Review

Underlying Signaling Pathways and Therapeutic Applications of Pulsed Electromagnetic Fields in Bone Repair

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Key Words
Pulsed electromagnetic fields • Signaling pathways • Therapeutic applications • Bone repair • Bone tissue engineering

Abstract
Pulsed electromagnetic field (PEMF) stimulation, as a prospective, noninvasive, and safe physical therapy strategy to accelerate bone repair has received tremendous attention in recent decades. Physical PEMF stimulation initiates the signaling cascades, which effectively promote osteogenesis and angiogenesis in an orchestrated spatiotemporal manner and ultimately enhance the self-repair capability of bone tissues. Considerable research progresses have been made in exploring the underlying cellular and subcellular mechanisms of PEMF promotion effect in bone repair. Moreover, the promotion effect has shown strikingly positive benefits in the treatment of various skeletal diseases. However, many preclinical and clinical efficacy evaluation studies are still needed to make PEMFs more effective and extensive in clinical application. In this review, we briefly introduce the basic knowledge of PEMFs on bone repair, systematically elaborate several key signaling pathways involved in PEMFs-induced bone repair, and then discuss the therapeutic applications of PEMFs alone or in combination with other available therapies in bone repair, and evaluate the treatment effect by analyzing and summarizing recent literature.

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Introduction

Bone loss and defective repair mechanisms brought by trauma, osteonecrosis, osteoporosis, arthritis, tumors, and other diseases affecting bone cause severe pain, dyskinesia, psychological agony, and economic burden to patients [1, 2]. Therefore, effective treatment strategy for promoting bone growth and remodeling is needed. Pulsed electromagnetic fields (PEMFs) have been recently employed as a effective method to enhance bone repair because of their non-invasiveness, safety, lack of side effects, convenience, and superior treatment prospects in several refractory bone diseases, such as non-unions and delayed healings of

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fractures [3-5], osteoporosis [6, 7] and osteonecrosis of the femoral head (ONFH) [8, 9]. In this review, we analyze and summarize the latest research progress on the underlying signaling pathways of PEMFs-induced bone repair and its therapeutic application.

Basic knowledge of PEMFs for bone repair

In 1892, Wolf indicated that mechanical stress determines bone growth and remodeling [10]. In 1953, Yasuda revealed that bending the long tubular bone is related with the development of electric currents and this instance is defined as piezoelectric phenomenon [11]. Since then, the theory that electrical stimulation is the path for bone formation in response to applied load has been gradually recognized, and various devices have been developed to produce electrical stimulation for promoting the healing of bone fracture. In 1978, Bassett first applied noninvasive PEMFs to treat delayed union or non-union fractures and have achieved good clinical effect [12]. Shortly thereafter, PEMFs were approved as a safe and effective method for treating delayed union or non-union fractures by the US Food and Drug Administration [13, 14]. Inductive coupling is the rationale for the application of PEMFs [15]. PEMFs consist of a wire coil wherein a current passes and a pulsed magnetic field is generated. The pulsed magnetic field, in turn, induces a time-varying secondary electrical field within the bone. The secondary electrical field is dependent on the characteristics of the applied pulsed magnetic field and the tissue properties. Magnetic fields of 0.1–20 G are usually applied to produce electrical fields, ranging from 1 mV/cm to 100 mV/cm in the bone [16]. Through the PEMF device, a time-varying electrical field is produced to simulate the normal response of bone cells physiologically to the applied mechanical stress [17], and the subsequent enhanced growth and remodeling bioeffects on the bone are initiated by the time-varying electrical field.

Underlying signaling pathways

Recently, considerable research progresses have been made in exploring the underlying cellular and subcellular mechanisms of PEMF promotion effect in bone repair. Several key signaling pathways during the osteogenesis and angiogenesis which are two essential aspects for bone repair, were revealed by various studies when the bone was exposed to PEMFs. In this section, we will elaborate the roles of some of these pathways, including Ca^{2+}, Wnt/β-catenin, mitogen-activated protein kinase (MAPK), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β/ bone morphogenetic proteins (BMP), insulin-like growth factor(IGF), Notch, and cAMP/protein kinase A (PKA), in PEMF-induced bone repair.

Ca^{2+} signaling

The therapeutic effect of non-thermal bioeffects of PEMFs on bone disorders is yet to be elucidated because these photons are insufficiently energetic to directly influence the chemistry of cells. Intracellular Ca^{2+} is generally considered as one of the main actors to translate the PEMF signal into a biological signal [18]. Many studies revealed that PEMF signal passes through the cell membrane to set up a time-varying electrical field within the cytosol; this electrical field subsequently induces the release of intracellular Ca^{2+}, leading to increases in cytosolic calcium and activated calmodulin and the enhancement of bone cell viability [17, 19, 20]. Voltage-gated Ca channels (VGCCs), especially the L type, play a pivotal role in intracellular Ca^{2+} release. PEMF exposure significantly elevated the expression levels of VGCCs in MSCs during osteogenesis [21, 22]. PEMF-initiated Ca^{2+} signaling strikingly accelerates the osteogenic differentiation of MSCs as represented by the upregulated osteogenic markers, such as collagen I and ALP, and the increased deposition of extracellular calcium [21]. Accumulated studies indicated that increased intracellular Ca^{2+} caused by PEMF

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stimulation leads to increased nitric oxide levels, which in turn increases the synthesis level of cGMP and the subsequent activation of protein kinase G. Through the Ca^{2+}/nitric oxide/cGMP/protein kinase G pathway, PEMFs promote osteoblast differentiation and maturation, exert their therapeutic effect on bone repair, and remarkably reduce the pain of patients by modulating the release of inflammatory cytokines, such as interleukin-1 beta (IL-1β) [20, 23-27]. Moreover, the activated Ca^{2+}/nitric oxide/cGMP cascade is also closely related to the increased expression of FGF-2 and VEGF, two key regulators of angiogenesis [27]. In addition, the crosstalk between Ca^{2+}, ERK, PKA, and PKG signaling under PEMF stimulation was also reported [19, 22]. All these findings show the prominent role of Ca^{2+} signaling in PEMFs-induced bone repair.

Wnt/β-catenin signaling pathway

Extracellular Wnt ligands bind to their seven-pass transmembrane Frizzled receptors simultaneously with a co-receptor of the arrow/Lrp family (e.g., LRP5 and LRP6), thus stabilizes β-catenin in the cytoplasm and initiates the canonical Wnt/β-catenin signaling pathway [28].This signaling pathway is conserved throughout metazoans and is essential for cell proliferation, differentiation, development, self-renewal, and cell fate determination [29, 30]. Much evidence has suggested that the Wnt/β-catenin signaling pathway acts as a key regulator in PEMF-induced osteogenic differentiation of mesenchymal progenitor cells, bone formation and repair. For instance, *in vitro* assay studies, gene and protein expressions of canonical Wnt/β-catenin signaling pathway, including Wnt1, LRP6, and β-catenin, were all significantly enhanced after PEMF exposure at both proliferation and differentiation stages of osteoblast-like MC3T3-E1 cells [31]. In addition, except the upregulation of mRNA expressions of Wnt1, Wnt3a, LRP5 and β-catenin in tissue derived mesenchymal stem cells (ADSCs), PEMFs intervention could also reduce the expression of dickkopf1 (DKK1) which usually acts as an inhibitor of Wnt signaling pathway [32]. Furthermore, the enhanced Wnt/β-catenin signaling induced by PEMFs notably elevated the expression of proliferation phase related target genes, Ccnd 1 and Ccne 1, and differentiation phase related genes, ALP, OCN, COL1, and Runx2, in osteoblast cells, which accelerated the osteoblasts proliferation, differentiation, and mineralization, three pivotal processes of bone formation [31, 32]. On the other hand, according to *in vivo* assay studies, PEMFs effectively reversed the bone mass loss and deterioration of bone microarchitecture analyzed by microCT and attenuated biomechanical strength deterioration evaluated by three-point bending test in hind limb-suspended ovariectomized rats through the Wnt/Lrp5/β-catenin signal pathway [33, 34], indicating that activating this pathway by PEMF exposure is beneficial for bone disorders.

MAPK pathway

The MAPK pathway is important in the transduction of extracellular signals to various cellular compartments and is involved in cell proliferation, differentiation, migration, and death [35]. Conventional MAPKs include Erk1/2, JNK, and p38. The MAPK pathway plays a critical role in PEMF-induced osteogenic differentiation and osteoblasts' viability and function. For example, extremely low-frequency pulsed electromagnetic field (ELF-PEMF) treatment could significantly increase the total protein content, mitochondrial activity, and ALP activity and enhance the formation of mineralized matrix of human osteoblasts with a poor initial osteoblast function through triggering the ERK1/2 signaling pathway. When the cells were treated with U0126, an inhibitor of the ERK1/2 signaling cascade, the positive effects of the ELF-PEMF treatment on osteoblast function were abolished [36]. Other studies also revealed that the MEK/ERK signaling pathway regulated the promoting effects of PEMF on bone marrow mesenchymal stem cell (BMSC) proliferation, expression of osteogenic genes (RUNX2, BSP, OPN), ALP activity, and calcium deposition [22, 32, 37, 38]. Additionally, one study reported that the p38 MAPK pathway is involved in the increased production of collagen synthesis in osteoblast-like cells stimulated by ELF-EMF exposure [39]. Interestingly, a recent research suggested that a 45 Hz EMF promoted the osteogenic differentiation of adipose-derived stem cells, whereas a 7.5 Hz EMF directly augmented the

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expression of osteoclastogenic markers and regulated the osteoclast differentiation through ERK and p38 MAPK activation [40]. This finding indicated that PEMFs can simultaneously influence osteoblastic and osteoclastic activities under defined electromagnetic conditions.

FGF and VEGF pathways

Osteogenesis and angiogenesis, including cell–cell communication between blood vessel cells and bone cells, are essential for bone repair. Many studies suggested that PEMFs play a promotion effect not only in osteogenesis but also in angiogenesis [41-44]. PEMFs may facilitate bone repair by augmenting the interaction between osteogenesis and blood vessel growth. During this complex process, FGF and VEGF, two key angiogenesis-related cytokines, may play critical regulatory roles. The FGF signaling pathway has been demonstrated to contribute in the regulation of proliferation and differentiation of osteoblasts and in angiogenesis [45] and the VEGF signaling pathway has also been reported to be involved in a reciprocal, functional, and regulatory relationship between osteoblasts and endothelial cells during osteogenesis [46-48]. A study indicated that a 150% increase in FGF-2 mRNA and a fivefold elevation of FGF-2 proteins in human umbilical vein endothelial cells (HUVECs) exposed to PEMF were monitored and the release of functional FGF-2 from PEMF-stimulated HUVECs specially increased endothelial cell proliferation and tubulization, processes that are important for vessel formation [49]. KDR/Flk-1, a tyrosine kinase receptor of VEGF, is autophosphorylated in response to VEGF stimulation and is capable of transducing VEGF signals. One research has revealed that PEMF stimulation significantly increased the expression and phosphorylated levels of KDR/Flk-1 and promoted proliferation, migration, and tube formation of HUVECs [43]. The proangiogenesis effect through the FGF and VEGF signaling pathways of PEMFs provide another explanation for the therapeutic function of PEMFs in bone repair. Many studies are still required to further clarify the efficacy of FGF and VEGF in PEMF-induced bone repair.

TGF-β/BMP pathway

TGF-βs and BMPs, as multifunctional growth factors, belong to the TGF-β super family. The interaction of TGF-βs/BMPs with TGF-β specific type 1 and type 2 or BMP serine/threonine kinase receptors initiates the signaling cascade via canonical (or Smad-dependent pathways) and non-canonical pathways (or Smad-independent signaling pathways) [50]. The TGF-β/BMP signaling pathway plays an important regulatory role in bone repair [51-56]. It is also confirmed to be involved in PEMF-induced osteogenesis. Several studies demonstrated that PEMF stimulation could significantly increase the expression of TGF-β in both osteoblast-like cells and cells from atrophic or hypertrophic non-unions [17, 57-60]. Moreover, a recent research suggested that PEMFs activated the TGF-β signaling via Smad2 in differentiated and mineralizing osteoblasts and augmented the expression of osteoblast differentiation marker genes, such as ALP and type I collagen, andexerted its osteogenesis promotional function [3]. The expression of BMPs in osteogenesis was also enhanced by PEMFs according to *in vitro* and clinical studies [5, 61, 62]. Furthermore, another recent study revealed that PEMFs stimulate osteogenic differentiation and maturation of osteoblasts by primary cilium-mediated upregulated expression of BMPRII, one of the receptors of BMPs, and subsequently activation of BMP–Smad1/5/8 signaling [63]. Given the separate promotional effects

Table 1. Signaling pathways involved in PEMF-induced bone repair

Signaling pathway	Role of PEMF stimulation	References
Ca^{2+}	Activate	17,19,20
Wnt/β-catenin	Activate	31,32,33
MAPK	Activate	22,36,39
FGF	Activate	45,49
VEGF	Activate	43,46
TGF-β/BMP	Activate	3,63
IGF	Activate	70,71
Notch	Activate	73
cAMP/PKA	Activate	38,74

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on the differentiation and maturation of osteoblasts of BMPs and PEMFs, many studies found that combined BMP and PEMF stimulation would augment bone formation to a greater degree than treatment with either stimulus [64-67].

Other pathways

IGF signaling pathway is also an important signaling implicating in osteoblast differentiation and bone formation [68, 69]. It was reported that PEMFs significantly increase the level of mRNA expression of IGF-1 and promote bone formation in rat femoral tissues *in vitro* [70]. In addition, IGF-1 in combination with PEMFs augmented cartilage explant anabolic activities, increased PG synthesis, restricted the catabolic effect of IL-1b, and showed a synergistic chondroprotective effect on human articular cartilage [71]. Another study showed that dexamethasone combined with PEMF upregulated the mRNA expression of IGF-1 and improved dexamethasone-induced bone loss and osteoporosis [72]. Notch signaling is a highly conserved pathway that regulates cell fate decisions and skeletal development. A recent research advocated that the expression levels of Notch receptor (Notch4) and its ligand DLL4 and nuclear target genes (Hey1, Hes1, and Hes5) were upregulated during the PEMF-induced ostogenic differentiation of hMSCs. Moreover, the Notch pathway inhibitors effectively inhibited the expression of osteogenic markers, including Runx2, Dlx5, Osterix, as well as Hes1 and Hes5, indicating that the Notch signaling plays an important regulatory role in PEMF-induced osteogenic differentiation of hMSCs [73]. The cAMP/PKA signaling pathway is another signaling involved in the PEMF-induced bone repair. Recent studies have demonstrated that PEMFs notably increased the cAMP level and PKA activity and accelerated the osteogenic differentiation of MSCs [32, 38, 74]. (Table 1.)

Therapeutic applications of PEMFs in bone repair

The promotional effects of PEMFs on osteogenesis and angiogenesis in bone repair have been well established in either vitro or *in vivo* animal studies. Several key signaling pathways involved in PEMF-induced bone repair were elaborate above. Moreover, several decades of PEMF applications in the treatment of skeletal diseases have clearly proved its potential benefit in augmenting bone repair. This part of review will tackle the recent therapeutic applications of PEMFs in bone repair and evaluate their clinical treatment effect.

Fractures, delayed unions, and non-unions

Fractures, particularly those that had developed into delayed unions or even non-unions, have a substantial clinical, economic, and quality of life impact [75]. Apart from traditional surgical management and rigid fixation (either internal or external), noninvasive PEMFs have already been used effectively in clinics as physical therapy to accelerate and finalize the healing process of a fresh fracture and reactivate the healing process of delayed unions and non-unions for nearly forty years since they were first approved by the US Food and Drug Administration [13, 14]. A recent systematic review and meta-analysis of randomized controlled trials showed that PEMFs significantly shortened the time to radiological union for acute fractures undergoing non-operative treatment and acute fractures of the upper limb and accelerated the time to clinical union for acute diaphyseal fractures [76]. Moreover, a prospective study that evaluated the treatment effect of PEMFs on 64 patients undergoing hindfoot arthrodesis (144 joints) revealed that the adjunctive use of a PEMF in elective hindfoot arthrodesis may increase the rate and speed of radiographic union of these joints [77]. Despite the relative scarcity of well-organized randomized controlled trials, many studies highlight the practice usefulness of PEMFs in treating tibial delayed unions or non-unions, with efficacy up to 87% [13, 15, 78, 79]. Furthermore, in a broad literature review comparing PEMF treatment of non-unions with surgical therapy, Gossling noted that 81% of reported cases healed with PEMF versus 82% with surgery. Obvious therapeutic advantages of PEMFs were showed compared with surgery in treatment for infected non-unions (81%

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versus 69%) and closed injury caused non-unions (85% versus 79%) [80]. In addition, a recent double-blind randomized study advocated that the adjunctive use of PEMF for fifth metatarsal fracture non-unions significantly shortened the average time to complete radiographic union from 14.7 weeks to 8.9 weeks compared with the control group without PEMF exposure; the elevated expression levels of PIGF, BMP-5, and BMP-7, key regulators of angiogenesis and osteogenesis, were first detected in the non-union environment before and after the application of PEMFs [5]. These studies strikingly support PEMFs as an optional and effective method to accelerate fracture healing.

Osteonecrosis of the femoral head

ONFH is the endpoint of a disease process that results from insufficient blood flow and bone tissue necrosis, leading to joint instability, collapse of the femoral head, and joint arthritis that necessitates total hip arthroplasty in many patients [81]. As the mean age of the patients is only approximately 40 years, long-term results of total hip arthroplasty in these young patients are not always satisfactory. PEMFs have been regarded as a prospective noninvasive treatment strategy for ONFH because of their positive effects on osteogenesis and chondroprotective effect of articular cartilage. To date, six clinical studies have investigated and evaluated the therapeutic effect of PEMFs on ONFH [82]. Three studies have used PEMFs as a single management to treat ONFH [83-85] and have revealed that PEMFs can prevent the progression of the disease and significantly preserve majority of femoral heads (80.2% by Massari [83], 88.57% by Cebrian [84], 83.9% by Bassett [85]) in the first stages of avascular necrosis of the femoral head at Ficat 0, I, and II or Steinberg II and III. Moreover, according to two of these studies, PEMFs have also been shown to reverse disease progression. Bassett found that 9 hips showed improvement, and they were all in Steinberg stages II to III, demonstrating a 60% improvement rate. Of these 9 hips, 3 of these even returning to normal [85], whereas Massari showed improvements in Ficat stages [83]. Additionally, PEMFs were also effective in improving osteonecrosis symptoms, including relieving joint pain and alleviating subchondral bone marrow edema [83]. However, for Ficat stage III patients, PEMFs may be beneficial only for younger patients and show no beneficial effect to patients whose hip has already collapsed or is biomechanically compromised. The effect of PEMF therapy as an adjunct to other treatments, such as core decompression and bone grafting, was also assessed in other three studies [8, 16, 86, 87]. By combining PEMFs with core decompression and autologous bone grafts, 81% of patients with Steinberg II scores showed good results radiographically and clinically and had no pain or limp [8]. Moreover, 68% patients treated with PEMFs alone achieved the clinical success determined as marginal pain with retention of the femoral head, while only 44% of those treated with core decompression alone [87]. In sum, all these studies showed the non-invasive therapeutic effect of PEMFs on ONFH, either alone or in combination with other treatments.
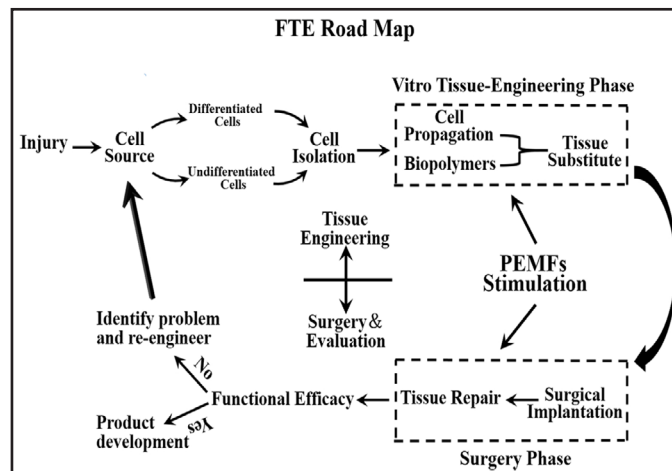
Osteoporosis

Osteoporosis is a worldwide health problem with high morbidity, especially in postmenopausal women [88-90]. It is generally defined as a systemic skeletal disease characterized by low bone mineral density (BMD) and compromised bone strength, leading to enhanced bone fragility, increased fracture risk, and resultant disability, which strikingly affects patients' quality of life [91, 92]. As PEMFs were verified to be equally effective with mechanical stimulation in maintaining or improving bone mass according to experiments of NASA between 1976 and 1979, many clinical studies have gradually achieved positive therapeutic effects for osteoporosis by PEMF exposure [93-99]. Chronic pain is a common symptom of people with osteoporosis [100]. Many randomized controlled trials indicated that PEMF exposure could relieve chronic pain caused by osteoporosis [97, 98]. Moreover, in a study of 126 patients with primary osteoporosis, PEMF provided a faster and significant effect in relieving pain for patients with type I osteoporosis than those with type II [99]. BMD is the gold standard for diagnosing osteoporosis and the best quantitative indicator for forecasting the risk of osteoporotic fracture, monitoring the natural course of osteoporosis,

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and evaluating the effect of osteoporosis. Tabrah indicated that BMD of the treated radii was elevated notably in the sixth week in a clinical study of 20 women with PMOP treated with PEMFs [94]. In Garland's research, which evaluated the effect of PEMFs on knee osteoporosis in individuals with spinal cord injury, BMD was also elevated. At three months, BMD was increased by 5.1% in the stimulated knees but declined to 6.6% in the control knees. PEMFs as a noninvasive physical therapy method avoids the defects of pharmacotherapy for osteoporosis, including the multiple side effects, the more cost and the low persistence.

Fig. 1. Functional Tissue Engineering (FTE) Road Map. This road map was adapted from Ref. 113 and described the combination of PEMFs and tissue engineering to obtain effective tissue substitutes.

More importantly, a randomized, active-controlled clinical trial on postmenopausal osteoporosis (PMO) in Southwest China revealed that PEMFs had the same effect as alendronate, which is, currently, the most commonly prescribed medication for treating PMO within 24 weeks [101]. Furthermore, the hemorheological safety of PEMFs for treating osteoporosis was also observed by a randomized, placebo-controlled clinical study [102]. All these results support the efficiency and safety of PEMFs for osteoporosis treatment and as an advantageous treatment strategy in the future.

Bone tissue engineering

Although the bone has a large self-healing capacity, in some complex clinical conditions, such as large bone defects created by trauma, infection, tumor resection, and skeletal abnormalities, or in cases where bone repair failed, a large quantity of bone regeneration are required [103]. In this case, bone tissue engineering has emerged as a promising alternative to augment insufficient bone repair. Bone tissue engineering generally starts with the *in vitro* culturing of BMSC cells with high osteogenic differentiation potential alone or in the presence of scaffold carriers to develop and manipulate a tissue-engineered construct followed by implanting into the defected site to augment bone repair [104]. Despite bone tissue engineering possess the advantages that the same mechanical and functional properties and superior integration to the host bone tissue and has already acquired some better satisfactions in the clinical treatment of bone defect [105-108], the extended clinical application is hampered by major limitations, such as the poor availability and the time required to differentiate up to a stage suitable for implantation of the BMSCs, the inflammatory environment of implanted site triggered by the bone defect itself and the surgical procedure and the further new bone tissue and surrounding host tissue degeneration after construct implantation [21, 109, 110]. Therefore, the improvement of the present available technologies is still needed to acquire more satisfactory clinical outcomes in bone defect repair. PEMFs, as described above, have a marked function to accelerate the proliferation, osteogenic differentiation, and mutation of BMSCs by activating a series of signaling pathways [7, 21, 25, 31, 38, 73]. Moreover, the expressions of many osteogenesis- and angiogenesis-promoting cytokines, including TGF-β, BMPs, IGFs, FGFs, and VEGFs, in BMSCs are strikingly elevated by PEMF exposure. In addition, the anti-inflammatory effect of PEMFs was also verified by studies [27, 111, 112]. PEMFs could upregulate the expression of A_{2A} AR, which is linked to G proteins and stimulates the activity of adenylate cyclase, mediating an increase in cAMP accumulation [111]. The

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presence of cAMP mediates a number of anti-inflammatory pathways, resulting in the inhibition of TNF-α and IL-1β [111, 112].Altogether, these data display the potential positive functions of PEMFs in bone tissue engineering on the vitro construct culture, in favoring the anabolic activities of the implanted cells, and in protecting the construct from the catabolic effects of inflammation after vivo implantation. An functional tissue engineering (FTE) roadmap to describe the combination of PEMFs and tissue engineering was drawn based on the benefits of combining PEMFs with bone tissue engineering to obtain effective tissue substitutes to realize the structural and functional repair of bone defects and its feasibility of this paradigm was also evaluated (Fig.1) [104, 113]. In spite of these encouraging results, additional studies are needed to promote this therapeutic strategy for bone defect repair in clinics in the future.

Conclusion

In recent decades, PEMF stimulation has received tremendous attention as a prospective, noninvasive, and safe physical strategy to accelerate bone repair. Physical PEMF stimulation initiates the signaling cascades, which effectively promote osteogenesis and angiogenesis in an orchestrated spatiotemporal manner, ultimately enhancing the self-repair capability of bone tissue. Although the bone repair promotion potential of PEMF stimulation has showed positive benefits in the treatment of various skeletal diseases, many studies about PEMFs in experimental biology and clinical therapy are still needed to make them more effective and extend their clinical applications.

In this review, we elaborated the involvement of various key molecular signaling pathways in PEMF-induced bone repair. Targeting the molecular signaling pathways described above may be a prospective strategy to further enhance the bone repair promotion effect of PEMFs via increasing the number of osteoblasts and their maturation and elevating endothelial cell proliferation and tubulization, processes important for osteogenesis and angiogenesis. For instance, a small molecule inhibitor termed 603281-31-8 could impair the activity of GSK3b, which plays a negative regulatory role in the Wnt signal transduction pathway, and result in considerable increase in bone mass [114]. Inhibiting DKK1 activity or using anti-sclerostin antibody in mice increased bone formation and bone mass [115]. Combining PEMF exposure with these indirect Wnt/β-catenin signaling pathway activators may further activate this pivotal signaling pathway and enhance the biological response of bone tissue to PEMF stimulation, leading to more effective bone repair. However, risk of cancer, osteoarthritis symptoms and osteophytes are some the evils of the long-term activation of the Wnt/β-catenin signaling pathway. Additionally to the Wnt signaling pathway, many studies have showed that combining PEMF stimulation with BMPs or IGFs could also augment bone formation [65, 70]. We also discussed the recent clinical therapeutic application of bone repair promotion potential of PEMFs in the treatment of skeletal diseases, such as fractures, delayed unions and non-unions, ONFH, and osteoporosis. The clinical latent benefits of the incorporation of PEMFs and bone tissue engineering for large bone defect repair were also evaluated. Despite positive effects of PEMF stimulation for bone repair alone or as an adjunct to other treatments were definite in clinics, sometime, the effectiveness is discrepant for the same disease in different studies [6, 15]. This is mainly because of the lack of a standardized intensity, frequency, and therapeutic course and time of PEMFs. In this regard, more studies need to be conducted to determine unitive and high-efficiency parameters. In summary, as PEMF stimulation offers noninvasive, effective, safe, and convenient effects, it opens up a new avenue for bone repair. However, much work remains to be done to extend its clinical application in the future.

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Jie Yuan conceived and wrote the manuscript and prepared figure; Wenxue Jiang and Fei Xin provided expert comments and edits. All authors reviewed the manuscript.

Disclosure Statement

No conflict of interest exists.

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