

Barrier Membranes for Guided Bone Regeneration

Subjects: Dentistry, Oral Surgery & Medicine

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Guided bone regeneration (GBR) has become a clinically standard modality for the treatment of localized jawbone defects. Barrier membranes play an important role in this process by preventing soft tissue invasion outgoing from the mucosa and creating an underlying space to support bone growth. Different membrane types provide different biological mechanisms due to their different origins, preparation methods and structures. Among them, collagen membranes have attracted great interest due to their excellent biological properties and desired bone regeneration results to non-absorbable membranes even without a second surgery for removal.

Keywords: absorbable membrane ; polytetrafluoroethylene (PTFE) ; titanium ; collagen sources

1. Nonabsorbable Barrier Membranes

1.1. Polytetrafluoroethylene (PTFE)

PTFE is the base material of the most representative and earliest clinically used non-absorbable membranes ^{[1][2]}. This material is based on an unbranched, linear, semi-crystalline polymer combining fluorine and carbon ^[3]. PTFE belongs to the class of polyhaloolefins, and to the so-called thermoplastics ^[4]. It is also considered to be very inert ^[5]. One reason is the particularly strong bond between the carbon and fluorine atoms. Thus, many substances are unable to break the bonds and react chemically with PTFE ^[3]. Furthermore, PTFE is kinetically inhibited by the compact shell of fluorine atoms that protects the inner carbon strand ^[4]. It is therefore extremely resistant to all bases, alcohols, ketones, etc. ^[6]. Moreover, PTFE has a very low coefficient of friction ^[7]. No materials exist that will stick to PTFE because the surface tension is extremely low ^[8]. This inert material is difficult to wet and almost impossible to bond ^[9]. However, Korzinkas and colleagues showed that PTFE-based barrier membranes induce a slight (inflammatory) tissue reaction comparable to collagen-based materials.

1.1.1. e-PTFE and d-PTFE

Different representative PTFE membranes have been developed according to different clinical requirements:

- expanded polytetrafluoroethylene (e-PTFE);
- high-density polytetrafluoroethylene (d-PTFE).

Biomaterials based on e-PTFE are fabricated via extrusion of PTFE molecular fibers, resulting in two different fiber orientations, i.e., mono- and multidirectional materials ^{[3][10]}. The production of monodirectional e-PTFE results in a material whose molecular fibers are oriented in one direction, while multidirectional e-PTFE, on the other hand, is oriented in many directions ^[11]. This creates a complex fiber structure that gives the material exceptional strength and creep resistance in both longitudinal and transverse directions ^[12]. Furthermore, its production in combination with a lubricant results in a microporous material structure characterized by connection nodes that are interconnected by longitudinal fibrils of less than 0.5 µm in diameter. The degree of porosity of an e-PTFE material can be controlled by the distance between the nodes ^[3].

The porous structure of e-PTFE facilitates nutrient transport and has proven its clinical stability and excellent biocompatibility ^{[13][14]}. Although there is still controversy regarding the relationship between membrane type and exposure rate ^{[15][16]}, a clinical systematic evaluation showed a significantly higher incidence of membrane exposure for non-absorbable membranes (20%) than for absorbable membranes (5%) ^[17]. A meta-analysis of membrane exposure noted that areas without membrane exposure achieved 74% higher horizontal bone gain than areas with membrane exposure in edentulous ridges ^[18]. Conventional e-PTFE membranes demonstrated a weak barrier effect against bacterial infection after membrane exposure, which increases the difficulty of postoperative care and the risk of bone regeneration failure

[16]. In contrast, dense polytetrafluoroethylene (d-PTFE) is a less porous form of polytetrafluoroethylene, which has also been on the market for many years, especially in combination with titanium grids for an enhancement of the volume stability (see next paragraph). Although both PTFE membranes showed similar clinical outcomes in the treatment of peri-implant vertical bone defects [14], the dense structure of d-PTFE is considered to be effective in preventing bacterial invasion while retaining the potential for oxygen diffusion and small molecule transport [19]. In addition, postoperative removal of the d-PTFE membrane is easier than that of the e-PTFE membrane, which is essential for subsequent recovery and overall healing [14]. However, the accumulation of thicker biofilms on d-PTFE membranes observed in some studies suggests that bacterial infection appears to be related not only to porosity. In vitro evaluation of a novel bilayer e-PTFE membrane with optimized layer thickness as well as the extent and direction of swelling by Trobos et al. showed better resistance to bacterial permeability and biofilm formation than d-PTFE [11]. This conclusion is also supported by clinical randomized studies where more biomass accumulation and thicker biofilms were observed on d-PTFE membranes [10].

1.1.2. Titanium-Reinforced PTFE-Membranes

Although e-PTFE and d-PTFE have demonstrated adequate barrier function and space maintenance, the osteogenic spaces they create are prone to deformation under pressure in the face of large vertical clinical bone defects, which is detrimental to bone regeneration [20]. Titanium-reinforced membranes have been created to overcome this deficiency. A titanium skeleton with high strength and stiffness is inserted into the PTFE membrane to give it excellent plasticity and volume stability [21]. Ti struts not only provide excellent mechanical support but also allow for easy clinical placement under the flap [22]. Currently, titanium-reinforced membranes are an established core material for providing volume-stable osteogenic space to promote bone tissue regeneration in clinical procedures. In a recent meta-analysis, titanium-reinforced d-PTFE supporting the highest vertical bone regeneration with a low complication rate was considered to be the best choice for GBR/GTR [23].

2.2. Titanium Meshes and Cages

Titanium is a popular metal material in dentistry and other medical fields. In particular, its clinical suitability for GBR procedures is unmatched by other GBR membranes. Traditionally, titanium meshes have been used clinically, primarily to stabilize the bone grafts and maintain the desired bone morphology and volume rather than providing a barrier functionality, as this material class does not have a space maintenance function due to the large pore size [24]. Due to their exceptional volume stability, titanium meshes are indispensable in the management of vertical or large horizontal bone defects. Titanium meshes not only demonstrate high strength and stiffness but also exhibit good plasticity, allowing them to be perfectly adapted to various bone defects through bending and shaping [25][26]. Although the sharp edges created by cutting, trimming, or bending of titanium mesh can raise concerns about membrane exposure, titanium mesh has a significantly lower postoperative exposure rate than most barrier membranes and does not usually need to be removed immediately because infection does not usually occur after exposure [27][28]. Based on these advantages, a systematic clinical evaluation of titanium meshes for alveolar bone reconstruction noted a mean success rate of 89.9%, a mean survival rate of 100%, and a failure rate of 0% [29]. To further improve the clinical suitability of titanium meshes, digitally tailored titanium mesh technology has been used in the clinic. The titanium meshes manufactured by 3D printing and other technologies are often imaginatively referred to as titanium cages, which allow for a perfect fit to the bone defect and avoid the undesirable consequences of incorrect placement [30][31]. A clinical study involving 40 patients (65 implant sites) demonstrated that digital titanium mesh significantly reduced postoperative vertical and horizontal bone resorption and performed well in maintaining hard tissue stability. In this investigation, the exposure rate of digital titanium meshes was only 10%, which is lower than the exposure rate reported in most previous studies [32].

The combination of titanium mesh + PTFE membrane or titanium mesh + collagen membrane is usually used in clinical practice, where the PTFE or collagen membrane provides space maintenance, and the titanium mesh provides volume stability [33][34][35]. Notably, a recent case study involving 106 patients with perioral repair showed that collagen membrane coverage prevents peripheral tissue adhesion, fibrosis, and associated problems, which are common inflammatory responses to titanium mesh [36]. This proven combination strategy means that space maintenance is not clinically necessary for titanium mesh application. More systematic histological evidence is therefore needed to elucidate the effect of titanium mesh structure (thickness and porosity) on bone healing mechanisms to guide the manufacture of clinically meaningful titanium meshes.

2. Absorbable Barrier Membrane

2.1. Modification of Collagen Membranes

2.1.1. Tissue Sources of Collagen Membranes

Collagen from different sources differs greatly in structure and composition, which also greatly affects the cellular response and degradation pattern of collagen membranes *in vivo* [37][38]. Altogether, conclusions can be made about the origin of the tissue and the resultant properties of the barrier membrane. The main collagen currently available is mainly from pericardium, and skin of mammals with a high homology to human collagen [38][39]. Of these, skin and tendon are favored due to their high collagen content [40].

Mammalian dermis contains up to 60–70% collagen, and its fibers are anisotropically distributed along the longer line [41]. The collagen fibers in the dermis are arranged in a loose network and contain a mixture of macromolecules such as hyaluronic acid, dermatan sulfate and chondroitin sulfate, which in combination with a large amount of water, fill the spaces between the collagen fibers [38]. In addition, the skin tissue contains a large number of blood vessels, lymphatic vessels, hair follicles and sweat glands, so that the purification step is more demanding [42]. Although native porcine collagen membranes showed temporal differences in their biodegradation pattern, it seems that this membrane type degrades faster compared to membranes based on materials won from other tissue or animal sources [43].

The collagen of tendon accounts for up to 85% of its dry weight and is composed almost entirely of type I collagen [44][45]. Therefore, this area has the lowest level of collagen contaminants and is the best site for type I collagen extraction. In addition, the structure of the tendon allows the collagen fibers to curl and align in the main load bearing direction [39]. Even after the extraction procedure, collagen fibers from tendon retain lateral stacking arrangement [46]. The above theory supports the hypothesis that devices derived from the Achilles tendon have a higher chemical–physical stability. However, collagen membranes derived from tendon are rare on the market due to the high cost. Biocollagen® (Biotech by Biotech SpA, Torino, Italy), a collagen membrane derived from the equine Achilles tendon, has also not shown a satisfactory degradation pattern, with a standing time of only 4–6 weeks [47], which seems to contradict the initial hypothesis. However, this rapid degradation could also be attributed to the species; thus, more evidence is still needed to clarify the degradation pattern of the device derived from the Achilles tendon.

Collagen from the pericardium is also attractive in terms of mechanical properties because it retains the biomechanical properties of the pericardial tissue [48]. It often exhibits excellent multidirectional tearing resistance due to the inclusion of fine, wavy and multidirectional-oriented collagen fibers within [49]. Moreover, the natural crosslinking degree seems to increase the standing time, as it has been revealed that such materials are still providing barrier functionality up to 12 weeks post implantation [50].

Moreover, it was shown in a preclinical study by Alkildani et al. that a pericardium-based barrier membrane was completely ossified over a period of 16 weeks and thus contributes to bone tissue regeneration in combination with a bone substitute material (manuscript in preparation).

Among mammals, bovine and porcine are the most important sources of collagen extraction because they are the most consumed meat *per capita* [51]. However, it is still partly assumed that they might face exaggerated immune reactions and transfer infectious diseases beside different religious restrictions [52]. Collagen from horses is considered to be generally free of infectious disease risks and immune reactions [53]. Equine collagen also has the highest homology to human collagen similar to that of bovine collagen, making it an effective alternative to bovine collagen [51]. Equine tendon collagen has been reported to have higher levels of lysine and hydrogen lysine compared to other mammalian tendon, making its biologics theoretically more resistant to degradation and tear resistance [40][54]. This hypothesis is highly controversial, however, as Toledano et al. showed that of the three collagen membranes tested, collagen membranes from porcine dermis had the greatest resistance to degradation compared to equine pericardium and equine lyophilized collagen felt [55]. Similar results were confirmed by Vallecillo-Rivas et al. that equine collagen membranes showed the weakest degradation resistance among the five membranes tested [47]. Equine meat and its biological products are not accepted by Jews and Muslims.

In this context, non-mammalian marine organisms become a very attractive alternative source [56]. Jellyfish can contain up to 60% collagen, which is homologous to mammalian collagen types I, II and V; hence, the term type 0 collagen [57]. Jellyfish collagen has been shown to induce higher fibroblast and osteoblast viability than bovine collagen [58][59]. Although barrier membranes from jellyfish are not currently available on the market, a study by Flaig et al. showed that jellyfish collagen scaffold (Jellagen®-3D scaffolds, Jellagen® Ltd., Cardiff, UK) induced an overall weaker immune response than

porcine pericardial collagen scaffolds. It induced long-term M2 cell responses and optimal vascularization patterns within the implantation bed [60].

2.1.2. Collagen Crosslinking Strategies

Poor mechanical properties and high degradation rates of native collagen-based barrier membranes are still dominant limitations in clinical applications. To enhance durability and mechanical strength, crosslinking as an efficient method has attracted extensive studies. In principle, crosslinking inhibits sliding between collagen molecules under pressure by introducing intramolecular and intermolecular covalent or non-covalent bonds, which increases the stiffness, tensile strength, compressive modulus, and reduced extensibility of collagen fibers [61]. At the same time, intermolecular crosslinking also improves the resistance of collagen against enzymatic degradation by masking the cleavage site of collagen [62]. Crosslinking of collagen can be induced by a variety of techniques, which are briefly reviewed in the following.

Physical Strategies

Physical crosslinking methods of collagen mainly comprise dehydrothermal (DHT) and ultraviolet (UV) irradiation. Both processes do not require the incorporation of any chemical agents avoiding the threat of biological toxicity.

UV induces the formation of highly reactive free radicals, which mediates the formation of intra- and extra-fibrillar carbonyl-based covalent bonds at aromatic amino acid residues [63]. This method is highly germicidal, as the UV light destroys the genetic material of microorganisms [64]. However, UV-induced collagen denaturation, which counteracts the stabilizing effect, occurs continuously during crosslinking [65]. The presence of water in UV crosslinking is necessary to initiate free radical production, and the rate and amount of free radical production is the main limiting factor for crosslinking degree [66]. It has been stated that high crosslinking densities cannot be achieved by UV induction alone [64]. Combination with light-activated reagents, such as riboflavin as the source of reactive oxygen species, appears to be more effective. In 2019, Zhang et al. fabricated a UVA/riboflavin crosslinking amniotic membrane, which exhibited bamboo-like structural changes accompanied by increased brittleness and stiffness, further prolonging the degradation rate in vivo [67]. UV crosslinking strategies based on photoactive atelocollagen precursors have also been developed recently. Liang et al. designed atelocollagen functionalized with 4-vinyl benzyl chloride (4VBC) and methacrylic anhydride (MA) to fabricate a UV-cured GBR membrane. MA as the highly reactive monomer has been widely proofed to generate crosslinked networks rapidly through photo-induced free radicals [68]. Furthermore, 4VBC-functionalized collagen was demonstrated to exhibit significantly increased compression properties compared to methacrylated collagen [69]. The introduction of 4VBC was also found to inhibit the activity of matrix metalloproteinases (MMPs) [70]. The resultant membrane showed excellent compressibility, swelling ratios, and increased proteolytic stability with respect to Bio-Gide® as one of the most common commercial collagen membranes. Altogether, the UV crosslinking membrane is mainly limited by the difficulty of achieving satisfactory mechanical properties compared to chemical crosslinking. It is therefore often used as an auxiliary crosslinking method, in combination with other crosslinking methods. In addition, UV crosslinking is more suitable for fabricating thin or transparent membrane considering the penetration of UV irradiation.

Dehydrothermal (DHT) is another common physical method for collagen crosslinking that involves exposure to high temperatures in a vacuum condition to cause the formation of intermolecular amide and ester bonds through dehydration [71]. As early as 1996, it was shown that DHT-induced crosslinking exhibits a higher contraction temperature of collagen fibrils while reducing their solubility in solutions containing collagenase in comparison to UV crosslinking [72]. The temperature and the period of this treatment are the main regulators of crosslinking degree [63]. It is well known that the crosslink density increases with temperature and time within a certain range [73]. However, excessive temperatures and processing periods can lead to disruption of the triple helix structure of collagen, which usually deteriorates the mechanical properties [74]. It is now generally accepted that the optimum temperature for DHT is around 140–150°. Chen et al. demonstrated that the mechanical properties of collagen membranes were severely impaired when the DHT treatment temperature exceeded 145° or the treatment time exceeded 5 days [75]. However, considering the foreign body reaction after material implantation, the optimal treatment time may be further reduced. The study by Nakada et al. showed that excessive heat treatment results in little to no cellular infiltration of the collagen material and a large number of foreign body giant cells around the material, ultimately resulting in no tissue regeneration [76]. In addition, their study in 2017 showed that thermal treatment at 140 °C for 6 h supports new bone formation and gingival fiber regeneration, which is considered to be a favorable outcome for GBR [77]. This result is also supported by the study of An et al. where DHT membranes showed better enzymatic resistance and tensile strength than Bio-Gide® besides exhibiting well tissue integration in vivo [78]. Thus, DHT shows the potential to produce barrier membranes, especially to handle thick materials that are difficult to treat with UV.

Chemical Strategies

Glutaraldehyde (GA) is the most widely used traditional crosslinking agent for collagen, due to its low cost, high reactivity, and high solubility in aqueous solutions. However, it has been rarely used for tissue engineering studies in recent years due to its local cytotoxicity and induction of calcification as well as inflammatory responses (Shi 2020).

In contrast, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC-NHS) is a “zero-length” crosslinker that chemically activates the carboxylic acid groups of aspartic acid and glutamic acid on collagen to conjugate with hydroxylysine and amines of lysine residues through direct covalent bonds without any linkers or spacers [63][65]. All residues of this method are water-soluble and therefore can be easily washed out from the material by distilled water after crosslinking [79]. DHT/EDC crosslinked collagen membranes exhibit good enzyme resistance, mechanical properties, and excellent peripheral tissue integration compared to commercially available noncrosslinked collagen membranes (Bio-Gide®) in a rat subcutaneous model [78][80]. The bone regeneration ability of EDC/NHS crosslinked membranes has also been demonstrated both in the Beagle mandible model and the rabbit calvaria defects model [80]. However, recent studies on the interaction properties of EDC/NHS-modified collagen with cells show that both the affinity and pattern of cellular interactions are modulated by carbodiimide treatment. The study by Bax et al. seems to indicate that the depletion of carboxyl groups of glutamic acid on collagen by EDC/NHS crosslinking hinders its binding to integrins and thus reduces integrin-mediated cell adhesion. Furthermore, with increasing EDC concentration, the cell adhesion pattern to collagen shifts from divalent metal cation-dependent binding to metal ion non-dependent binding [81].

Natural crosslinkers have significant advantages over traditional chemical crosslinkers in terms of biocompatibility. Genipin is the best-known natural crosslinking agent mainly extracted from the fruits of *Gardenia jasminoides* L. or *Gardenia jasminoides* [82]. It is only 0.01% as cytotoxic as glutaraldehyde and exhibits significant anti-inflammatory properties [83]. Nair et al. showed that collagen membranes crosslinked by Genipin provided higher viability of human dermal fibroblasts than EDC/NHS crosslinked membranes [84]. However, Genipin is currently limited by its high cost in mass production and is mainly used in laboratory studies. He et al. prepared a bilayer collagen membrane with controlled pore size and significantly improved mechanical strength by crosslinking with sodium alginate (OSA) [85]. This showed that OSA crosslinking significantly improved the compressive strength and swelling properties of collagen membranes and prolonged the degradation period [85]. With increasing OSA content, the residual mass ratio increased from 14.9% to 59.0% after 21 days in vitro enzymatic degradation [85]. Natural polyphenols are also widely used as natural crosslinkers for collagen with excellent anti-inflammatory, anti-bacterial and anti-cancer properties [86]. Proanthocyanidins (PAs) or tannins are the most common flavonoid natural polyphenolic compounds and are widely considered to be effective in stabilizing collagen [87][88][89]. With a highly hydroxylated structure, PAs can form strong hydrogen bonds with soluble collagen making it a good candidate for crosslinking agents. Incorporation of grape seed proanthocyanidins into dental adhesives can promote the enzymatic resistance of collagen at the dentin/adhesive interface and significantly prolong the degradation period of collagen fibers [88]. PAs also showed significant inhibition and anti-adhesion against principal cariogenic bacteria (*Streptococcus mutans* and *Lactobacillus acidophilus*) [90] and microorganisms causing oral infections (*Enterococcus faecalis*, *Porphyromonas gingivalis*, and *Clostridium difficile*) [91][92]. In addition, oligomeric proanthocyanidins (OPCs) released from dentin can induce differentiation of dental pulp cells (DPC) to a phenotype favoring biomineralization [93]. The collagen membrane crosslinked with procyanidins developed by Yang et al. could well block the migration of WS-1 and MG-63 cells. In vitro experiments showed that the proliferation, differentiation, and mineralization of MG-63 cells were promoted on the resultant membrane [94]. This is consistent with the study by Li et al. that OPCs crosslinked collagen membranes support the proliferation of L929 and MG-63 cells, in addition to exhibiting up to 50 days of standing time and supporting new bone growth in vivo [95]. Epigallocatechin-3-gallate (EGCG), which has a high structural similarity to PAs, is another commonly used natural crosslinking agent. EGCG crosslinked collagen membranes significantly downregulated the level of inflammatory factors secreted by MG63 cells in in vitro experiments. However, higher concentrations of EGCG showed a slight inhibition of cell viability [96]. The incorporation of polyethylene glycol (PEG) into the collagen membrane of EGCG could offset the dose limitation to some extent [97]. EGCG crosslinked small intestinal submucosa (E-SIS) also showed enhanced adhesion of fibroblasts and pro-osteoblasts and promoted osteogenic differentiation of MC3T3-E1 cells cultured on E-SIS. The E-SIS membrane also accelerated bone regeneration in a rat cranial defect model (Gou 2019). Furthermore, studies by Chu et al. and Rung et al. showed that EGCG crosslinked collagen membranes facilitate the recruitment of macrophages [96][98]. Notably, EGCG modification has a strong ability in promoting vascularization involving the secretion of M2-related cytokines [96].

Enzymatic Strategies

The crosslinking and stability of collagen in vivo largely depend on enzymatic reactions. The most representative one is the transglutaminase that catalyzes the formation of ϵ -(γ -glutaminy)-lysine isopeptide bonds to assemble various proteins related to mineralized tissue formation (e.g., collagen, fibronectin, osteopontin, and bone sialoprotein) into polymeric

forms involved in matrix stabilization, chondrocyte and osteoblast differentiation, and matrix mineralization [99]. Natural type I collagen treated with tissue transglutaminase (TG2) and microbial transglutaminase (mTG) has been shown to enhance the adhesion, spreading, and proliferation of human osteoblasts (HOB) and human foreskin dermal fibroblasts (HFDF). It also exhibited increased endogenous protease resistance and differentiation rate of HOB cells [100]. Fortunati et al. showed similar results and proposed a mechanism by which TG2-modified collagen induced enhanced osteoblast adhesion mediated by promoting integrin expression in human osteoblasts [101]. The microbial transglutaminase (mTGase) crosslinked HA/Coll scaffold also showed significantly improved thermal stability and compression modulus. mTGase modification also increased the adhesion, proliferation, and differentiation of MG63 osteoblast-like cells and human umbilical vein endothelial cells (HUVEC) on the scaffolds [102]. Enhanced differentiation of human mesenchymal stem cells to osteoblasts was also observed on microbial transglutaminase crosslinked tilapia scale collagen scaffolds and collagen type XI scaffolds [103][104]. Yang et al. compared gelatin sponges prepared by different crosslinking methods, where mTG crosslinking showed the best comprehensive performance in terms of mechanical strength and biocompatibility [105]. Although enzymatic crosslinking provides theoretically optimal biocompatibility and biomimetic properties, its improvement of mechanical properties is much lower than chemical crosslinking. Coupled with the low economic benefits associated with high costs, mass production applications of enzymatic crosslinking are impractical in the short term.

2.1.3. Incorporation of Bioactive Molecules

Cytokines and Growth Factors

The binding of active molecules to the membrane is based on the hypothesis that exposure of the treated area to multiple different growth factors can trigger the development of a favorable microenvironment and promote bone regeneration [106][107]. Platelet-derived growth factor (PDGF) is a potent mitogenic and chemo-inductive agent, and in particular, PDGF-BB is more effective than other isoforms such as PDGF-AA and PDGF-AB in promoting mitosis in periodontal cells [108]. The development of recombinant PDGF-BB (rhPDGF-BB) has given momentum to its use in bone regeneration. rhPDGF-BB also showed potent mitogenic, angiogenic and chemotactic effects on bone and periodontal cells [109]. The binding of rhPDGF-BB to collagen membranes has been shown to release 60% of the factor within the first three days, followed by a sustained release in vitro for approximately 3 weeks [110]. Recently, Joshi et al. demonstrated in a clinical study that PDGF-BB can be loaded on collagen membranes and released slowly for up to 1 month at sites of intraosseous defects [111]. Bone morphogenetic proteins (BMP) are also bioactive molecules in the field of bone regeneration and have been considered in several reviews to be the most promising growth factor for bone regeneration [107][112]. Among the various isoforms, BMP-2 and BMP-7 are thought to play an important role in osteogenic differentiation [113]; especially, BMP-2 has been shown to induce both cartilage and sclerogenesis [114][115]. Even low doses of rhBMP-2 (0.2 mg/mL) loaded in the Hydroxyapatite/ β -tricalcium phosphate/Collagen (HAp/TCP/Col) complex exhibit strong osteogenic potential in the Beagle dog model [116]. However, some recent studies seem to suggest that BMP-9 possesses a stronger osteoinductive potential than BMP-2 [117][118]. Saulacic et al. showed that in a rabbit cranial defect model, BMP-9 loaded on collagen membranes induced better horizontal bone defect closure than loading on deproteinized bovine bone mineral, and both combinations positively induced bone regeneration [119][120]. The significant bone-promoting potential of the combination of BMP-9 and collagen membranes has also been demonstrated in an anti-resorptive therapy (AMART) mouse model [106]. In other studies, stromal cell-derived factor-1 α (SDF-1 α) has been widely accepted to promote the recruitment, proliferation, and differentiation of bone marrow-derived stromal stem cells (BMSCs) as a classical chemokine, mediating significant bone regeneration and angiogenesis [89][121]. The combination of SDF-1 and basic fibroblast growth factor (bFGF) plays an active role in BMSCs-mediated periodontal membrane regeneration, as they induce BMSCs to differentiate into cells with periodontal membrane fibroblast characteristics [122][123]. In the subject of active compound delivery, the way it is attached to the GBR membrane is fundamentally important for in situ tissue regeneration. Yu et al. showed that collagen membranes chemically conjugated to SDF-1 α significantly promoted the formation of new bone and microvessels compared with SDF-1 α physisorption and showed a similar effect on new bone formation to the BMSC seeding method [123].

Although all these studies demonstrate the feasibility of delivering active molecules through membranes, the instability (e.g., conformational changes and degradation) and early burst release of protein factors greatly hinder their clinical application. The supraphysiological dose of active molecules to compensate for their instability also raises toxicity and cost concerns [124]. Delivery of DNA or RNA encoding the relevant regenerative factor rather than its protein form is a promising solution. Non-viral vector delivery of pDNA encoding PDGF-B on a collagen scaffold was demonstrated in a rat cranial defect model with a significant increase in new bone volume/total volume (BV/TV) % (14-fold and 44-fold higher) compared to empty defects or empty scaffolds, respectively [125]. Synergistic delivery of pDNA encoding FGF-2 and BMP-2 also shows significant improvement in bone regeneration in diaphyseal long bone radial defects [126]. Delivery of

chemically modified ribonucleic acid (cmRNA) may be more efficient and safer because the absence of nuclear trafficking can effectively improve transfection efficiency [127]. Elangovan et al. demonstrated that the polyethylenimine (PEI)-cmRNA (encoding BMP-2) complex promoted significantly enhanced bone regeneration compared to PEI-DNA (encoding BMP-2) [125]. The team also reported that collagen sponges containing cmRNA (BMP-9) had stronger bone regeneration efficacy than those containing cmRNA (BMP-2), with a two-fold higher junctional density of regenerated bone [126]. The functionality of pDNA (BMP-9) and cmRNA (BMP-9) integration into collagen membranes was also confirmed in vitro and in vivo, with enhanced osteogenic differentiation and bone volume fraction [128].

Metal Ions

Many studies have been conducted to demonstrate that the doping of trace elements, such as zinc (Zn), magnesium (Mg), cobalt (Co), and strontium (Sr), can further enhance the biological activity of collagen. In addition, the accompanying release of trace elements can regulate the local biological environment. The interest in the osteogenic properties of Sr stems from the therapeutic effects of strontium ranelate in osteoporosis. Sr supports osteoblast differentiation and activates the expression of one of the osteoblast markers, osteopontin, a marker of late osteoblasts [129]. Sr also has a concomitant inhibitory effect on bone resorption by osteoclasts [130][131]. In this dual mode of action, Sr creates a favorable environment for bone tissue remodeling and healing. Furthermore, in vitro studies with human mesenchymal stem cells (MSCs) have shown that Sr-doped matrices are not cytotoxic, regardless of the amount of Sr incorporated [132]. Zn is also known to be a potent bone immunomodulator, affecting macrophage polarization and osteoblast differentiation [133]. Wu et al. showed that 1% and 2% nZnHA-doped collagen membranes exhibited superior biocompatibility and stronger promotion of multinucleated giant cells (MNGC) formation in vitro and in vivo [134]. On the other hand, zinc seems to modulate the biological activity of matrix metalloproteinases (MMP) to regulate collagen degradation [135]. There is also evidence that both transforming growth factor- β (TGF- β) and osteoprotegerin (OPG) are upregulated when osteoblasts are exposed to zinc ions [136]. Metal-organic framework (MOF) crystal-modified electrospun asymmetric bilayer polycaprolactone/collagen (PCL/Col) membranes further achieved PH-responsive release of zinc ions, showing enhanced osteoinductivity and angiogenesis both in vitro and in vivo [137]. The important role of magnesium in maintaining bone strength and bone formation makes it promising for bone regeneration therapy [138][139]. Magnesium has been shown in vitro to have a promotive effect on a variety of bone cells [140]. For example, it enhances the proliferation and migration of human osteosarcoma MG-63 cells and alkaline phosphatase (ALP) activity [141], promotes integrin $\alpha 2$ and $\alpha 3$ mediated proliferation, and enhances ALP expression and activity in bone marrow-derived stromal cells (hBMSC) [142]. The above evidence suggests a beneficial role of trace elements in bone tissue regeneration, which can be considered as effective bioactive modulators without cytotoxicity. However, the effects of metal ions are usually concentration-dependent and should still be considered with caution until sufficient clinical confirmation is obtained.

Antimicrobials and Antibiotics

Antibacterial agents and antibiotics, such as tetracyclines [143], metronidazole [144], and silver ions, are added mainly to prevent bacterial infections especially when membrane exposure occurs. In vitro studies have shown that AgNP-coated collagen membranes show excellent antibacterial efficacy against *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) without obvious cytotoxicity. The AgNP-coated membrane also has effective anti-inflammatory effects by inhibiting the expression and release of anti-inflammatory cytokines such as IL-6 and TNF- α . In addition, the resultant membrane was able to induce osteogenic differentiation of mesenchymal stem cells, demonstrating its osteogenic potential [145]. Amoxicillin-loaded poly (D, L-lactic acid) membranes implanted in vivo show an early reduction in inflammation and accelerate periodontal repair [146]. Polysaccharide membranes containing gentamicin also support osteoblast growth [147]. In particular, Ghavimi et al. recently developed an asymmetric GBR membrane benefiting from curcumin and aspirin reported a striking ability to promote bone regeneration [148]. The asymmetric membrane achieved complete bone regeneration after 28 days in the animal test, while the area of commercial membrane remained empty. The above results seem to indicate that the addition of antimicrobial agents and antibiotics is also beneficial for bone and tissue regeneration rather than just anti-infection. However, its effects on cells and tissues are highly dose-dependent. Xie et al. showed that PMMA membranes loaded with relatively low concentrations of vancomycin (1–4 g/cement dose) can slightly promote osteoblast viability and angiogenesis [149]. In contrast, relatively high vancomycin concentrations (6–10 g/cement dose) showed decreased osteoblast viability and reduced angiogenesis. In addition, although many antimicrobial strategies have been developed in in vitro and in vivo experiments, there are widespread concerns about the risk of multi-resistant bacterial strains associated with the overuse of antibiotics, especially broad-spectrum antibiotics, making it difficult to assess the clinical safety of antimicrobial strategies. In this dilemma, the development of novel natural antimicrobial agents seems to be necessary. Among them, antimicrobial peptides (AMP) offer new possibilities for this idea because of their difficulty in causing bacterial resistance and the versatility that can be obtained through flexible

amino acid sequence design. Zhou et al. designed antimicrobial peptides containing osteogenic fragments attached to AgNP through hydrogen bonding [150].

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