Chapter 8

Polycaprolactone-Based Biomaterials for Guided Tissue Regeneration Membrane

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Abstract

Guided tissue regeneration (GTR) is a clinical procedure promoting regeneration of periodontal tissues. In general, this technique provides spaces for periodontal cells to repopulate and regenerate in the periodontal defect by physically preventing an invasion of gingival tissues in the affected area. Although various reports certify clinical success of GTR, high variation of favourable outcome among studies leads to the investigation to improve clinical GTR efficiency for periodontal tissue regeneration. Recent development of GTR membrane aims to augment bioactivity for facilitating and enhancing tissue healing and regeneration. Various approaches are examined, for example, the release of growth factor, the incorporation of bioactive ceramics and the delivery of antimicrobial agents. Polycaprolactone (PCL) is widely used in biomedical application due to its acceptable biocompatibility and degradability. Physical characteristics are easy to manipulate. Various forms and shapes are simple to fabricate. PCL can be employed as GTR membrane and scaffold filling in the periodontal-defect area. Bioactive PCL could be fabricated by various techniques to enhance periodontal tissue regeneration. The present chapter reviews the bioactive approaches for GTR membrane, and the potential utilization of PCL for GTR application is described.

Keywords: guided tissue regeneration, periodontal tissues, polycaprolactone, biomaterials

1. Introduction

The guided tissue regeneration (GTR) aims to regenerate the periodontal tissue apparatus in its original architecture. GTR procedure is well established and has proven to be a

successful clinical procedure to regenerate periodontal tissues [1]. Treatment is conducted by applying a membrane barrier over the affected area in order to exclude the gingival tissues, connective tissues and epithelial tissues from the defect area, allowing specific cells to regenerate in the affected site [1]. Various materials have been employed and investigated in both clinical and experimental setting [2]. However, the results from systemic review and meta-analysis demonstrated that guided tissue regeneration technique exhibited highly variable between and within the studies [3, 4]. In human, the weighted-average bone-filling ration in the infrabony defect treated by GTR alone ranges from 42 to 77%, implying the variety of response [5]. One possibility of this discrepancy is the different types of membrane employed in the studies [4]. Thus, it suggests that the clinical available membranes are still needed for further improvement to efficiently promote periodontal tissue regeneration.

In order to advance the healing capability of the periodontal tissues, the membrane modification is widely investigated. In this regard, the development of drug/bioactive agent-containing membrane has been developed. Various specific agents, such as bioactive ceramics, antimicrobials, growth factors and small molecules, have been added into the membrane aiming to facilitate and/or enhance periodontal tissue regeneration [2, 6]. Many studies have proven the incremental effect imposed by the combination of these agents with traditional guided tissue regeneration membranes [6].

Polycaprolactone (PCL) has been introduced as a candidate biomaterial for tissue regeneration. It has many properties that satisfied the criterion for GTR membrane. For example, it exhibits biocompatibility properties and is not toxic [7]. It has been widely investigated as a scaffold material for tissue-engineering application [8, 9]. In addition, it has been approved for clinical application, for example, suture materials, confirming the biocompatibility and safety in clinical use. Besides, the physical characteristics (e.g. strength and degradability) could be easily manipulated. Further, a precise control of membrane architecture could be simply fabricated. PCL also has less chance to induce immunological reaction. Together, it may imply the potential use of PCL as a material-based for GTR membrane.

2. Periodontal tissue healing and regeneration

Like healing processes of the other tissues, periodontal tissue-healing processes are divided into four phases: inflammation, proliferation, matrix formation, and remodelling [10]. First, the stability of blood clot at the defect site is crucial for periodontal tissue regeneration as it supports cell migration and proliferation in the affected area [10, 11]. However, periodontal tissue healing requires a unique healing process due to the complex nature of periodontal apparatus, which composes of cementum, periodontal ligament and alveolar bone. In addition, the distinctive periodontal ligament character requires the formation of collagen fibril embedding on the root surface of the teeth and alveolar bone. This contributes as another

unique factor for periodontal tissue healing [10]. It is postulated that connective tissues recognize the exposed root dentin as a foreign body. Therefore, the formation of parallel collagen fibres is noted along the root surface [10]. The exposed root dentin provides a substrate for cementoblast-like cells to attach and differentiate. Further, cementoblasts form extracellular matrix where collagen fibres are anchored [10].

There are several cell types involved in periodontal regeneration/healing, for example, periodontal fibroblasts, osteoblasts, gingival fibroblasts and epithelial cells. A majority of cells in periodontal tissues is fibroblasts [12]. Fibroblastic cell population contains stem/progenitor cells that can differentiate into fibroblast, osteoblast and cementoblasts, depending on the stimulator [13–15]. These cells further participate in the regeneration and healing of periodontal tissues. However, it has been reported that gingival fibroblasts exhibited significantly higher *in vitro* wound-healing rate than periodontal ligament cells [16], implying that the speed of periodontal tissue healing is relatively slower than gingival tissues. Further, the bone healing is relatively slower than epithelium [15, 17]. Thus, normal periodontal tissue healing results in the formation of long junctional epithelium rather than the organized periodontal tissue formation [17]. This information indicates the complex and distinct regeneration/healing process of periodontal tissues. The control of specific time for each cell type to migrate into periodontal defect area is critical in the success of periodontal tissue regeneration/healing.

3. Guided tissue regeneration

GTR is one of the procedures that could ultimately regenerate the damaged periodontal tissues and restore them to a functional state [18]. GTR procedure is accomplished by placing the GTR membrane over the defect. This membrane acts as a physical barrier separating the gingival tissues and epithelium from the periodontal defect, allowing the required cell population (periodontal ligament cells and osteoblasts) to formulate a new attachment apparatus and functional periodontal tissues (**Figure 1**) [1, 17–19]. At the same time, the migration of epithelial cells and gingival fibroblasts is prevented. Thus, the formation of long junctional epithelium healing is attenuated [12].

GTR is well known for its successful clinical uses in an intrabony and furcation defect treatment [1, 18]. A systematic review of literature reports that GTR treatment results in better clinical outcomes than open-flap debridement procedure, for example, the improvement of clinical attachment levels, the reduction of probing depth and gingival recession [4, 20, 21]. Although other benefits of GTR for other types of periodontal defects are not as recognizable, GTR remains a beneficial treatment [1]. In this regard, GTR therapy results in a higher amount of clinical attachment gain than a therapy of accessing flap alone [22]. The disadvantage of GTR is that the result of the treatment varies due to the difference of host response, patient's oral hygiene, surgical technique and the lack of biological property to facilitate periodontal healing [1, 23–27].

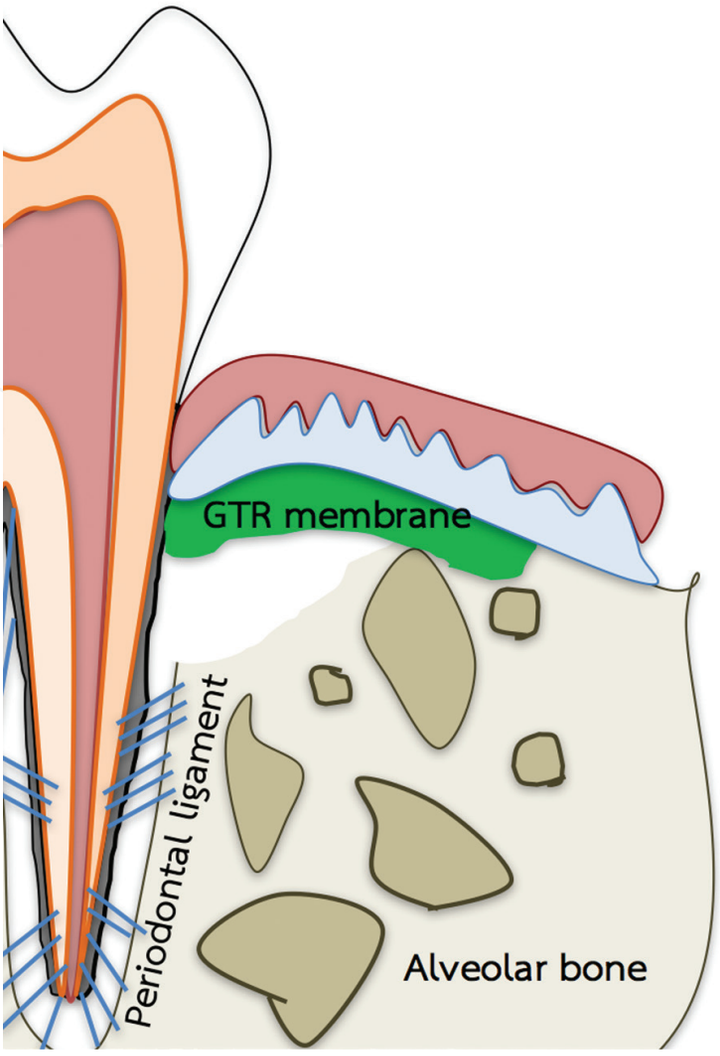

Figure 1. GTR membrane is positioned over the periodontal defect to separate gingival tissues and epithelium from the affected area, allowing the regeneration of periodontal tissues.

4. Guided tissue regeneration membrane materials

In general, like other biomaterials, GTR membrane should exhibit a biocompatibility. The degradation ability should match with the rate of new tissue formation, and the degradation product should not elicit host-inflammatory response. GTR should have the suitable mechanical and physical properties to maintain its shape *in vivo* and to easily manipulate. In this regard, GTR should have the adequate strength to maintain its form as a separating barrier and the clinical manageability [2, 6]. Materials for GTR membrane can be roughly categorized into two groups according to their degradation property, namely non-resorbable and resorbable materials. Both types of GTR materials exert similar clinical results [28, 29]. The non-biodegradable material currently available is polytetrafluoroethylene (PTFE) and methylcellulose acetate [1]. Major disadvantage of non-resorbable-guided tissue regeneration membranes is owing to the need for re-entering into the surgical site in order to remove the placed membranes, thus creating extra pain and discomfort to patients [2, 6, 29, 30].

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Due to the disadvantage of the non-resorbable membrane, the resorbable membranes are created in order to eliminate the second surgery to remove the membrane [28]. The bioresorbable membranes can be further grouped into two categories: the natural and the synthetic membranes. The advantage of the natural membrane is that these can be degraded by normal physiological or pathological process in vivo [6]. In addition, the natural-derived membranes inherit biological properties that can induce or maintain biological activity of local cells and tissues. Collagen is widely used as a resorbable GTR membrane as it is an abundant structural protein in various types of connective tissues [31]. Although collagen exhibits low immunogenicity, the antigenic response and autoimmunization are noted [29, 31]. Another drawback of collagen is the fast degradation period leading to the failure of GTR treatment due to the downgrowth of epithelial cells, forming long junctional epithelium [6].

A resorbable membrane made from synthetic materials has the advantage in several aspects. Firstly, the desirable physical and chemical properties can be altered with simple methods [32]. Secondly, fabrication methods are controllable, easy and reproducible. In general, synthetic materials are biocompatible but the degradation products of some synthetic materials induce tissue reaction [33]. Many types of polyester-based material have been clinically utilized as synthetic resorbable membranes [2]. Synthetic materials for GTR membrane include polyglycolic acid (PGA), polylactic acid (PLA), polydioxanone (PDS), and polycaprolactone PGA is an alpha-polyester. PGA is able to hold their mechanical strength for 2–4 weeks after implantation [32]. PLA has higher solubility in organic solvents than PGA because of its molecular structure. PLA has an amorphous poly(D,L-lactide) which is useful for further application in drug delivery. PGA and PLA can be copolymerized to form high-molecular weight copolymers [32]. Periodontal ligament cells attach better on PLA and co-PLA-PGA than on PTFE, and cell proliferation is observed on PLA and co-PLA-PGA but not on PTFE, implying their biocompatibility [34]. PDS is a homopolymer of p-dioxanone. PDS can maintain its strength for 4–8 weeks and completely resorb in 4–6 months [32]. PDS membrane treatment for human infrabony defects demonstrated the reduction of probing depth and the increase of vertical clinical attachment levels as well as bony filling in the defect sites [35]. These results are similar to those defects treated with polylactide acetyltributyl citrate [35].

5. Bioactive-guided tissue regeneration membrane

With the evolution of tissue-engineering approach, the recent development of GTR membranes is not only used as a physical barrier but also used as a delivery device of specific agents such as antimicrobials, growth factors and stem cells [6]. This development of bioactive GTR membranes aims for facilitating the regeneration and healing of periodontal tissues [6]. This type of membrane is considered as bioactive-guided tissue regeneration membrane. The first approach is to incorporate antimicrobial agents with GTR membrane to attenuate the risk of bacterial infection, leading to the reduction of inflammation process [36]. The bacterial contamination and infection could effect on the healing and regeneration outcome and it has been shown that bacterial infection may be associated with gingival recession and impediment

Subjects	Materials	Agents	Results	Reference
Human	ePTFE	Tetracycline (3%)	Additional gain of clinical periodontal attachment	Zarkesh et al. [45]
Dog	PGA and PLA copolymer	Doxycycline (25%)	More pronounced new bone formation and less crestal bone resorption	Chang and Yamada [46]
Human	Collagen	Minocycline	Not significantly beneficial	Minabe et al. [47]
Dog	Polytetrafluoroethylene (ePTFF)	Platelet-derived growth factor-BB (PDGF-BB)	Effectively promoted periodontal regeneration	Cho et al. [48]
Dog	Polytetrafluoroethylene (ePTFF) (GORE-TFX)	Platelet-derived growth factor-BB (PDGF-BB)	Effectively promoted periodontal regeneration with reproducibility	Park et al. [49]
Rat	Poly L-lactide (PLLA)	Platelet-derived growth factor-BB (PDGF-BB)	Enhanced regenerative efficacy	Park et al. [50]
Human	Collagen	1. Recombinant human platelet-derived growth factor-BB (rhPDGF-BB) 2. Platelet-rich plasma (PRP) 3. Commercially available enamel matrix derivative (cEMD) 4. Peptide P-15 (P-15)	1. cEMD effectively used to treat intra-osseous defects 2. The combined use of rhPDGF-BB and P-15 has shown beneficial effects in intra-osseous defects 3. PRP and graft combinations are not beneficial	Trombelli and Farina [51]
Dog	Polytetrafluoroethylene (ePTFF) (GORE-TFX)	Recombinant human transforming growth factor-beta1 (rhTGF-β1)	Restricted potential to enhance alveolar bone regeneration in conjunction with guided tissue regeneration	Wikesjö et al. [52]
Dog	Collagen	Basic fibroblast growth factor (bFGF)	Enhance periodontal regenerative results, both mineralized and non-mineralized tissues	Rossa et al. [53]
Dog	Sandwich membrane: collagen and gelatin	Basic fibroblast growth factor (bFGF)	Active vascularization and osteogenesis Successful regeneration of the periodontal tissues in a short period of time	Nakahara et al. [54]
Human	Cellulose	human fibroblast growth factor-2 (FGF-2)	Efficacious in the regeneration of human periodontal tissue	Kitamura et al. [55]
Rat	Alginate/nanofibre	Recombinant bone morphogenetic protein-2 (rhBMP-2)	Effective in repair of critical-sized segmental defect	Kolambkar et al. [56]

Table 1. Studies on the bioactive-guided tissue regeneration membrane.

of attachment gain [37, 38]. Local minocycline application in combination with GTR treatment results in the significant higher clinical attachment gain [39]. In addition, GTR loaded with metronidazole reduces inflammatory response in vivo [40]. Further, the antimicrobial-incorporated GTR membrane has been shown to improve the attachment of periodontal ligament cells by effective oral pathogen eradication [41]. The second approach is to incorporate bioactive calcium phosphate in GTR membrane [6]. The addition of hydroxyapatite improves the biocompatibility and osteoconductivity of GTR membrane [42, 43]. These composite membranes also enhance osteoblast cell proliferation *in vitro* [42, 44]. In addition, the different response could be obtained by varying the concentration of calcium phosphate in the composite membrane [42].

The last approach is to incorporate with growth factor. Growth factors regulate various biological processes, for example, cell differentiation, cell proliferation, angiogenesis and chemotaxis, resulting in the promotion of tissue healing and regeneration. Various growth factors have been identified as factors enhancing periodontal tissue healing. The exemplification of these growth factors is platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-I), fibroblast growth factor-2 (FGF-2), transforming growth factor β-1 (TGFβ-1), bone morphogenetic protein-2 (BMP-2), bone morphogenetic protein-4 (BMP-4), bone morphogenetic protein-7 (BMP-7), bone morphogenetic protein-12 (BMP-12) and enamel matrix derivative (EMD). The example of the development of bioactive GTR membrane is demonstrated in **Table 1**.

6. Polycaprolactone in guided tissue regeneration

PCL is a semi-crystalline, aliphatic polyester [57]. The structure of PCL comprises a repeating unit of one ester group and five methylene groups (**Figure 2**). PCL has an excellent biocompatibility and slow degradation rate [7, 58]. In regard to many studies, there is no evidence revealing that PCL could potentially induce any cytotoxic effects nor accumulate in human

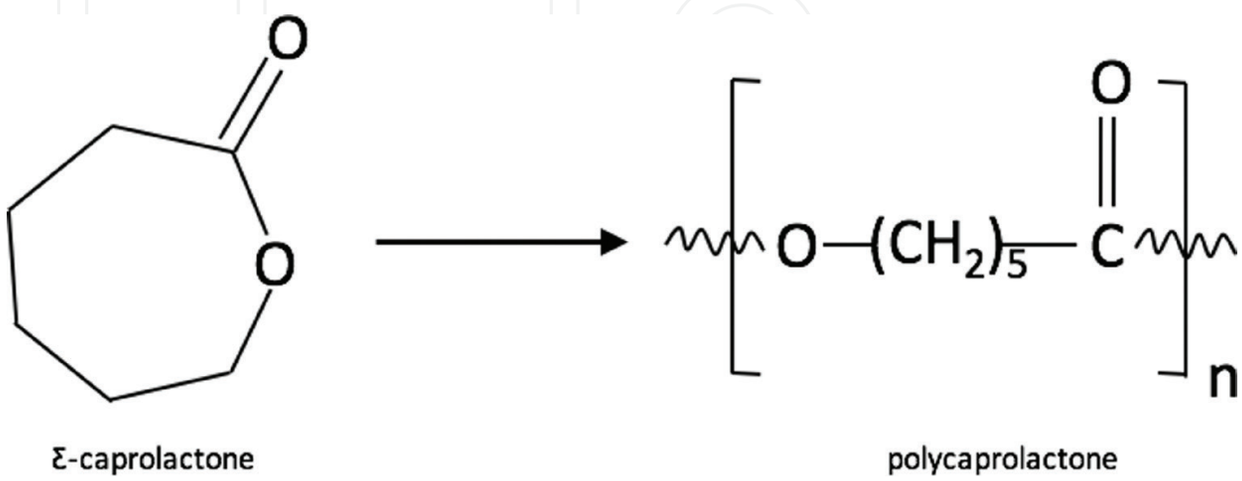

Figure 2. Structure of polycaprolactone.

body [59]. Its ester linkages can be hydrolysed and excreted under normal physiological conditions. The degradation rate of PCL is slower than other aliphatic polyester [60]. In this regard, the degradation of PCL and its copolymers can be altered with different form and molecular weight of the materials. The high-molecular-weight (≥50,000 g/mol) PCL requires 3 years to degrade in host [60].

Therefore, PCL is a practicable option for many applications in tissue-engineering approaches. PCL been approved by the Food and Drug Administration (FDA) for several medical applications, for example, suture materials and subdermal contraceptive implants [57, 61, 62]. It has been applied as a beneficial biomaterial for drug delivery devices [63, 64]. The drug-releasing property is able to be controlled [64]. Thus, the biological activity could be lengthened [8]. For example, PCL was employed as wound-dressing materials, which released chemical antiseptic agent [65]. In dentistry, PCL has been introduced as root canal-filling materials. It was noted that PCL-filled root canal gave a predictable seal in an aqueous environment [66]. PCL is also employed as materials for bone tissue-engineering scaffolds that could be used for bone augmentation [58, 67–69]. Furthermore, PCL composites are recognized for its significant uses in tissue-engineering scaffolds in order to regenerate bone, ligament, cartilage, skin, nerve and vascular tissues [57]. PCL-based biomaterials have demonstrated the osteoconductive properties as they support various cell proliferations and differentiations, including bone marrow-derived mesenchymal stem cells (BMSCs), dental pulp stem cells (DPSCs) and adipose-derived mesenchymal stem cells (ADSCs) in PCL scaffold which was confirmed [68, 69]. Further, PCL implantation in murine calvarial defect model does not significantly increase the total IgG levels as compared with sham surgery group, demonstrating the immune compatibility of PCL-based materials [70].

As aforementioned, there has been a development in manufactured membrane used for GTR in order to meet its basic requirements. PCL is considered as satisfactory candidate for GTR due to its useful properties such as biocompatibility, proper mechanical strength, biodegradability and ease of fabrication [71–73]. Many studies investigated on the effectiveness of PCL membrane in GTR reveals an improvement of bone formation in the presence of noticeable bone cell attachment and proliferation [74, 75]. PCL and hydroxyapatite-incorporated PCL membrane were biocompatible and able to support human periodontal ligament cell attachment, spreading and proliferation (**Figure 3**). It was also shown that nano-apatite-incorporated PCL membrane facilitates osteoblast-like cell proliferation and differentiation [76]. Moreover, hydroxyapatite and gelatin nanocomposite-incorporated PCL supported osteoblast proliferation, induced alkaline phosphatase activity and enhanced mineralization [77]. For further study, the researcher has invented a new polymer/calcium phosphate composite for guided tissue regeneration use. Osteoblast alkaline phosphatase activity and expression of osteoblast marker gene, which indicates the promotion in bone maturation, have been recorded as the result [78]. The basic fibroblast growth factor-releasing heparin-conjugated PCL membrane has been successfully developed and exhibits biocompatibility. This basic fibroblast growth factor-releasing PCL membrane promotes human osteoblast-like cell attachment, proliferation and differentiation as compared

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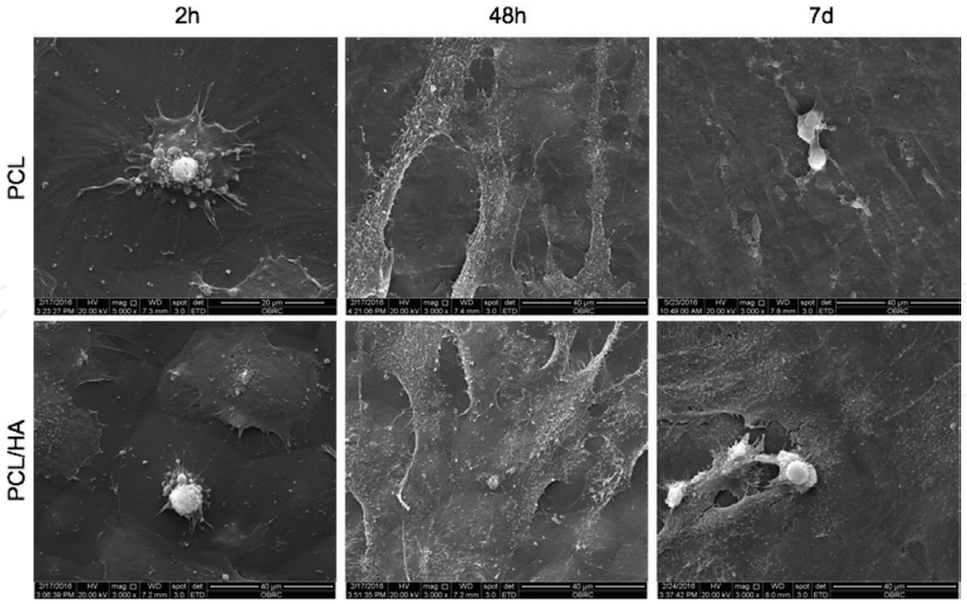

Figure 3. Scanning electron micrographs demonstrated the morphology of human periodontal ligament cell attachment, spreading and proliferation on polycaprolactone (PCL) and hydroxyapatite-incorporated PCL (PCL/HA) membrane. At 2 h, cells exhibited lamellipodia extension and completed cell spreading covering the surface was noted at 48 h after seeding. Cell monolayer was observed on the membrane at day 7.

with the naïve PCL membrane [79]. Metronidazole-incorporated PCL-based membranes decrease inflammatory response, determined in subcutaneous implantation model as compared to the unmodified PCL membrane [40, 80]. According to these studies, PCL become an appropriate material for the use of GTR membrane and advantageous prototype for further clinical membrane invention [76].

Beside GTR membrane, PCL has been developed as bone-defect-filling materials aiming to promote bone regeneration in periodontal defects. The scaffolds aim to support periodontal ligament and alveolar bone cell migration and repopulation in the affected site, facilitating the regeneration process. Three-dimensional PCL scaffolds can be fabricated by a modified solvent casting and particulate-leaching techniques, resulting in the highly porous and interconnected structure in PCL scaffolds [81]. Hydroxyapatite incorporation in PCL scaffolds exhibited biocompatibility and degradability [67]. These scaffolds have osteoconductive property which enhanced primary human osteoblast response *in vitro* and promoted bone formation in rat calvarial defect *in vivo* [67]. The incorporation of hydrophilic polyethylene glycol into hydrophobic PCL enhanced the overall hydrophilicity and cell culture performance of PCL/PEG copolymer as an optimal guided tissue regeneration material [82]. PCL/PEG scaffolds supported growth and osteogenic differentiation of human periodontal ligament cells *in vitro* [70]. Huynh et al. demonstrated that PCL/PEG scaffolds incorporated with epigenetic-modified human periodontal ligament cells could promote bone formation in calvarial defect [70]. Together, these findings strongly support the potential application of PCL as the potential guided scaffold in periodontal tissue regeneration therapy.

7. Notch signalling as a potential bioactive molecule in guided tissue regeneration of periodontal tissues

Notch ligands, Jagged1, promote cell differentiation towards osteoblast lineages of human periodontal ligament stem cells and bone marrow-derived mesenchymal stem cells [83–85]. Other studies also demonstrated that Jagged1-immobilized surface could reduce epithelial cell proliferation and enhanced epithelial cell differentiation [86, 87]. In addition, in rafted organ culture model, Jagged1-coated porous biomaterial significantly reduced the formation of epithelial tongue [87]. In other words, Jagged1 could prevent epithelial cells migration down into the dermis. For this reason, Jagged1 is considered as a beneficial molecule to be coated on a guided tissue regeneration membrane to enhance periodontal tissue formation. The schematic diagram of the propose idea is demonstrated in **Figure 4**. The Jagged1-coated PCL membrane firstly acts as a physical barrier to prevent epithelial down-growth into periodontal-defect site. In biological events, Jagged1 inhibits proliferation and induced the differentiation of epithelial cells. Further, Jagged1 promoted osteogenic differentiation of periodontal ligament cells and alveolar osteoblast cells. Together, these effects prevent the epithelium downgrowth in the lesion and promote the formation of alveolar bone, leading to the achievement of successful guided tissue regeneration.

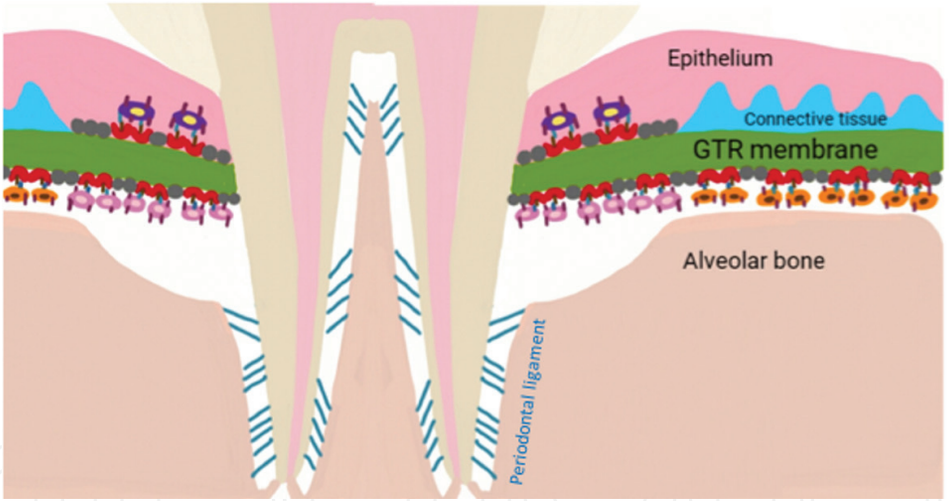

Figure 4. Schematic diagram of Jagged1-coated PCL membrane for GTR therapy.

8. Conclusion

The present chapter reviews the biological basis of GTR membrane in periodontal tissue healing and regeneration. In the past, GTR acts as a physical barrier to allow required cells to facilitate periodontal tissue formation. Recently, bioactive GTR membrane has been investigated and developed aiming to fabricate membrane that not only act as a physical barrier but also induce biological events to enhance periodontal tissue regeneration. PCL has been introduced

as candidate materials for bioactive GTR membrane due to its biocompatibility and simple fabrication procedure. The modification with other agents/biomolecules could be easily constructed. With the use of proposed Notch ligands, PCL-decorated Jagged1 could be beneficial to promote periodontal tissue formation. However, further investigations are indeed required.

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References

[1] Villar CC, Cochran DL. Regeneration of periodontal tissues: Guided tissue regeneration. Dental Clinics of North America. 2010;**54**:73-92. DOI: 10.1016/j.cden.2009.08.011

[2] Bottino MC, Thomas V, Schmidt G, Vohra YK, Chu TM, Kowolik MJ, Janowski GM. Recent advances in the development of GTR/GBR membranes for periodontal regeneration—A materials perspective. Dental Materials. 2012;**28**:703-721. DOI: 10.1016/j.dental.2012.04.022

[3] Needleman I, Tucker R, Giedrys-Leeper E, Worthington H. Guided tissue regeneration for periodontal intrabony defects—A cochrane systematic review. Periodontology 2000. 2005;**37**:106-123. DOI: 10.1111/j.1600-0757.2004.37101.x

[4] Murphy KG, Gunsolley JC. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. Annals of Periodontology. 2003;**8**:266-302. DOI: 10.1902/annals.2003.8.1.266

[5] Yen CC, Tu YK, Chen TH, Lu HK. Comparison of treatment effects of guided tissue regeneration on infrabony lesions between animal and human studies: A systematic review and meta-analysis. Journal of Periodontology Research. 2014;**49**:415-424. DOI: 10.1111/jre.12130

[6] Sam G, Pillai BR. Evolution of barrier membranes in periodontal regeneration-"Are the third generation membranes really here?" Journal of Clinical and Diagnostic Research. 2014;**8**:ZE14-ZE17. DOI: 10.7860/JCDR/2014/9957.5272

[7] Shi R, Xue J, He M, Chen D, Zhang L, Tian W. Structure, physical properties, biocompatibility and in vitro/vivo degradation behavior of anti-infective polycaprolactone-based electrospun membranes for guided tissue/bone regeneration. Polymer Degradation and Stability. 2014;**109**:293-306. DOI: http://dx.doi.org/10.1016/j.polymdegradstab.2014.07.017

[8] Dash TK, Konkimalla VB. Polymeric modification and its implication in drug delivery: Poly-epsilon-caprolactone (PCL) as a model polymer. Molecular Pharmaceutical. 2012;**9**:2365-2379. DOI: 10.1021/mp3001952

[9] Vieira A, Medeiros R, Guedes RM, Marques A, Tita V, editors. Visco-Elastic-Plastic Properties of Suture Fibers made of PLA-PCL. Materials Science Forum. Trans Tech Publ; 2013. Zurich, Switzerland

[10] Wikesjo UM, Selvig KA. Periodontal wound healing and regeneration. Periodontology 2000. 1999;**19**:21-39

[11] Baker DL, Stanley Pavlow SA, Wikesjo UM. Fibrin clot adhesion to dentin conditioned with protein constructs: An in vitro proof-of-principle study. Journal of Clinical Periodontology. 2005;**32**:561-566. DOI: 10.1111/j.1600-051X.2005.00714.x

[12] Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, Stevens M, Romberg E. Histologic evaluation of new attachment apparatus formation in humans. Part III. Journal of Periodontology. 1989;**60**:683-693. DOI: 10.1902/jop.1989.60.12.683

[13] Yin X, Li Y, Li J, Li P, Liu Y, Wen J, Luan Q. Generation and periodontal differentiation of human gingival fibroblasts-derived integration-free induced pluripotent stem cells. Biochemical and Biophysical Research Communication. 2016;**473**:726-732. DOI: 10.1016/j.bbrc.2015.10.012

[14] Kim BC, Bae H, Kwon IK, Lee EJ, Park JH, Khademhosseini A, Hwang YS. Osteoblastic/cementoblastic and neural differentiation of dental stem cells and their applications to tissue engineering and regenerative medicine. Tissue Engineering Part B: Reviews. 2012;**18**:235-244. DOI: 10.1089/ten.TEB.2011.0642

[15] Listgarten MA, Rosenberg MM. Histological study of repair following new attachment procedures in human periodontal lesions. Journal of Periodontology. 1979;**50**:333-344. DOI: 10.1902/jop.1979.50.7.333

[16] Lackler KP, Cochran DL, Hoang AM, Takacs V, Oates TW. Development of an in vitro wound healing model for periodontal cells. Journal of Periodontology. 2000;**71**:226-237. DOI: 10.1902/jop.2000.71.2.226

[17] Xu C, Lei C, Meng L, Wang C, Song Y. Chitosan as a barrier membrane material in periodontal tissue regeneration. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2012;**100**:1435-1443. DOI: 10.1002/jbm.b.32662

[18] Laurell L, Gottlow J. Guided tissue regeneration update. International Dental Journal. 1998;**48**:386-398

[19] Nyman S, Gottlow J, Karring T, Lindhe J. The regenerative potential of the periodontal ligament. An experimental study in the monkey. Journal of Clinical Periodontology. 1982;**9**:257-265. DOI: 10.1111/j.1600-051X.1982.tb02065.x

[20] Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. Cochrane Database of Systematic Reviews. 2006;**19**(2):CD001724. DOI: 10.1002/14651858.CD001724.pub2

[21] Parrish LC, Miyamoto T, Fong N, Mattson JS, Cerutis DR. Non-bioabsorbable vs. bioabsorbable membrane: Assessment of their clinical efficacy in guided tissue regeneration technique. A systematic review. Journal of Oral Science. 2009;**51**:383-400

[22] Tonetti MS, Cortellini P, Suvan JE, Adriaens P, Baldi C, Dubravec D, Fonzar A, Fourmousis I, Magnani C, Muller-Campanile V, Patroni S, Sanz M, Vangsted T, Zabalegui I, Pini Prato G, Lang NP. Generalizability of the added benefits of guided tissue regeneration in the treatment of deep intrabony defects. Evaluation in a multi-center randomized controlled clinical trial. Journal of Periodontology. 1998;**69**:1183-1192. DOI: 10.1902/jop.1998.69.11.1183

[23] Abou Neel EA, Chrzanowski W, Salih VM, Kim HW, Knowles JC. Tissue engineering in dentistry. Journal of Dentistry. 2014;**42**:915-928. DOI: 10.1016/j.jdent.2014.05.008

[24] Machtei EE, Oettinger-Barak O, Peled M. Guided tissue regeneration in smokers: Effect of aggressive anti-infective therapy in Class II furcation defects. Journal of Periodontology. 2003;**74**:579-584. DOI: 10.1902/jop.2003.74.5.579

[25] Rosenberg ES, Cutler SA. The effect of cigarette smoking on the long-term success of guided tissue regeneration: A preliminary study. Annals of the Royal Australasian College of Dental Surgeons. 1994;**12**:89-93

[26] Machtei EE, Cho MI, Dunford R, Norderyd J, Zambon JJ, Genco RJ. Clinical, microbiological, and histological factors which influence the success of regenerative periodontal therapy. Journal of Periodontology. 1994;**65**:154-161. DOI: 10.1902/jop.1994.65.2.154

[27] Verma PK, Srivastava R, Gupta KK, Chaturvedi TP. Treatment strategy for guided tissue regeneration in various class II furcation defect: Case series. Dental Research Journal. 2013;**10**:689-694

[28] Wolff LF, Mullally B. New clinical materials and techniques in guided tissue regeneration. International Dental Journal. 2000;**50**:235-244

[29] Bottino MC, Thomas V. Membranes for periodontal regeneration—A materials perspective. Frontiers in Oral Biology. 2015;**17**:90-100. DOI: 10.1159/000381699

[30] Jovanovic SA, Nevins M. Bone formation utilizing titanium-reinforced barrier membranes. International Journal of Periodontics and Restorative Dentistry. 1995;**15**:56-69

[31] Sheikh Z, Qureshi J, Alshahrani AM, Nassar H, Ikeda Y, Glogauer M, Ganss B. Collagen based barrier membranes for periodontal guided bone regeneration applications. Odontology. 2017;**105**:1-12. DOI: 10.1007/s10266-016-0267-0

[32] Hutmacher D, Hürzeler MB, Schliephake H. A review of material properties of biodegradable and bioresorbable polymers and devices for GTR and GBR applications. The International Journal of Oral & Maxillofacial Implants. 1995;**11**:667-678

[33] Schmidmaier G, Baehr K, Mohr S, Kretschmar M, Beck S, Wildemann B. Biodegradable polylactide membranes for bone defect coverage: Biocompatibility testing, radiological and histological evaluation in a sheep model. Clinical Oral Implants Research. 2006;**17**:439-444. DOI: 10.1111/j.1600-0501.2005.01242.x

[34] Takata T, Wang HL, Miyauchi M. Attachment, proliferation and differentiation of periodontal ligament cells on various guided tissue regeneration membranes. Journal of Periodontal Research. 2001;**36**:322-327

[35] Eickholz P, Kim TS, Steinbrenner H, Dorfer C, Holle R. Guided tissue regeneration with bioabsorbable barriers: Intrabony defects and class II furcations. Journal of Periodontology. 2000;**71**:999-1008. DOI: 10.1902/jop.2000.71.6.999

[36] Machtei EE, Dunford RG, Norderyd OM, Zambon JJ, Genco RJ. Guided tissue regeneration and anti-infective therapy in the treatment of class II furcation defects. Journal of Periodontology. 1993;**64**:968-973. DOI: 10.1902/jop.1993.64.10.968

[37] Gottlow J, Nyman S. Barrier membranes in the treatment of periodontal defects. Current Opinion in Periodontology. 1996;**3**:140-148

[38] Selvig KA, Kersten BG, Chamberlain ADH, Wikesjö UM, Nilvúus RE. Regenerative surgery of intrabony periodontal defects using ePTFE barrier membranes: Scanning electron microscopic evaluation of retrieved membranes versus clinical healing. Journal of Periodontology. 1992;**63**:974-978

[39] Yoshinari N, Tohya T, Kawase H, Matsuoka M, Nakane M, Kawachi M, Mitani A, Koide M, Inagaki K, Fukuda M, Noguchi T. Effect of repeated local minocycline administration on periodontal healing following guided tissue regeneration. Journal of Periodontology. 2001;**72**:284-295. DOI: 10.1902/jop.2001.72.3.284

[40] Xue J, He M, Niu Y, Liu H, Crawford A, Coates P, Chen D, Shi R, Zhang L. Preparation and in vivo efficient anti-infection property of GTR/GBR implant made by metronidazole loaded electrospun polycaprolactone nanofiber membrane. International Journal of Pharmaceuticals. 2014;**475**:566-577. DOI: 10.1016/j.ijpharm.2014.09.026

[41] Hung SL, Lin YW, Chen YT, Ling LJ. Attachment of periodontal ligament cells onto various antibiotics-loaded GTR membranes. International Journal of Periodontics and Restorative Dentistry. 2005;**25**:265-275

[42] Talal A, McKay IJ, Tanner KE, Hughes FJ. Effects of hydroxyapatite and PDGF concentrations on osteoblast growth in a nanohydroxyapatite-polylactic acid composite for guided

tissue regeneration. Journal of Material Science: Materials in Medicine. 2013;**24**:2211-2221. DOI: 10.1007/s10856-013-4963-9

[43] Liao S, Wang W, Uo M, Ohkawa S, Akasaka T, Tamura K, Cui F, Watari F. A three-layered nano-carbonated hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. Biomaterials. 2005;**26**:7564-7571. DOI: 10.1016/j.biomaterials.2005.05.050

[44] Hurt AP, Getti G, Coleman NJ. Bioactivity and biocompatibility of a chitosan-tobermorite composite membrane for guided tissue regeneration. International Journal of Biological Macromolecules. 2014;**64**:11-16. DOI: 10.1016/j.ijbiomac.2013.11.020

[45] Zarkesh N, Nowzari H, Morrison JL, Slots J. Tetracycline-coated polytetrafluoroethylene barrier membranes in the treatment of intraosseous periodontal lesions. Journal of Periodontology. 1999;**70**:1008-1016. DOI: 10.1902/jop.1999.70.9.1008

[46] Chang CY, Yamada S. Evaluation of the regenerative effect of a 25% doxycycline-loaded biodegradable membrane for guided tissue regeneration. Journal of Periodontology. 2000;**71**:1086-1093. DOI: 10.1902/jop.2000.71.7.1086

[47] Minabe M, Kodama T, Kogou T, Fushimi H, Sugiyama T, Takeuchi K, Miterai E, Nishikubo S. Clinical significance of antibiotic therapy in guided tissue regeneration with a resorbable membrane. Periodontal Clinical Investigations. 2001;**23**:20-30

[48] Cho MI, Lin WL, Genco RJ. Platelet-derived growth factor-modulated guided tissue regenerative therapy. Journal of Periodontology. 1995;**66**:522-530. DOI: 10.1902/jop.1995.66.6.522

[49] Park JB, Matsuura M, Han KY, Norderyd O, Lin WL, Genco RJ, Cho MI. Periodontal regeneration in class III furcation defects of beagle dogs using guided tissue regenerative therapy with platelet-derived growth factor. Journal of Periodontology. 1995;**66**:462-477. DOI: 10.1902/jop.1995.66.6.462

[50] Park YJ, Ku Y, Chung CP, Lee SJ. Controlled release of platelet-derived growth factor from porous poly(L-lactide) membranes for guided tissue regeneration. Journal of Controlled Release. 1998;**51**:201-211

[51] Trombelli L, Farina R. Clinical outcomes with bioactive agents alone or in combination with grafting or guided tissue regeneration. Journal of Clinical Periodontology. 2008;**35**:117-135. DOI: 10.1111/j.1600-051X.2008.01265.x

[52] Wikesjo UME, Razi SS, Sigurdsson TJ, Tatakis DN, Lee MB, Ongpipattanakul B, Nguyen T, Hardwick R. Periodontal repair in dogs: Effect of recombinant human transforming growth factor-beta1 on guided tissue regeneration. Journal of Clinical Periodontology. 1998;**25**:475-481. DOI: 10.1111/j.1600-051X.1998.tb02476.x

[53] Rossa Jr C, Marcantonio Jr E, Cirelli JA, Marcantonio RA, Spolidorio LC, Fogo JC. Regeneration of Class III furcation defects with basic fibroblast growth factor (b-FGF) associated with GTR. A descriptive and histometric study in dogs. Journal of Periodontology. 2000;**71**:775-784

[54] Nakahara T, Nakamura T, Kobayashi E, Inoue M, Shigeno K, Tabata Y, Eto K, Shimizu Y. Novel approach to regeneration of periodontal tissues based on in situ tissue engineering: Effects of controlled release of basic fibroblast growth factor from a sandwich membrane. Tissue Engineering. 2003;**9**:153-162. DOI: 10.1089/107632703762687636

[55] Kitamura M, Akamatsu M, Machigashira M, Hara Y, Sakagami R, Hirofuji T, Hamachi T, Maeda K, Yokota M, Kido J, Nagata T, Kurihara H, Takashiba S, Sibutani T, Fukuda M, Noguchi T, Yamazaki K, Yoshie H, Ioroi K, Arai T, Nakagawa T, Ito K, Oda S, Izumi Y, Ogata Y, Yamada S, Shimauchi H, Kunimatsu K, Kawanami M, Fujii T, Furuichi Y, Furuuchi T, Sasano T, Imai E, Omae M, Yamada S, Watanuki M, Murakami S. FGF-2 stimulates periodontal regeneration: Results of a multi-center randomized clinical trial. Journal of Dental Research. 2011;**90**:35-40. DOI: 10.1177/0022034510384616

[56] Kolambkar YM, Dupont KM, Boerckel JD, Huebsch N, Mooney DJ, Hutmacher DW, Guldberg RE. An alginate-based hybrid system for growth factor delivery in the functional repair of large bone defects. Biomaterials. 2011;**32**:65-74. DOI: 10.1016/j.biomaterials.2010.08.074

[57] Ulery BD, Nair LS, Laurencin CT. Biomedical applications of biodegradable polymers. Journal of Polymer Science Part B: Polymer Physics. 2011;**49**:832-864. DOI: 10.1002/polb.22259

[58] Woodruff MA, Hutmacher DW. The return of a forgotten polymer-–Polycaprolactone in the 21st century. Progress in Polymer Science. 2010;**35**:1217-1256. DOI: 10.1016/j.progpolymsci.2010.04.002

[59] Lo HY, Kuo HT, Huang YY. Application of polycaprolactone as an anti-adhesion biomaterial film. Artificial Organs. 2010;**34**:648-653. DOI: 10.1111/j.1525-1594.2009.00949.x

[60] Rezwan K, Chen QZ, Blaker JJ, Boccaccini AR. Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. Biomaterials. 2006;**27**:3413-431. DOI: 10.1016/j.biomaterials.2006.01.039

[61] Darney PD, Monroe SE, Klaisle CM, Alvarado A. Clinical evaluation of the Capronor contraceptive implant: Preliminary report. American Journal of Obstetrics & Gynecology. 1989;**160**:1292-1295

[62] Bezwada RS, Jamiolkowski DD, Lee IY, Agarwal V, Persivale J, Trenka-Benthin S, Erneta M, Suryadevara J, Yang A, Liu S. Monocryl suture, a new ultra-pliable absorbable monofilament suture. Biomaterials. 1995;**16**:1141-1148

[63] Wang Q, Jiang J, Chen W, Jiang H, Zhang Z, Sun X. Targeted delivery of low-dose dexamethasone using PCL-PEG micelles for effective treatment of rheumatoid arthritis. Journal of Controlled Release. 2016;**230**:64-72. DOI: 10.1016/j.jconrel.2016.03.035

[64] Pohlmann AR, Fonseca FN, Paese K, Detoni CB, Coradini K, Beck RC, Guterres SS. Poly(ε-caprolactone) microcapsules and nanocapsules in drug delivery. Expert Opinion on Drug Delivery. 2013;**10**:623-638. DOI: 10.1517/17425247.2013.769956

[65] Scaffaro R, Botta L, Sanfilippo M, Gallo G, Palazzolo G, Puglia AM. Combining in the melt physical and biological properties of poly(caprolactone) and chlorhexidine to

obtain antimicrobial surgical monofilaments. Applied Microbiology and Biotechnology. 2013;**97**:99-109. DOI: 10.1007/s00253-012-4283-x

[66] Álvarez AL, Espinar FO, Méndez JB. The application of microencapsulation techniques in the treatment of endodontic and periodontal disease. Pharmaceutics. 2011;**3**:538-571. DOI: 10.3390/pharmaceutics3030538

[67] Chuenjitkuntaworn B, Inrung W, Damrongsri D, Mekaapiruk K, Supaphol P, Pavasant P. Polycaprolactone/hydroxyapatite composite scaffolds: Preparation, characterization, and in vitro and in vivo biological responses of human primary bone cells. Journal of Biomedical Materials Research Part A. 2010;**94**:241-251. DOI: 10.1002/jbm.a.32657

[68] Chuenjitkuntaworn B, Osathanon T, Nowwarote N, Supaphol P, Pavasant P. The efficacy of polycaprolactone/hydroxyapatite scaffold in combination with mesenchymal stem cells for bone tissue engineering. Journal of Biomedical Materials Research Part A. 2016;**104**:264-271. DOI: 10.1002/jbm.a.35558

[69] Osathanon T, Chuenjitkuntaworn B, Nowwarote N, Supaphol P, Sastravaha P, Subbalekha K, Pavasant P. The responses of human adipose-derived mesenchymal stem cells on polycaprolactone-based scaffolds: An in vitro study. Tissue Engineering and Regenerative Medicine. 2014;**11**:239-246. DOI: 10.1007/s13770-014-0015-x

[70] Huynh NC, Everts V, Nifuji A, Pavasant P, Ampornaramveth RS. Histone deacetylase inhibition enhances in-vivo bone regeneration induced by human periodontal ligament cells. Bone. 2017;**95**:76-84. DOI: 10.1016/j.bone.2016.11.017

[71] Fecek C, Yao D, Kacorri A, Vasquez A, Iqbal S, Sheikh H, Svinarich DM, Perez-Cruet M, Chaudhry GR. Chondrogenic derivatives of embryonic stem cells seeded into 3D polycaprolactone scaffolds generated cartilage tissue in vivo. Tissue Engineering Part A. 2008;**14**:1403-1413. DOI: 10.1089/tea.2007.0293

[72] Li WJ, Tuli R, Okafor C, Derfoul A, Danielson KG, Hall DJ, Tuan RS. A three-dimensional nanofibrous scaffold for cartilage tissue engineering using human mesenchymal stem cells. Biomaterials. 2005;**26**:599-609. DOI: 10.1016/j.biomaterials.2004.03.005

[73] Li WJ, Jiang YJ, Tuan RS. Cell-nanofiber-based cartilage tissue engineering using improved cell seeding, growth factor, and bioreactor technologies. Tissue Engineering Part A. 2008; **14**:639-648. DOI: 10.1089/tea.2007.0136

[74] Zhang LJ, Webster TJ. Nanotechnology and nanomaterials: Promises for improved tissue regeneration. Nano Today. 2009;**4**:66-80. DOI: 10.1016/j.nantod.2008.10.014

[75] Basile MA, d'Ayala GG, Malinconico M, Laurienzo P, Coudane J, Nottelet B, Ragione FD, Oliva A. Functionalized PCL/HA nanocomposites as microporous membranes for bone regeneration. Materials Science & Engineering C Materials for Biological Applications. 2015;**48**:457-468. DOI: 10.1016/j.msec.2014.12.019

[76] Yang F, Both SK, Yang X, Walboomers XF, Jansen JA. Development of an electrospun nano-apatite/PCL composite membrane for GTR/GBR application. Acta Biomaterial. 2009;**5**:3295-304. DOI: 10.1016/j.actbio.2009.05.023

[77] Venugopal JR, Low S, Choon AT, Kumar AB, Ramakrishna S. Nanobioengineered electrospun composite nanofibers and osteoblasts for bone regeneration. Artificial Organs. 2008;**32**:388-397. DOI: 10.1111/j.1525-1594.2008.00557.x

[78] Osathanon T, Linnes ML, Rajachar RM, Ratner BD, Somerman MJ, Giachelli CM. Microporous nanofibrous fibrin-based scaffolds for bone tissue engineering. Biomaterials. 2008;**29**:4091-4099. DOI: 10.1016/j.biomaterials.2008.06.030

[79] Cao C, Song Y, Yao Q, Yao Y, Wang T, Huang B, Gong P. Preparation and preliminary in vitro evaluation of a bFGF-releasing heparin-conjugated poly(epsilon-caprolactone) membrane for guided bone regeneration. Journal of Biomaterials Science, Polymer Edition. 2015;**26**:600-616. DOI: 10.1080/09205063.2015.1049044

[80] Xue J, He M, Liu H, Niu Y, Crawford A, Coates PD, Chen D, Shi R, Zhang L. Drug loaded homogeneous electrospun PCL/gelatin hybrid nanofiber structures for anti-infective tissue regeneration membranes. Biomaterials. 2014;**35**:9395-405. DOI: 10.1016/j.biomaterials.2014.07.060

[81] Thadavirul N, Pavasant P, Supaphol P. Development of polycaprolactone porous scaffolds by combining solvent casting, particulate leaching, and polymer leaching techniques for bone tissue engineering. Journal of Biomedical Materials Research A. 2014;**102**:3379-3392. DOI: 10.1002/jbma.35010

[82] Hoque ME, San WY, Wei F, Li S, Huang MH, Vert M, Hutmacher DW. Processing of polycaprolactone and polycaprolactone-based copolymers into 3D scaffolds, and their cellular responses. Tissue Engineering Part A. 2009;**15**:3013-3024. DOI: 10.1089/ten.TEA.2008.0355

[83] Osathanon T, Nowwarote N, Manokawinchoke J, Pavasant P. bFGF and JAGGED1 regulate alkaline phosphatase expression and mineralization in dental tissue-derived mesenchymal stem cells. Journal of Cell Biochemistry. 2013;**114**:2551-2561. DOI: 10.1002/jcb.24602

[84] Osathanon T, Ritprajak P, Nowwarote N, Manokawinchoke J, Giachelli C, Pavasant P. Surface-bound orientated Jagged-1 enhances osteogenic differentiation of human periodontal ligament-derived mesenchymal stem cells. Journal of Biomedical Materials Research A. 2013;**101**:358-367. DOI: 10.1002/jbm.a.34332

[85] Dishowitz MI, Zhu F, Sundararaghavan HG, Ifkovits JL, Burdick JA, Hankenson KD. Jagged1 immobilization to an osteoconductive polymer activates the Notch signaling pathway and induces osteogenesis. Journal of Biomedical Materials Research A. 2014;**102**:1558-1567. DOI: 10.1002/jbm.a.34825

[86] Beckstead BL, Santosa DwM, Giachelli CM. Mimicking cell-cell interactions at the biomaterial-cell interface for control of stem cell differentiation. Journal of Biomedical Materials Research A. 2006;**79**:94-103. DOI: 10.1002/jbm.a.30760

[87] Beckstead BL, Tung JC, Liang KJ, Tavakkol Z, Usui ML, Olerud JE, Giachelli CM. Methods to promote Notch signaling at the biomaterial interface and evaluation in a rafted organ culture model. Journal of Biomedical Materials Research A. 2009;**91**:436-446. DOI: 10.1002/jbm.a.32214