REVIEW ARTICLE

Progress of Periosteal Osteogenesis: The Prospect of In Vivo Bioreactor

Xiaoxue Chen, MD, PhD[†], Baofu Yu, MD, PhD[†] , Zi Wang, MD, PhD[†], Qingfeng Li, MD, PhD, Chuanchang Dai, MD, PhD, Jiao Wei, MD, PhD

Department of Plastic and Reconstructive Surgery, The Ninth Affiliated Hospital of Shanghai Jiaotong Medicine University, Shanghai, China

Abstract
Repairing large segment bone defects is still a clinical challenge. Bone tissue prefabrication shows great translational potentials and has been gradually accepted clinically. Existing bone reconstruction strategies, including autologous periosteal graft, allogeneic periosteal transplantation, xenogeneic periosteal transplantation, and periosteal cell tissue engineering, are all clinically valuable treatments and have made significant progress in research. Herein, we reviewed the research progress of these techniques and briefly explained the relationship among *in vivo* microenvironment, mechanical force, and periosteum osteogenesis. Moreover, we also highlighted the importance of the critical role of periosteum in osteogenesis and explained current challenges and future perspective.

Key words: *in vivo* bioreactor; periosteal microenvironment; periosteum osteogenesis; regeneration medicine

Introduction

The periosteum is connective vascularized tissue which covers all bone surfaces. It consists of fibrous and cambium layers (Figure 1A). Numerous studies have confirmed the critical role of periosteum in osteogenesis.

Infection, congenital abnormalities, traumatic incidents, and cancer resections may result in a significant volume of bony defects. Approximately 5%–10% of cases may suffer delayed bone healing or non-union in patients with fractures, resulting in significant social and economic burdens[1]. Autologous bone grafting is the golden standard treatment. This procedure requires harvesting bone from the donor site, which injures the donor site and prolongs the surgical process. Besides, the available bone volume of autologous bone grafting is also limited.

However, bone healing induced by periosteum creates excellent bone integrity including minimal ectopic ossification and appropriate vascularization, indicating an advantage in repairing bone defects. The periosteum outer layer mainly concludes elastic fibers and collagen as well as a vascular network. Thus, it supplies blood and structural support. The cambium layer has rich osteoblasts and mesenchymal stem cells (MSCs). The MSCs have multipotential differentiation potential, which helps them to form chondroblasts and osteoblasts when bone formation is required[2]. Various cells collaborate during the biomineralization process. Noncollagenous proteins (dentin matrix protein 1, alkaline phosphatase, bone sialoprotein), proteoglycans, and collagens are secreted in different steps[3]. There is amorphous calcium phosphate formation, apatite nucleation, and crystal growth under the coordinated operation of the periosteum. Therefore, periosteal osteogenesis *in vivo* is critical for treating bone defects in a clinical setting.
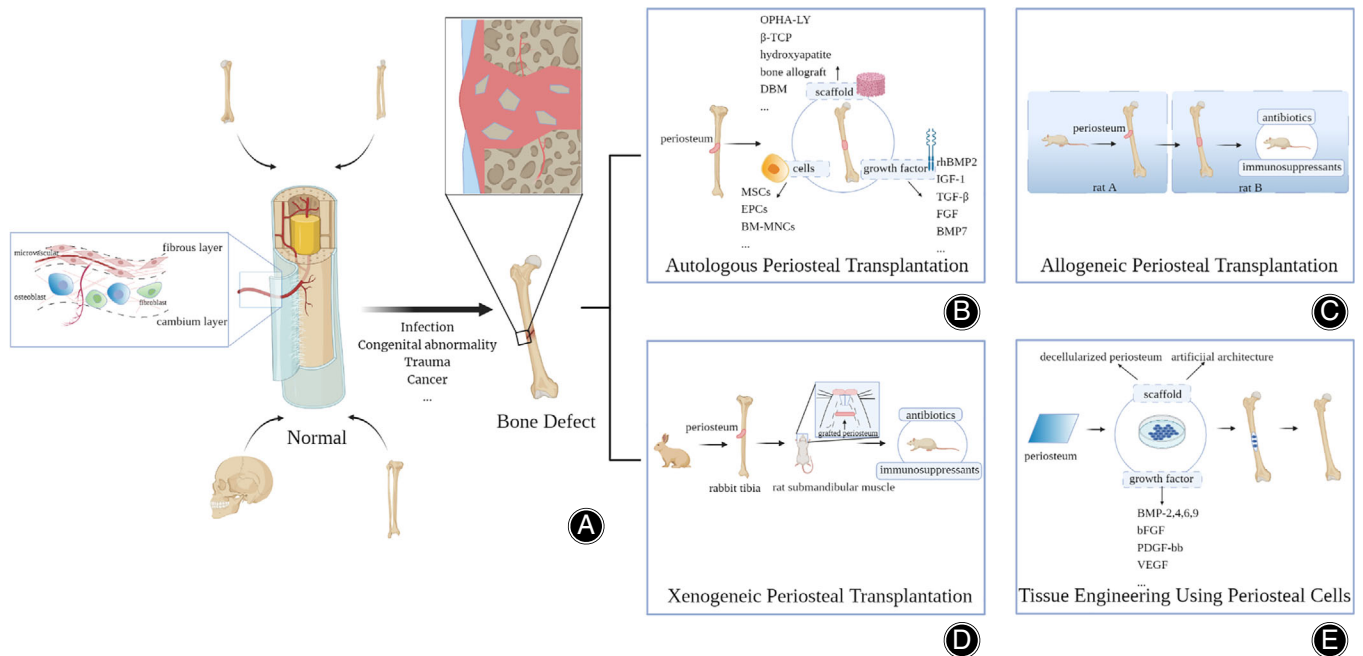
The current research mainly focuses on the role of periosteal osteogenesis after fracture or bone injury, and little has been done on the process of periosteal pre-installation osteogenesis *in vivo*. The *in vivo* microenvironment (IM) of the periosteum is essential during osteogenesis. Extensive research focusing on periosteal osteogenesis *in vivo* has shown promising clinical outcomes. Below, we briefly explain them.

Fig. 1 Periosteal osteogenesis *in vivo*. (A) Periosteum structure. (B) Autologous periosteal transplantation procedure. (C) Allogeneic periosteal transplantation procedure. (D) Example of xenogeneic periosteal transplantation. (E) Tissue engineering using periosteal cells procedure. MSCs, mesenchymal stem cells; EPCs, endothelial progenitor cells; BM-MNCs, bone marrow mononuclear cells; β-TCP, beta-tricalcium phosphate; DBM, demineralized bone matrix; BMP-2,4,6,9, bone morphogenetic protein 2,4,6,9; IGF-1, insulin-like growth factors-1; TGF-β, transforming growth factor-β; FGF, fibroblast growth factor; BMP-7, bone morphogenetic protein 7; bFGF, basic fibroblast growth factor; PDGF-bb, platelet derived growth factor-bb; VEGF, vascular endothelial growth factor

Search Strategy and Selection Criteria

Materials for this review were identified by searches of PubMed and references from relevant articles. Keyword search terms included "periosteum osteogenesis," "periosteal microenvironment," "mechanical osteogenesis," and "periosteal distraction osteogenesis." Most of the references published in English between 1990 and 2022 were included. The criteria and process of literature screening flowchart is shown as Figure 2.

Periosteal Osteogenesis *In Vivo*

Constructing the Subperiosteal Space

Maintaining a certain submembrane space plays a vital role in inducing bone regeneration. The periosteum acts as a physical barrier and the submembrane space can be created with materials, such as hydroxyapatite or expander. In a rabbit model, the new bone was transplanted to the defected area after injecting calcium alginate gel with fibroblast growth factor (FGF), transforming growth factor-β (TGF-β) and other ingredients under the tibial periosteum. Consequently, calcification and bone formation increase in the defected area[4]. Huang *et al.*[5] reported a calcium-containing colloidal scaffold material, which could recruit many seed cells and cytokines from the subperiosteal layer. Using a
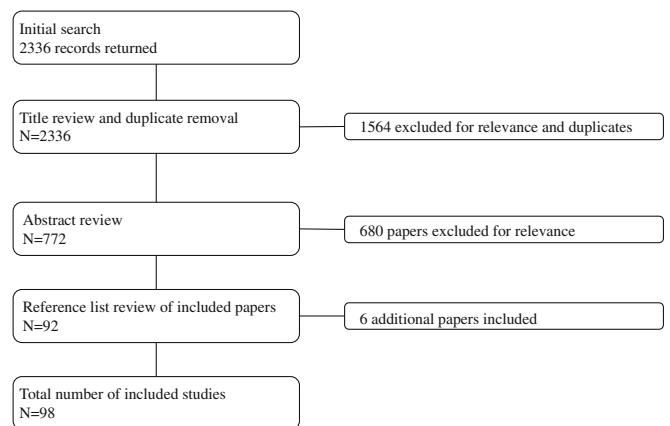
Fig. 2 The criteria and process of literature screening flowchart

calcium-containing colloidal scaffold, they successfully repaired autologous long bone defects in rabbit and dog models[5]. There are also successful models for flat bone defects. The subperiosteal injection of simvastatin (SIM) with strontium hydroxyapatite/alginate (SrHA/Alg) could stimulate vertical bone augmentation of rat calvaria, and the 0.02 mg of SIM seems to be the optimal dose[6]. The main disadvantages of this method are: (1) if the *in vitro* preparation of

materials is not strict aseptic operation, an infection may happen; (2) the subperiosteal injection process may cause pain; (3) the injection of foreign bodies may produce transient inflammatory reactions; (4) it is not yet possible to supply bone in large quantities; (5) if the objection strays into the surrounding tissues, it may cause local adhesion or scarring, etc.[7]

Autologous Periosteal Transplantation

Many studies have confirmed the osteogenesis of free periosteal transplantation, its common composition is shown in Figure 1B. Free periosteum transplantation is often in a collapsed state, affecting bone formation. Some researchers used autologous periosteum to wrap the tendon combined with cancellous bone homogenate and recombinant human bone morphogenetic protein-2 (rhBMP-2). The lunar bone was successfully reconstructed after implanting the complex substance into the autologous joint cavity. The beta-tricalcium phosphate (β-TCP) scaffold is also commonly used. When combining β-TCP scaffold, tibial upper pedicle periosteum with autologous bone marrow mesenchymal stem cells (BMSCs), it is feasible to prefabricate vascularized bone *in vivo*[8]. It has been reported that large craniofacial defects

in the ovine model have been successfully reconstructed[9]. Pedicled periosteum and a demineralized bone matrix scaffold can prefabricate bone graft with higher osteo-inductive angio-inductive properties and increase biomechanical properties compared to the muscular pouch strategy[10]. At present, autologous periosteal transplantation is relatively mature in animal models, and some explorations have also been carried out in clinical operations[11–29]. Du *et al.*[11] found that acetabuloplasty with autologous tibial periosteal transplantation might be a promising and effective adjunctive treatment for hip articular cartilage defects. Outcomes of associated clinical and preclinical autologous periosteal osteogenesis repairing bone defects studies are summarized in Tables 1 and 2.

Allogeneic and Xenogeneic Periosteal Transplantation

Allografts are relatively easy to obtain and can be used in large quantities. However, their activities and the ability of bone formation are significantly reduced after processing and sterilization. The bone allograft was reported decades before, and it has been widely used in a clinical setting. However, there are few studies on the pure periosteal allograft. The basic process is shown in Figure 1C. Currently published

TABLE 1 Autologous periosteal transplantation clinical studies							
References	Periosteum size	Defect size	Periosteum acquisition site	Defect treated	No. of patients	Follow-up time	Detection
Kademani et al.[10]	No report	5 cm in length, 2 cm in height and width	Femur	Maxilla	1	4 months	Frontal view, imaging detection
Vegas et al.[11]	No report	3.5 cm	Femur	Ulna	2	7 months	Orthopedic Surgeon, imaging detection
		3 cm		Ulna	1		
		4.5 cm		Humerus	1		
		3.5 cm		Phalanx	1		
		1 cm		Phalanx	1		
		5 cm		Clavicle	1		
		3.5 cm		Tibia	1		
Soldado et al.[12]	21.4 cm → 13.9 cm	No report	Fibula	Ulna	1	32 months	Imaging detection
				Femur	3		
				Geniculum	2		
				Face	1		
				Tibia	2		
Soldado et al.[13]	19 cm → 14 cm	2 cm	Fibula	Tibia	1	1 year	Imaging detection
Neiva et al.[14]	Larger than the width of the residual hard palate cleft	>15 mm	Calvarium	Palate	45	6 years	Cast analysis, imaging detection
Soldado et al.[15]	20 cm → 15 cm in length and 4 cm in width	~18 cm limb-length discrepancy	Tibia	Femur	1	2 months	Imaging detection
	No report	1/3 tibia	Tibia	Tibia	1	3.5 months	
Sierra et al.[16]	9 × 3 cm	6.2 cm	Fibula	Mandible	1	6 months	Intraoral view, imaging detection
Soldado et al.[17]	15 cm × 3.9 cm	6 cm	Tibia	Tibia	1	48 months	Imaging detection
	15 cm × 3.9 cm	15 cm		Humerus	1	24 months	
	9 cm × 3.4 cm	2 cm		Clavicle	1	42 months	
	10 cm × 2.7 cm	2.5 cm		Clavicle	1	12 months	
	14 cm × 3.8 cm	2 cm		Femur	1	12 months	
	14 cm × 3.9 cm	2 cm		Femur	1	8 months	

TABLE 2 Autologous periosteal transplantation animal model studies

References	Animal model	Periosteum size	Defect size	Periosteum acquisition site	Defect treated	Addenda	Follow-up time	Detection
Ueno et al.[18]	Rabbit	7 × 15 mm	5 × 15 mm	Tibia	Jaw	None	28 days	Imaging detection, histology
Ueno et al.[19]	Rabbit	7 mm × 15 mm	Unilateral mandibular head	Tibia	Mandible	None	45 days	Imaging detection, histology
Caria et al.[20]	Rat	No report	2 mm diameter	Femur	Premaxilla	Hydroxyapatite	16 weeks	Imaging detection, histology
Ueno et al.[21]	Rat	7 × 5 mm	7 mm diameter	Tibia	Calvaria	β-TCP	30 days	Imaging detection, histology
Ueno et al.[22]	Rat	3 × 5 mm	4 mm diameter	Tibia	Calvaria	None	30 days	Histology
Gemalmaz et al.[23]	Rabbit	13 mm × 7 mm → 1 to 2 mm^2 pieces	5 mm diameter, 12 to 15 mm deep	Tibia	Femur	0.4 cc of Cem-Ostetic™granules	6 weeks	Histology
Barutca et al.[24]	Rat	10 × 10 mm	Starting at the anterior margin of the first deciduous molar and ending on the posterior margin of the second molar	Calvaria	Palate	None	12 weeks	Histology
Yu et al.[25]	Beagle	No report	15 mm	Femur	Radius	Fascia lata	20 weeks	Imaging detection, histology
Nau et al.[26]	Rat	15 mm perimeter	7 mm	Femur	Femur	β-TCP + MSCs/EPCs	8 weeks	Imaging detection, histology
Pan et al.[27]	Rabbit	30 × 10 mm	20 mm	Tibia	Femur	β-TCP + BMP-2	8 weeks	Imaging detection, histology, clinical observation

β-TCP, beta-tricalcium phosphate; BMP-2: bone morphogenetic protein; EPCs: endothelial progenitor cells; MSCs: mesenchymal stem cells.

results on allogeneic periosteum transplantation often include transplantation of cortical bones together[14]. Some scholars transplanted the allogeneic periosteum into the muscle and observed bone formation[30].

Xenotransplantation of periosteum has also been explored. Ueno et al.[31] harvested young rabbit tibia periosteum and grafted it into old rats, and observed the osteogenic potential, as shown in Figure 1D.

These two kinds of transplantation have several disadvantages, including the risks of immunologic rejection, disease transmission, infection, delayed bone healing, cartilage calcification, osteoma, bone metabolic disease, inflammatory arthritis, etc. Besides, when massive allografts are used, their avascular condition may result in subsequent multiple complications, such as nonunion and late fractures[14].

Tissue Engineering Using Periosteal Cell
Periosteum-derived cells (PDCs) have relatively stable directional differentiation ability and maintain good osteogenic activity after in vivo implantation[32]. They exhibit higher clonogenicity and differentiation capacity than BMSCs[32]. PDCs from older adults have comparable capability to the younger patients' cells in producing bone, significantly expanding the beneficiary population[33]. Strong osteogenic potential is showed by CD90(+) periosteum-derived cells for cell types and composition[34]. Equal amounts of MSCs and osteoprogenitor cells can better mimic the production of

natural periosteal cell population and paracrine factors, thereby promoting the healing of allografts[35]. However, they have not yet reached the significant level of autograft[35].

The bone formation process is slow, and the amount of new bone is usually limited. When cytokines are added, the effect of bone forming will be promoted. There is the most quantity bone formation in BMP-6 and bone morphogenetic protein 2 (BMP-2)-coated scaffolds in vivo implantation among BMP-2, −4, −6, and −9[36]. The use of combined cytokines is also feasible. It has also been confirmed that BMP-2 combined with platelet-derived growth factor-bb (PDGF-bb) or vascular endothelial growth factor (VEGF) could sufficiently stimulate osteoblast differentiation in vivo, allowing effective bone regeneration[37]. The scaffolds have also been constantly improved. For instance, polycaprolactone nanofiber scaffold has various applications; adding silica nanoparticles (silica or $nSiO_2$) can enhance periosteal cells' growth in vivo for humans[38]. Introducing phosphate groups also improves the efficiency of chitosan/xanthan-based scaffolds[39]. The delicate balance between cytokines and scaffolds needs to be explored, such as matching BMP6 dosage and calcium phosphate properties[40].

The operation process of periosteal cell tissue engineering is shown in Figure 1E. The clinical application still has many concerns, including immunologic rejection, exogenous cell survival, and viral infection risk. It cannot support matrix synthesis and cell survival because of lacking its own nerve and vascular networks, the overall complexity of new tissue is

limited[7]. So, it must wait for the ingrowth of these network structures from its surroundings[5]. Besides, researchers mainly focus on certain structural features of the periosteum, ignoring the functional environment such as nervous, immune, and hormonal systems. Bolander *et al.*[41] presented a bioinspired approach closely resembling the natural endochondral process. It uses serum-free human periosteum cells and can successfully bridge the critical size long-bone defect.

Influencing Factors of Periosteal Osteogenesis

Explore the Mechanism of In Vivo *Microenvironment*
The feasibility of bone and complex joints generation without exogenous factors has been demonstrated, and the IM plays a pivotal role, as shown in Figure 3. Self-regenerated bone based on the IM alone has a neurovascular bundle and perfect vascularization, showing similar biomechanical and biological function to native controls[42–45].

There are three main components of IM, including periosteum cambium layer, mechanical stimulation, and stem cell chemotaxis.

The cambium layer is highly cellular. The pluripotent cells in the cambium layer can differentiate into chondroblasts, osteoblasts, and osteoprogenitor cells. Hypertrophic chondrocytes locate around the cancellous and cortical bone in the subperiosteal space[42]. Cells in the periosteum have now been shown to have potent osteogenic regeneration capabilities. Periosteum-derived progenitor cells (PDPCs) are promising for bone tissue engineering since it can move towards osteoblastic differentiation[46]. Periosteal stem cells (PSCs) have more robust self-renewable potential and multipotency than BMSCs. Macrophage-lineage tartrate-resistant acid phosphatase–positive (TRAP+) cells in the cambium layer are capable of promoting periosteal osteogenesis and regeneration by recruiting periosteum-derived cells[47].

Various types of stem cells have enhanced bone regeneration and repair. During the ossification process, various immune cells (e.g. macrophages), cytokines, chemokines, enzymes, and adenosine participate in recruiting and modulating mesenchymal stem cells (MSCs)[48,49]. Vascular endothelial growth factor (VEGF)/insulin-like growth factors-1 (IGF-1) can activate phosphatidylinositol 3′-kinase (PI3K)-AKT and mitogen-activated protein kinase (MAPK) pathways of PDPCs[46]. Paracrine stimuli can differently regulate genes related to PDPC stemness, such as Nanog transcription factors, Sox2 and Oct4[46]. Increased growth factors such as basic fibroblast growth factor (bFGF), angiopoietin-1 (ANG-1), Ca^{2+}, Zn^{2+}, Wnt and BMP-signaling, as well as reduced TGF-β-signaling, can promote osteogenesis[48,50,51]. MSCs can promote osteogenesis by secreting TGF-β, VEGF, and stromal cell-derived factor-1 (SDF-1)[50]. When there is an injury site, periosteal stem cells will rapidly migrate, supply osteoblasts, and promote growth of new periosteum[52]. Consequently, the osteogenesis process is the result of the precise regulation of numerous cells and cytokine networks, and the understanding of the osteogenic microenvironment can help for better osteogenesis.

Abandoning exogenous additives reduces unknown risks (e.g. growth factors can stimulate malignancy) and accelerates clinical translation[42]. However, it still has several challenges, such as a long period of several months for osteogenesis, the need for constant mechanical stimulation and the limited construct sizes, etc. The in-depth study of the IM is expected to improve them and realize the clinical translation.

Mechanical Force and Periosteum Osteogenesis
Mechanical stress is easier to control than biochemical signals, and it lacks the adverse effects of additives and genetic approaches. The supra-periosteal transport distraction osteogenesis has been successfully performed to reconstruct the mandible segmental defects in patients[53]. Mechanical forces
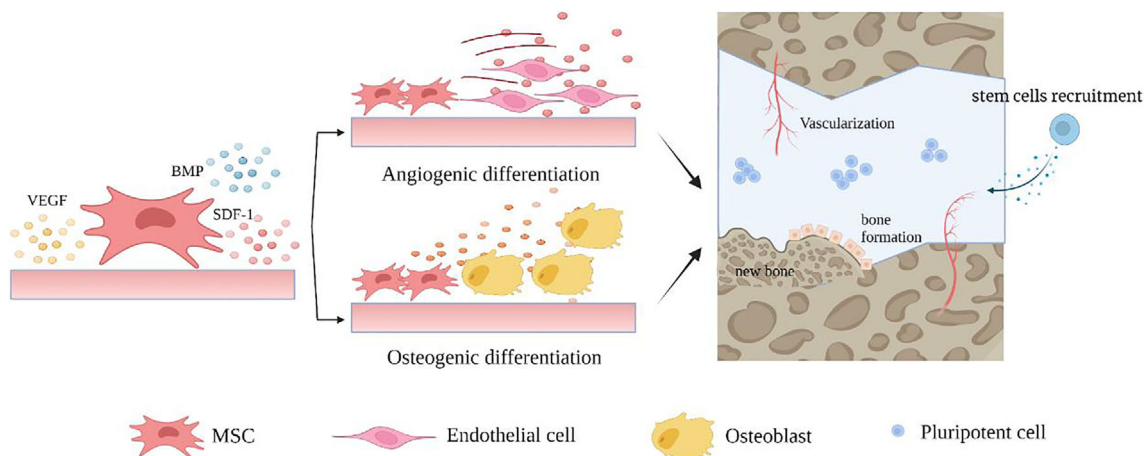
Fig. 3 Periosteal osteogenesis *in vivo* microenvironment (IM). MSC, mesenchymal stem cell; VEGF, vascular endothelial growth factor; BMP, bone morphogenetic protein; SDF-1, stromal cell-derived factor-1

on the periosteum can enhance periosteum's tissue regeneration *in vivo* and *in vitro*. The mechanism is shown in Figure 4. They activate osteogenic differentiation of progenitors, such as alpha-smooth muscle actin (αSMA)-labeled progenitors[54].

Periosteum Structure and Mechanical Induction

Periosteum exhibits smart mechanical and permeability properties. If there is no prestress, the degree of collagen crimps increases two-fold than the samples with prestress. Besides, the periosteum's stem cell niche may serve as a mechano-sensor and an actuator for healing through cellular and molecular trafficking[55]. The outer periosteum is more sensitive to tension than the inner periosteum. The basic mechanism of distraction to promote periosteal osteogenesis is that the osteoblasts in the periosteum are sensitive to the mechanical environment. The tension receptors on the osteoblast membrane respond to stress changes, inducing osteoblasts and other cells to migrate and secrete extracellular matrix, promoting bone healing. From this, it can be seen that the periosteal structure is very suitable for sensing mechanical force, and different parts have different characteristics.

Mechanical Force Sensing Mechanism

At a cellular level, the nucleus and cell membrane can both respond to mechanical forces. The periosteum mechanical environment concludes multiple content such as prevailing deviatoric, stresses and shape-changing due to the material properties and geometry of periosteum[56]. The putative role of shape and volume-changing stresses on stem cell differentiation has been extensively proved during the last decade[55].

Besides, the nucleus is a cellular mechanosensor. When prestress is removed from the periosteal tissue, the cells with rounded nuclei immediately increased before proliferation and migration. Moreover, there is mechanical coupling among the cell nucleus, structure, shape, extracellular matrix, and function[57].

Moore *et al.*[58] found that periosteal progenitors show osteogenic response to both direct physical stimulation and paracrine pathways. Besides, the primary cilium is significant in this procedure of periosteal osteo chondroprogenitors (OCPs)[58]. The cell membrane alone can transduce physical stimuli, too[59].

Mechanical Force and Gene Expression

Mechanical loading links to gene expression patterns, increasing the proliferation of periosteum-derived stem cells[55]. Deviatoric (shape-changing) stresses and exogenous dilatational (volume-changing) modulate changes in MSC gene expression. Many genes are involved in osteogenesis. Prx1 is confined to the perichondrium and periosteum after birth[60], and restricted to the periosteum during adulthood[56]. The callus is populated by Prx1-expressing cells during the fracture-healing procedure. The cells not only receive osteocytes' signals but also sense mechanical stimulation. Mechanical loading recruits Prx1-expressing progenitors and promotes their osteogenic differentiation[61]. RUNX2 and BMP-2 are bone-forming genes, and their expression can increase after mechanically stretching the periosteum. Upon mechanical stimulation of tissue, the soluble extracellular factors such as ATP and UTP are released and activate Runx2[62].
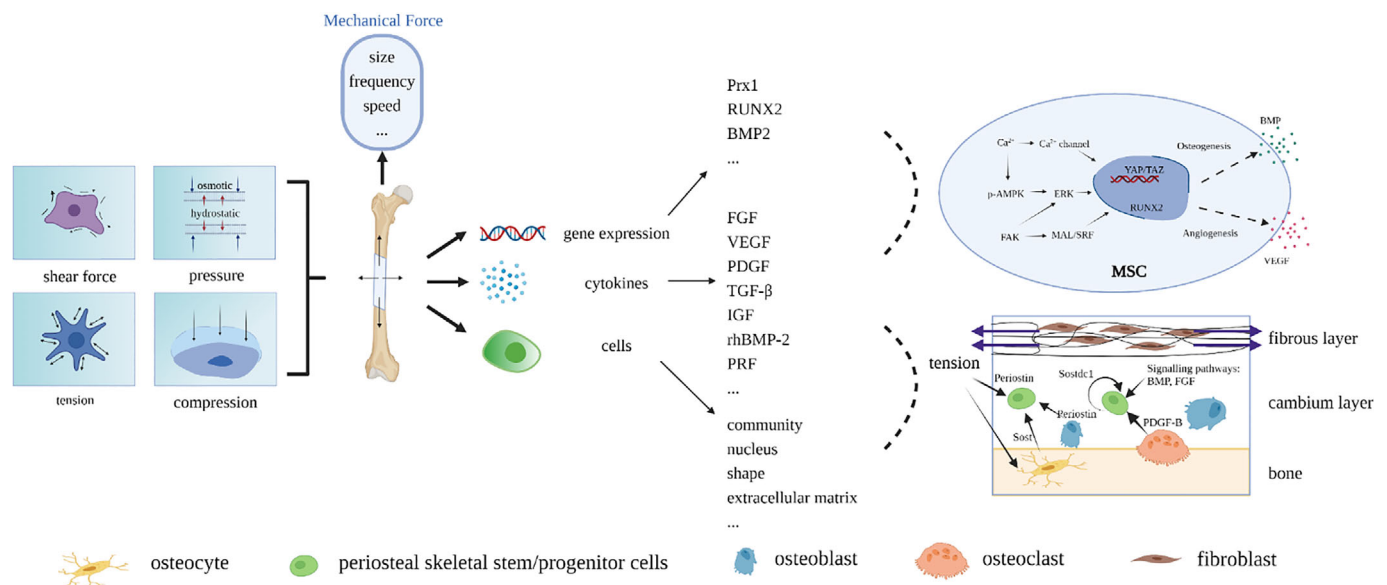
Fig. 4 Mechanical Force Parameters and its influence on gene expression, cytokines, and periosteum cells. FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; IGF, insulin-like growth factors; BMP-2, bone morphogenetic protein 2; PRF, platelet-rich fibrin.

Mechanical Force and Cytokines

The molecular biology of mechanotransduction is elusive. There are several key signaling pathways, such as the Wnt pathway, TGF-β, BMP, and retinoic acid. They compartmentalize and directly couple to mechano-sensitive cellular structures or proteins, such as focal adhesions, cilia, cell–cell junctions, or lamellipodia[63]. Protein β-catenin (βcat) can activate Lrp5; however, induced bone formation only requires low levels mechanical force on the periosteum[64]. The differentiation of MSCs can be regulated by osteogenic growth factors such as BMP-2, -4, -6 enhancing bone formation. Besides, some angiogenic growth and osteogenic factors, such as b-FGF, VEGF, PDGF, and platelet-rich fibrin are also upregulated[65,66]. They can promote not only the differentiation and proliferation of osteoblasts, chondrocytes, and osteoprogenitor cells but also the formation of an extracellular matrix. Adenovirus-NEL-like molecule-1 protein can improve regeneration of bones and efficiently accelerate bone union during femoral distraction osteogenesis in a rat model[67]. In addition to the factors that promote osteogenesis, some factors may also inhibit the osteogenic response. Low-dose ethynylestradiol represses the response to mechanical loading of large bone periosteal surface. However, it does not affect the endocortical bone surface of growing male rats. Nevertheless, more additional mediators need to be explored.

Influence of Mechanical Force Parameters

The osteogenesis of the periosteum in the traction is affected by the size, frequency, speed, and other factors of the distraction stress. Cyclic stress has higher osteogenic efficiency than continuous stress. Besides, dynamic distraction is more moderate, so that the osteogenic potential of the periosteum could be protected from excessive stretch[65]. If the periosteum is stretched with a low distraction speed, it assists the entry, differentiation, and proliferation of MSCs and osteoblasts and promotes blood vessel formation. Low magnitude and low frequency cyclic tension forces have a positive effect on osteoblast differentiation of stem cells derived from human periosteum[68]. The mid diaphysis periosteum surface increases relative mineralizing surface (rMS/BS) and relative bone formation rate (rBFR/BS) with mechanical strain in a dose-dependent method[69]. Besides, there is a dose–response relationship between the bone-forming periosteal surface and loading[54]. Fibrous tissue formation can be a result of a relatively high loading, while the cartilage formation can be suppressed by a relatively low frequency or loading strain, resulting in the endochondral ossification[70]. The tensile strain axial direction also correlates to osteogenic activity. Anisotropic axial moderate strain (5%–8%) is better than isotropic axial strain[71]. Cell mechanical parameters are mostly studied *in vitro* and only a few are associated with experiments *in vivo*. Sun *et al.*[72] observed a periosteal dose response with increasing magnitude loading, they assessed several loading parameters. Mechanics experiments in humans may be more inclined to use cadavers[73]. Further

experiments are needed on how to better tune mechanical parameters *in vivo*, as there is still a long way to go.

Periosteal Distraction Osteogenesis

It has been proposed that a slow, continuous, and steady stretch of any living tissue can bring it into a state of cellular proliferation and activation, ultimately regenerating new tissue[74–75]. Periosteum plays an important role in regeneration and repair of bone tissue as it contains a variety of undifferentiated cells and tissue. Schmidt *et al.*[76] reported periosteal distraction technique for inducing osteogenesis in a rabbit model. The number of osteoblasts increased, and the proliferation of the periosteum was shown. Some other animal experiments have also demonstrated that distracting periosteum can form new bone[65,77–78]. It should be noted that most of the research on periosteal distraction is carried out on experimental animals, and there is nearly no clinical application. These studies mostly concentrate on verifying that periosteal distraction can promote osteogenesis and angiogenesis. Therefore, more clinical observations and more application sites need to be explored.

Other Influencing Factors of Periosteal Osteogenesis

In addition to mechanical effects, electrical stimulation, electromagnetic field stimulation, hyperbaric oxygen[4,79], ultrasound, localized infection, hormonal status[80], and other treatments can also affect the osteogenesis of the periosteum. The electromagnetic field generated by mobile phones alter mechanical properties of bones such as stress and energy. The influencing factors are listed in Table 3. It should be noted that the role of influencing factors may be related to individual gender and growth stages[85]. More factors and specific adjustment conditions need to be further explored.

Outstanding Questions

The Source of Obtaining Periosteum

Given the good osteogenic properties and minimal morbidity in the donor area, periosteal osteogenesis has been identified. The cell populations and the structure of the periosteum are site-specific; thus, there is a different osteogenesis ability. Fujii *et al.*[93] described different differentiation patterns between tibia and calvaria periosteum cells. Load-bearing bones' periosteum is significantly more osteogenic than flat bones[94]. Higher alkaline phosphatase, osteocalcin expression, and greater neo-bone regeneration can be caused by the construct implanted with grafted tibial periosteum[95]. Different parts of the periosteum from the same bone also present differently. For example, periosteum populations of the distal and medial femur are different at birth and change with age[96]. Therefore, selecting the most suitable periosteal source site for different defect sites in the future is an important issue worthy of being explored.

Rib periosteum is a direction worth attention paying, since the rib defect repair is relatively fast[97]. Its source is abundant, and the surroundings provide a natural fixator, so

TABLE 3 Influencing factors of periosteum osteogenesis

Promote osteogenesis		Inhibit osteogenesis	
References	Influencing factor	References	Influencing factor
Rubin et al.[81]	Pulsed electromagnetic field	Pytlik et al.[90]	Retinol
Bowman et al.[82]	Progesterone	Metzger et al.[91]	Inflammation
Tang et al.[83]	Prostaglandin E2	Zhuang et al.[92]	Hypoxia
Pytlik et al.[84]	Simvastatin	-	-
Matsumoto et al.[85]	Estrogen	-	-
Uysal et al.[86]	Vitamin C	-	-
Hu et al.[87]	Magneto-mechanical stimulation	-	-
Vavva et al.[88]	Ultrasound	-	-
Gomes et al.[89]	Laser	-	-

there is less anatomical variation and relatively simple surgical procedure. Besides, it can be more easily manipulated because it is thicker than the femur[98]. Thirdly, the muscular layer of the chest wall is thin, and it is easily accessible and well-visible. Most importantly, respiratory mechanics is a key constant stimulus in bone formation[42]. It is more effective in humans than animals, as a human is bipedal and has greater breathing intensity.

From Preclinical to Clinical Application

Many successful animal models have been established in previously published studies; however, they mainly focus on autologous periosteum transplantation. It still needs more extensive animal experiments focusing on allogeneic transplantation and xenotransplantation. Whether these two strategies can efficiently repair bone defects in animals remains to be explored. As for clinical application, even for autologous periosteal grafts, the experimental subjects are primarily children, and the periosteum area is greater than the bone defect. Therefore, more clinical studies should be conducted for middle-aged and older adults. How to repair larger bone defects with a smaller periosteum area also needs to be improved.

Besides, bone defects in humans are more complicated than in animals. Thus, we need further evidence to better understand, such as clarifying the optimal force frequency and magnitude to improve the differentiation of osteoblasts.

Conclusion

Although each existing method has its challenges to overcome, existing studies have confirmed that periosteal osteogenesis has significant potential for further practical application, and the periosteum plays a central role in osteogenesis. During periosteum growth, the influence of micro-environment *in vivo* and mechanical force cannot be ignored and should be further investigated. We look forward to their practical application in future clinical work.

Author Contribution

Study design: X.X.C., B.F.Y., Q.F.L., C.C.D., J.W.; Data collection: X.X.C., B.F.Y.; Figures: X.X.C., B.F.Y., Z.W., J.W.; Tables: X.X.C., B.F.Y., J.W.; Writing: X.X.C., B.F.Y., Z.W., Q.F.L., C.C.D., J.W.

Conflicts of Interests

All authors declare that no conflicts of interest exist.

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