

**REVIEW ARTICLE****GROWTH FACTORS IN PERIODONTAL REPAIR AND REGENERATION**Jaskirat Sidhu<sup>1</sup>, Manjeet Singh Mani Biiir<sup>2</sup>, Suruchi Hans<sup>3</sup>, Anirudh Rana<sup>1</sup>, Heli Desai<sup>1</sup><sup>1</sup>P.G Student, <sup>2</sup>Professor, <sup>3</sup>Reader, Department of Periodontics, Maharaja Ganga Singh Dental College and Research Centre, Sri- Ganganagar**ABSTRACT:**

Growth factors are a group of naturally occurring proteins exhibiting varied potent local properties. These molecules are key regulators of such biological events as migration, attachment and proliferation of nearly all cell types. Regeneration of the periodontal tissues is a dynamic process involving cell to cell and cell-extracellular matrix interactions. Growth factors elegantly co-ordinate these interactions resulting in wound healing and regeneration of tissues. The present review discusses various researches available in the literature and enlightens knowledge on various growth factors involved in periodontal repair and regeneration.

Keywords: Platelet-derived growth factor (PDGF); Stem cells; Gene therapy

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This article may be cited as: Sidhu J, Biiir MSM, Hans S, Rana A, Desai H. Growth factors in Periodontal Repair and Regeneration. J Adv Med Dent Scie Res 2016;4(2):20-24.

**INTRODUCTION**

Clinicians are frequently faced with the challenge of treating patients with significant alveolar bone loss due to periodontitis.<sup>1</sup> Periodontitis depicts gingival inflammation that further leads to periodontal pocket formation along with loss of the supporting alveolar bone and connective tissue around the teeth. Therapeutic modalities aim at eliminating the gingival inflammatory process and preventing the progression of the disease along with re-establishing and regenerating the periodontal tissues previously lost to the disease.<sup>2</sup> Surgical treatment provides an opportunity to reconstruct destroyed periodontal tissues and to correct variety of mucogingival and anatomic anomalies that may be present.<sup>3</sup> Conventional treatment procedures may result ineffective in achieving bone regeneration, leaving both the clinician and the patient dissatisfied with the outcome.<sup>1</sup>

Periodontal tissue has the capacity for repair and regeneration. Periodontally regeneration definition implies the formation of new bone, new cementum and a functionally oriented periodontal ligament. Periodontal repair implies healing after periodontal

surgery which results in healing without restoration of the attachment apparatus.<sup>4</sup>

The regeneration of the periodontal tissues is dependent on four basic components. The appropriate signals, cells, blood supply and scaffold needed to target the tissue at the defect site. All these elements play a fundamental role in the healing process and in the reconstruction of the lost tissue. The cells provide the machinery for new tissue growth and differentiation where as the growth factors or morphogens modulate the cellular activity and provide stimuli to the cells to differentiate and produce matrix for the developing tissue. The new vascular networks provide the nutritional base for tissue growth and homeostasis. Finally, scaffolds guide and create a template structure three-dimensionally to facilitate the above processes required for tissue regeneration.<sup>5</sup>

The major cellular events in tissue repair are mitogenesis, migration and metabolism. In nature, the proteins responsible for co-ordinating these events are growth factors. These naturally occurring molecules with certain matrix proteins are key regulators of these biological events and shows pleiotrophic effects in wound repair, nearly all tissues including the periodontium.<sup>6,7</sup> They are

natural cell products that are released or activated when cell division is needed. This action typically occurs during such events as wound healing or tissue regeneration. If mesenchymal cells from periodontal ligament or perivascular region of the bone proliferate and colonize the root surface, regeneration occurs.<sup>8</sup>

Growth factors are believed to have the potential to accelerate the healing process and, therefore, enhance tissue regeneration in challenging clinical scenarios.<sup>1</sup> The hope is to discover how to use them to accelerate and direct the healing event into one that will produce periodontal regeneration.

### **GROWTH FACTORS AS MEDIATORS IN HEALING**

Wound healing is the process of tissue repair involving the tissue response to injury. It is a series of biologic events that begin as hemostasis but then involve an inflammatory response, the formation of connective tissue, the covering of the wound with epithelium, and the remodeling of the wound. Wound healing, therefore, is divided into three phases: inflammation, fibroplasia, and maturation. Each of these phases is controlled and regulated by biologically active substances called growth factors.<sup>9</sup> Growth factors are biologically active polypeptides affecting the proliferation, chemotaxis and differentiation of cells from epithelium, bone and connective tissue. They express their action by binding to specific cell-surface receptors present on various target cells including osteoblasts, cementoblasts and periodontal ligament fibroblasts. Regeneration of periodontal structures lost during periodontal diseases constitutes a complex biological process regulated among others by interactions between cells and growth factors.<sup>10</sup>

Neovascularization is required for providing nutrients to the wound and help maintain the granulation tissue bed. Angiogenesis has been attributed to various molecules, including fibroblast growth factor (FGF), VEGF, TGF-beta, angiogenin, the angiotropina, the angiopoietin-1 to tumor necrosis factor alpha (TNF-alfa) and thrombospondin.<sup>11</sup>

Activated platelets at the wound margins release several growth factors such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-alpha, epidermal growth factor etc. Cells adjacent to the injured site also are induced to release growth factors such as insulin-like growth factor-I, PDGF, TGF-alpha and TGF-alpha within a few hours after injury. In periodontal regeneration, the coronal re-establishment of the

periodontal ligament (PDL) is required together with corresponding cementum and supporting alveolar bone. Thus, agents which promote periodontal ligament fibroblast (PLF) proliferation and migration as well as collagen biosynthesis would appear to be mediators for enhancing new PDL formation. When combinations of different factors are used, greater repair is achieved than when individual factors are applied.<sup>8</sup>

PDGF is a key mediator in wound healing, and its importance is highlighted by being the first recombinant growth factor approved for topical application to accelerate wound closure. At baseline levels, platelets function as a natural reservoir for growth factors including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor-beta 1 (TGF-beta 1), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF-I), to name a few. Such growth factors are released from the alpha granules of activated platelets and are involved in important cellular processes including mitogenesis, chemotaxis, differentiation, and metabolism.<sup>12</sup>

Various growth factors involved in different phases of periodontal wound healing are PDGF, TGF- $\beta$  and VEGF evident in the inflammatory phase. PDGF are derived from platelets; TGF- $\beta$  are derived from platelets, leukocytes and fibroblasts and VEGF from platelets, leukocytes, fibroblasts. In the proliferative phase EGF, FGF-2, KGF (FGF-7), PDGF, TGF- $\beta$  and VEGF. EGF is derived from macrophages, mesenchymal cells, platelets; FGF-2 from macrophages and endothelial cells; KGF (FGF-7) from keratinocytes, fibroblasts; PDGF from macrophages, endothelial cells; TGF- $\beta$  from macrophages, leukocytes, fibroblasts and VEGF from macrophages. In bone remodelling matrix synthesis phase BMPs 2 – 4, BMP-7 derived from osteoblasts are involved; FGF-2 from macrophages and endothelial cells; IGF-2 derived from macrophages and fibroblasts; PDGF from macrophages; TGF- $\beta$  from fibroblasts and osteoblasts and VEGF derived from macrophages.<sup>13</sup>

### **EFFECT OF GROWTH FACTORS IN PERIODONTAL REPAIR AND REGENERATION**

Giannobile et al<sup>14</sup> revealed that IGF-1 synergistically increases osteoblast mitogenesis in cultured bone cells when combined with other growth factors such as bFGF or PDGF. Lynch et al<sup>15</sup> tested the hypothesis that a combination of PDGF and IGF-I may enhance regeneration of

both soft and hard tissue components of the periodontium in-vivo in 13 beagle dogs. Strayhorn et al<sup>16</sup> studied the effects of low molecular extract of bovine bone protein (BP) containing bone morphogenetic proteins (BMPs) 2,3,4,6,7, 12 and 13 alone or in combination with PDGF and or IGF on osteoblast differentiation invitro. Northern analysis revealed that PDGF blocked the gene expression of osteopontin and osteocalcin while BP and EGF promoted the gene expression of bone sialoprotein. They demonstrated that BP is a potent inducer of osteoblast differentiation and may act synergistically with IGF to promote osteoblast differentiation. Saygin et al<sup>17</sup> determined the effects of specific growth factors IGF-1, PDGF and TGF- $\beta$  on cementoblasts invitro and exvivo. Osteocalcin (OC) promoter driven transgenic mice were used to obtain immortalized cementoblasts. Growth factor effects on DNA synthesis were assayed by thymidine incorporation. All growth factors stimulated DNA synthesis compared to controls. Results indicated that growth factors influenced mitogenesis and biomineralization potential of cementoblasts suggesting that such factors alone or in combination with other agents may provide trigger factors required for regenerating periodontal tissues. Stavropoulos A et al<sup>18</sup> conducted a systematic overview on growth and differentiation factor technologies intended for periodontal wound healing or regeneration and evaluated clinically included platelet-derived growth factor, insulin-like growth factor-I and -II, basic fibroblast growth factor, bone morphogenetic protein-3 and growth differentiation factor-5 and found enhanced periodontal regeneration in sites receiving growth and differentiation factors compared with control.

Al-Hijazi AY et al<sup>19</sup> conducted an animal study using Albino rats to illustrate the biological actions of topical application of growth factors TGF- $\beta$ 1, VEGF on periodontal cells and tissues. The results demonstrated that the mean value of amount of new bone and the mean of the length of junctional epithelia was found to be higher in VEGF group, while the mean of periodontal ligament width and mean of rate of bone maturation were reported to be higher in combination group.

### SOURCE OF PERIODONTAL REGENERATION

Therapeutic application of growth factors aims to restore damaged periodontal tissues by regeneration through biomimetic processes or by imitating the processes that occur during embryonic and post-natal development.<sup>20</sup> Periodontal regeneration is dependent on the

recruitment of mesenchymal stem or stromal cells (MSCs) to the site of the intrabony defect. MSCs have been identified in the perivascular space and other special niches in adult tissues, including the PDL and stromal compartment of bone marrow. MSCs are multipotent cells capable of differentiating into the osteoblast and other specialized cell types. The PDL contains stem cell populations also capable of differentiating into cementoblasts. Therefore, both the PDL and alveolar bone marrow are considered critical sources of progenitor cells for periodontal regeneration. In an effort to enhance periodontal regeneration, some clinicians perform intramarrow penetration, or decortication, to promote bleeding and cellular movement from bone marrow into the defect site.<sup>21</sup>

### GROWTH FACTOR AND GENE THERAPY

The term Gene therapy originally is referred to the treatment of a disease by means of genetic manipulation. According to Strayer gene therapy may involve, supplying or increasing the expression of a mutant gene that is insufficiently expressed (e.g. to treat genetic enzymatic deficiencies), blocking a gene that is detrimental (e.g. using antisense constructs to inhibit tumor proliferation) and adding a foreign gene to treat a situation beyond the capability of the normal genome (e.g. introduce an enzyme into a cell or tissue that allows the tissue to become more sensitive to the effects of a pharmacologic agents).<sup>22</sup>

There are three approach of tissue engineering in periodontics:

- Protein based approach: Growth and differentiation factors are used for regeneration of periodontal tissues likes TGF- $\beta$ , BMP-2,6,7,12, bFGF, VEGF and PDGF.
- Cell based approach: Several studies using mesengymal stem cell have demonstrated efficient reconstruction of bone defect that are too large to heal spontaneously.
- Gene delivery approach: To overcome the short half-lives of growth factor peptides *in vivo*, gene therapy that uses a vector that encodes the growth factor is utilized to stimulate tissue regeneration. Two main strategies of gene vector delivery have been applied to periodontal tissue engineering. Gene vectors can be introduced by *in vivo* technique i.e. directly to the target site or *ex vivo* technique i.e. selected cells can be harvested, expanded, genetically transduced, and then reimplanted.<sup>23</sup>

The success of tissue engineering relies on the large scale purification and production of signalling molecules as well as method to deliver these factors to their targets. One problem with current growth factor delivery in periodontal wounds is the extremely short half-life of these factors. Topically administered growth factor remain in the periodontal defect for a limited duration, presumably due to proteolytic breakdown, receptor mediated endocytosis and the solubility of the delivery vehicle. Hence the use of DNA delivery systems may serve as an alternative method of targeting proteins to periodontal wounds.<sup>24</sup>

### CONCLUSION

A review of the current existing literature shows that a combination of growth factors in an optimal concentration is best suited for periodontal regeneration. A combination of PDGF and IGF have been considered attractive candidates for regenerative therapies. The capability of BMPs to induce bone formation is well proven and has been demonstrated in vivo. With the advent of the recombinant technique its now possible to provide large quantities of purified growth factors for use in in vivo studies. Ongoing human clinical trials assessing the potential therapeutic use of growth and differentiation factors for periodontal regeneration seek to provide the conclusive evidence for the addition of this therapy to the reconstructive periodontal treatment armamentarium.

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**Source of support:** Nil

**Conflict of interest:** None declared



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