradation, and more precise dosage control (40).

Covalent bonding of BMP to scaffold matrix: Here, BMPs are covalently bound to the scaffold and are only released in the presence of specific enzymes in the target tissue. This strategy enhances targeting, reduces systemic effects, and improves therapeutic efficacy. It is feasible through advanced chemical reactions and responsive systems (41).

Multifunctional scaffolds: These scaffolds

Table 1. Examples of classification of biomimetic scaffolds containing bone morphogenetic protein (BMP) (Abbreviation: BMPs: Bone Morphogenetic Proteins, PLGA: Poly (lactic-co-glycolic acid), PCL: Polycaprolactone, HA: Hydroxyapatite, β-TCP: Beta-Tricalcium Phosphate, GelMA: Gelatin Methacrylate)

	Scaffold Type	Examples	Advantages	Disadvantages
1	Natural	Collagen, Chitosan	Biocompatible, bioactive	Rapid degradation, low strength (42)
2	Synthetic	PLGA, PCL	Controlled degradation and structure	Requires surface modification (43, 44)
3	Inorganic	HA, β-TCP	Bioactive, bone-like	Brittle, high release rate (45)
4	Composite	PLGA/HA, GelMA/β-TCP, gelatin/HA/β-TCP, PCL/PLGA/β-TCP	Combines benefits	Complex manufacturing (46-48)

offer additional functionalities alongside BMP delivery, such as electrical conductivity, antibacterial properties, or co-delivery of other factors like Vascular Endothelial Growth Factor (VEGF) (49). Examples include:

1)PLGA(BMP-2) / CS (Pac-525) @ MC/PCL scaffold: Provides osteogenic and antibacterial effects (50).

2) 3D-printed PCL/bioglass (BGS-7) composite scaffolds: Offers customizable design and high bone regeneration potential (51).

3) Chitosan-loaded mesoporous silica nanoparticle scaffolds containing BMP-2 and dexamethasone: Significant Stimulation of Osteoblast Differentiation and Bone Regeneration by Simultaneous Delivery of BMP-2 and Dex (52).

Bone morphogenetic proteins, especially BMP-2 and BMP-7, are among the few growth factors that have received FDA approval for clinical use in bone regeneration (53). One of the most well-known commercial products in this field is Infuse® Bone Graft, developed by Medtronic, which combines BMP-2 with an absorbable collagen scaffold (54). This product is approved for:

1) Spinal fusion surgeries: Assists vertebral fusion, especially in high-risk patients.

2) Craniofacial bone defect reconstruc -tion reconstruction: Such as in large fractures or post-tumor resection repairs.

3) Orthopedic surgeries: For treating long bone diaphyseal defects, nonunions, and complex fractures (55, 56).

Clinical studies have shown that BMP-2 combined with collagen scaffolds enhances the rate and quality of bone formation, reduces the need for autografts, and facilitates healing in challenging cases (6). Similarly, BMP-2 incorporated into β-TCP scaffolds has been successfully used in alveolar bone reconstruction, yielding improved healing outcomes (57). Moreover, animal and clinical studies have reported that BMP-7-loaded scaffolds are effective in

treating nonunion fractures (58). However, concerns such as ectopic bone formation, excessive inflammation, and potential carcinogenic risks at high doses have been reported (59). Key challenges in BMP-based scaffold applications include:

1) Precise dosage control: High doses may cause ectopic bone or inflammation; low doses may be ineffective (60).

2) BMP stability in moist and enzymatic body environments (61).

3) Variable immune responses among patients (62).

4) Lack of standardization in clinical testing (63).

To address these challenges, emerging technologies such as smart scaffolds sensitive to pH and enzymes for the controlled release of BMP, the use of 3D bioprinting for precise design and spatial loading of BMP, the integration of BMP with exosomes (64-67) to enhance stability and efficacy, and "nano-hybrid" scaffolds for synergistic combination of BMP with other factors such as VEGF are currently under investigation (26, 68, 69)

Clinical Studies and Therapeutic Applications of BMPs in Bone Regeneration

BMPs, particularly rhBMP-2 and rhBMP-7, have played a key role in clinical treatments related to bone regeneration in recent years, including complex fractures, nonunions, large bone defects, and spinal and maxillofacial surgeries (10). These biological factors promote the differentiation of mesenchymal stem cells into osteoblasts and enhance osteogenesis, offering an effective alternative to autologous bone grafting. FDA-approved BMPs include the following:

1) rhBMP-2: This factor is used in lumbar interbody fusion, repair of mandibular bone defects, sinus lift in dental surgery, and in combination with absorbable collagen sponge (ACS).

2) rhBMP-7 (OP-1): This factor is used in the treatment of nonunion in long bones and complex orthopedic surgeries, often in combination with biological scaffolds or natural carriers (54, 70).

Currently, these factors are used in spinal surgery, delayed fracture healing, maxillofacial reconstruction, and dental implants (71). In lumbar spinal fusion surgeries, BMPs have served as an alternative to autologous bone grafts and have shown favorable outcomes (72).

In a systematic review and meta-analysis, the efficacy and safety of rhBMP-2 and autologous iliac crest bone graft (ICBG) in lumbar fusion were compared in 2,185 patients. The results showed that rhBMP-2 had a higher fusion success rate, a lower risk of reoperation, and a similar complication rate compared to ICBG. rhBMP-2 was recommended as an effective alternative to ICBG for lumbar fusion (73). In a study, existing research on the application of rhBMP-2 in spinal fusion surgery from 1965 to 2022 was reviewed. The evidence shows that the fusion rate with rhBMP-2 is similar to or even higher than the results achieved with autologous bone grafts. However, there are concerns regarding the cost, optimal dosage, and potential complications associated with the use of rhBMP-2 in spinal surgery (72).In a review study, the effect of rhBMP-2 in maxillofacial surgeries was investigated. The study showed that rhBMP-2 has high potential in maxillofacial surgeries due to its osteoinductive properties. Studies have indicated that rhBMP-2 can reduce donor site

morbidity and increase bone height in sinus and ridge augmentation procedures. Additionally, in the treatment of medication-related osteonecrosis of the jaw, rhBMP-2 has been used as an adjunct with promising results. Overall, rhBMP-2 is recognized as a promising graft material in maxillofacial surgery (74).

In a study, the safety and efficacy of local rhBMP-7 implantation in bovine-derived collagen paste for the treatment of resistant non-unions were evaluated in fifty-two patients. The results showed that 94% of patients achieved union, with a mean healing time of 5.6 months. This method was recognized as an effective adjunctive treatment, with only one case of synostosis reported as a complication (75). A study evaluated the treatment of nonunion of the femur using single-stage methods (with rhBMP-7 and RIA) and two-stage methods (Masquelet technique). A total of 88 patients were assessed, with 74% achieving bone consolidation on average within 9.3 months. Intramedullary reaming (83%) was more effective than osteosynthesis plates (60%), and smoking was associated with a reduced rate of consolidation. The Masquelet technique was effective for infections and large bone defects, and quality of life improved in both groups. Treatment with rhBMP-7 and RIA was recommended for small defects, while intramedullary nailing was advised for large defects (76).

Despite the widespread application of BMPs in clinical settings, side effects such as ectopic bone formation, severe swelling, and immune responses are notable (10). To overcome these side effects and limitations, new research strategies are being explored, such as the use of nanoparticles or hydrogels for controlled BMP release, combining BMP with other factors like VEGF to enhance both osteogenesis and angiogenesis, and gene editing (Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)) to improve endogenous BMP production by stem cells (77, 78).

Challenges, Innovations, and Future Directions in the Application of BMPs in Bone Tissue Engineering

While BMPs have been proposed as effective biological agents for bone regeneration, various challenges remain in optimizing their use (79). These challenges, ranging from safety concerns and side effects to economic barriers and the need for improved BMP production and release processes, can significantly impact the clinical application of these proteins (80). One common issue with the use of BMPs, especially at high doses, is ectopic bone formation (81). This problem arises from the non-targeted distribution of BMPs to surrounding areas during implantation (82). Bone formation in inappropriate locations such as soft tissues, nerves, or within the spinal cavity can lead to severe complications, including nerve compression and eventual nerve damage (83). The use of smart carriers that can precisely direct BMPs to the intended site and improvements in the design of biodegradable scaffolds to limit BMP release and prevent its spread to undesired areas can be effective solutions to address this issue (41).

In many cases, high doses of rhBMPs are required to achieve effective bone formation. These high doses can lead to severe inflammation, swelling, and immune system reactions (6). In some patients, the immune

response to BMPs may lead to the production of anti-BMP antibodies, reducing the therapeutic effect (84). The use of controlled-release systems that allow for more precise and gradual BMP delivery, along with reduced BMP doses through optimized scaffolds and carriers, could offer viable solutions to this problem (7). Another major challenge is the precise control of BMP release. Many current carriers, such as collagen sponges, are not capable of targeted and controlled BMP release (36). This issue results in diminished BMP effectiveness over time and increased side effects. Using nanoparticles or hydrogels that offer better control over drug release is a promising solution (85). Additionally, designing smart release systems that can respond to specific environmental conditions, such as pH or temperature, can lead to more effective BMP release (86, 87).

The use of biodegradable nanoparticles, such as PLGA (poly-lactic-co-glycolic acid), and liposomes for the gradual release of BMPs at the target site offers a more accurate and effective means of delivering BMPs to the target tissue, preventing unintended release (6, 88). This approach is associated with reduced side effects and prolonged BMP release at specific locations (89). An exciting innovation is the use of engineered stem cells for local BMP production. These cells can produce BMPs within the patient's body and aid in bone regeneration (90). Gene editing techniques using CRISPR-Cas9 could also be employed to engineer stem cells to enhance BMP production. This in-situ production technology reduces the need for external release and increases therapeutic efficiency (91, 92).

Nano-composite and micro-layered scaffolds that can stimulate cell differentiation into osteoblasts and precisely control BMP release are also an exciting advancement (1, 93, 94). These scaffolds, using biodegradable materials, allow the body to naturally build new bone structure (95). This technology controls BMP release and creates a favorable environment for bone growth (96). One of the most important areas of progress is combining BMPs with other growth factors such as VEGF or FGF (fibroblast growth factor). These combinations can simultaneously enhance processes like osteogenesis and angiogenesis (Table 2) (97). In recent decades, BMPs have become one of the most widely used tools in bone tissue engineering. These proteins are capable of stimulating bone production and repairing damaged tissues. Recent advances in production, scaffold design, and combination therapies have rapidly expanded the clinical and experimental applications of BMPs (98).

Discussion

BMPs have emerged as pivotal agents in the field of tissue engineering due to their potent osteoinductive capabilities. Their role transcends simple bone induction; they orchestrate complex signaling cascades that mediate stem cell differentiation, matrix synthesis, and angiogenesis, all of which are crucial for effective bone regeneration (99). The canonical Smad pathway remains the most studied route of BMP signaling, especially through BMP-2 and BMP-7, which have received FDA approval for clinical applications (100). These pathways not only induce osteoblast differentiation but also work in concert with non-canonical pathways such as MAPK and PI3K/Akt, creating a robust regulatory network (101). However, BMPs are

Table 2. Combination of BMPs with other growth factors to enhance bone formation and angiogenesis (BMP: Bone Morphogenetic Protein; VEGF: Vascular Endothelial Growth Factor; FGF-2: Fibroblast Growth Factor-2; PDGF: Platelet-Derived Growth Factor. Numbers in parentheses refer to references.)

	Combination	Benefit
1	BMP + VEGF	Simultaneous enhancement of osteogenesis and angiogenesis (102)
2	BMP + FGF-2	Stimulation of osteoblast differentiation and stem cell proliferation (103)
3	BMP + PDGF	Simultaneous repair of soft and hard tissues (104)

not without limitations. High doses are often required to achieve therapeutic efficacy, which can lead to adverse effects such as ectopic bone formation and inflammation (105). This has led to a growing interest in delivery strategies that can precisely control the spatial and temporal release of BMPs. Incorporating BMPs into smart biomimetic scaffolds, such as hydrogels or nanofiber composites, offers a promising solution by mimicking the native extracellular matrix and enhancing bioavailability (106, 107).

Another critical challenge lies in the fine-tuning of BMP signaling. Inhibitory molecules like Noggin, Gremlin, and Smad6 are essential for preventing aberrant ossification, but they can also hinder therapeutic outcomes if not carefully modulated (108, 109). Emerging technologies, including gene editing and controlled gene expression systems, provide new avenues for overcoming these challenges. Furthermore, combinatorial approaches involving BMPs and other growth factors such as VEGF or IGF may enhance vascularization and support complex tissue repair (109, 110). From a clinical standpoint, although BMP-based therapies have achieved notable success in spinal fusion and long bone defects, translation to broader applications requires addressing concerns over cost, reproducibility and safety (111). Continuous innovation in scaffold design, molecular biology, and regenerative medicine is therefore essential to maximize the therapeutic potential of BMPs in tissue engineering.

Conclusion

In summary, BMPs play an indispensable role in modern tissue engineering, particularly in bone regeneration. Their unique biological properties, ability to modulate multiple signaling pathways, and synergy with biomaterials position them at the forefront of regenerative strategies. However, to fully harness their potential, several obstacles—including dose optimization, delivery precision, and inhibition management—must be addressed. Future research should prioritize interdisciplinary approaches combining molecular biology, materials science, and clinical translational studies. Innovations in smart biomaterials, gene regulation, and combinatorial growth factor therapies hold the key to overcoming current limitations and broadening the clinical application of BMP-based tissue engineering. By bridging fundamental biological mechanisms with advanced scaffold technologies, the next generation of BMP-centered therapies can offer safe, effective,

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and personalized solutions for complex tissue regeneration challenges.

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