ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at:www.ijdsir.com

Volume – 7, Issue – 1, January- 2024, Page No. :07 - 16

Growth factors in periodontal regeneration: A review

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Citation of this Article: Dr Akash Warman, Dr. T Prasanth, Dr. Shreehari AK, Dr. Krishnaprasad KR, Dr. Harjeet Singh, Dr. Saravanan SP, Dr. Ankit Gupta, "Growth factors in periodontal regeneration: A review", IJDSIR- January - 2024, Volume –7, Issue - 1, P. No.07– 16.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Periodontal diseases are Immuno- inflammatory diseases affecting the population. After non-surgical treatments, advanced cases often show inflammation. In recent years, there has been a notable shift in periodontal surgical procedures towards regeneration. Regeneration involves recreating or damaged structures. Periodontology defines successful regeneration as the formation of new bone, cementum and properly oriented periodontal ligament. In contrast ,the term "periodontal repair" pertains to recovery after surgical intervention that does not fully restore the attachment apparatus. Regeneration happens when mesenchymal cells from the bone's periodontal ligament multiply and colonize the root surface, often facilitated by growth factors released during cell division in processes like wound healing. Platelet-derived growth factor (PDGF), transforming growth factor (TGF)-α, and other factors are released at wound edges, prompting nearby cells to release growth factors like insulin-like growth factor-I, PDGF, TGF-α, and TGF-β. Successful periodontal regeneration requires re-establishment of the periodontal ligament, cementum, and alveolar bone. Therefore, substances promoting collagen production, periodontal ligament fibroblast growth and migration play pivotal roles in facilitating new periodontal ligament formation. Combining various factors in cocktails seems more effective for promoting repair compared to using individual factors alone.

Keywords: Regeneration, Growth Factor, Fibroblast Growth Factors, Scaffolds, Platelet Derived Growth Factor, Transforming Growth Factor, Delivery Agents.

Introduction

Periodontitis, a condition characterized by inflammation of the tooth supporting structures and frequently culminates in the development of periodontal pockets and the degradation of the connective tissue and bone. . Therapeutic strategies aim to halt disease progression, reduce gingival inflammation, and regenerate the already damaged periodontal tissues [1]. Non-surgical interventions like scaling and root planing often fall

short, leaving pockets of plaque and calculus on root surfaces, especially in deep pockets [2,3]. Even after such treatments, moderate to advanced cases continue to display signs of inflammation. As a result, surgical access becomes essential to thoroughly cleanse the various components of the periodontium, fostering an environment that is conducive for periodontal health restoration [4,5]. Surgical procedures also offer an opportunity to regenerate damaged periodontal tissues and address potential mucogingival and anatomical irregularities.[6]Advancements in understanding the biological mechanisms essential for regenerating or repairing the attachment apparatus have been made by researchers. Cellular processes fundamental to tissue repair encompass mitogenesis (cell proliferation), migration, and metabolism. Orchestrating these processes are growth factors which are defined as "biologically active polypeptide hormones, which affect the immune function as well as proliferation, chemotaxis and differentiation of cells of epithelium, connective tissue and bon. Their wide-reaching positive impacts on wound healing have been observed across various tissues, including the periodontium.[7]. They bind to specific cell-surface tyrosine kinases receptors which are present on various target cells including cemetoblasts, periodontal ligament, fibroblasts .[8]

Development of growth factors

The concept of growth factors emerged as researchers observed that certain substances could stimulate cell growth and division. Early studies focused on factors like hormones and vitamins**.** In a fascinating journey of scientific discovery, the 1960s marked a significant milestone with the groundbreaking work of two remarkable individuals, Rita Levi-Montalcini and Stanley Cohen. Their research unveiled the intricate mechanisms governing cell growth and differentiation. Rita Levi-Montalcini, an Italian developmental biologist, unveiled the mysteries of nerve growth factor (NGF),while American biochemist Stanley Cohen shed light on epidermal growth factor(EGF).These pioneering discoveries in the 1960 opened the door to a world of signalling substances that would soon be explored in depth, each playing a unique role in controlling growth and development.

As the 1970s dawned, the quest for understanding the intricacies of cellular growth continued .In this decadeC.Ross and J.A. Heldin's work led to the discovery of platelet -derived growth factor(PDGF),a substance found in platelets that demonstrated a remarkable ability to stimulate cell division, especially within connective tissues and blood vessels[9].

Meanwhile ,the 1970s also witnessed the emergence of fibroblast growth factors(FGF).It was in 1973 that Armelin detected mitogenic growth factor activity in pituitary extracts.[10].Further research by Gospodarowicz in 1974 isolated specific proteins from cow brain extract.[11] When these proteins were tested in a bioassay they caused fibroblasts to proliferate, leading these biomolecules to be named as "Fibroblast growth factors".

The 1980s arrived with new revelations in the realm of growth factors. Michael Sporn and Anita Roberts embarked on a journey that resulted in the isolation of transforming growth factor-beta (TGF-β).This factor played a pivotal role in the processes of regeneration and wound healing, further expanding our understanding of how cells respond and adapt to their environment.[12],including IGF-1 and IGF-2 as it fully defined members. These molecules shared both structural and functional similarities, yet they were independently regulated, adding another layer of complexity to the web of growth regulation.

As the 1990s dawned, the quest for unraveling the secrets of cellular growth continued relentlessly. In 1989, Napoleone Ferrara and his colleagues at Genentech achieved a significant breakthrough by isolating and cloning vascular endothelial growth factor(VEGF).[13]This discovery opened up new avenues of research into the critical role VEGF played in the formation of blood vessels, expanding our knowledge of angiogenesis. Simultaneously, researchers isolated hepatocyte growth factors (HGF),also known as scatter factor. HGF emerged as a key player in tissue regeneration and organ development, adding another chapter to the ongoing saga of growth factor research. Throughout these decades, the tireless efforts of researchers around the world unveiled the intricate web of growth factors, each with its unique role in cellular growth and development. This ongoing narrative of discoveries continue to shape our understanding of the fundamental processes that govern life at cellular level.

Role, features and limitations of growth factors.

Growth factors act in autocrine and paracrine way [14] to stimulating cell proliferation (e.g., Platelet-derived growth factor), enhancing cellular function and differentiation (e.g., BMP), promoting matrix synthesis (e.g., TGF-β), and acting as co-factors for gene expression.[15]. Due to their inability to diffuse across cell membranes they must first bind to high-affinity cell membrane receptors to exert their action. [16,17]. Notably, tissue regeneration in vivo involves a interplay of numerous growth agents [18].

While growth factors have demonstrated clinical effectiveness, their potential as therapeutic agents have generally been constrained by inherent limitations present in their natural protein forms. Specifically, nature has shaped these growth factors with attributes like limited protein stability, a short duration in the bloodstream, swift cellular internalization, and targeted tissue activity. These attributes function as mechanisms to regulate their effects within specific timeframes and locations. For instance, fibroblast growth factor (FGF-1) exemplifies this with its inherent instability, displaying a functional half-life of just one hour in serum at 37 °C.[19] Utilizing exogenous growth factors as therapeutic agents faces further challenges, including low yield in recombinant expression, purification difficulties, high production costs, and a lack of suitable delivery techniques.[20] These combined constraints underscore a pressing need for innovative tools and technologies that can enhance the suitability of growth factors for therapeutic applications.

Types, sources and actions of various growth factors

1 Platelet Derived Growth Factor Platelet-derived growth factor (PDGF): It recognized as a primary factor contributing to wound healing, and its potential to trigger periodontal regeneration has been the subject of thorough investigation. In the late 1980s, Lynch and his team revealed that PDGF held the capacity to facilitate the regeneration of periodontal ligament, cementum, and bone. [22] The concentration of PDGF in the bloodstream varies between 15 to 50 mg/ml. PDGF consists of two distinct polypeptide chains, PDGF-A and PDGF-B, which are encoded by separate genes and connected by disulfide bonds. The major source of PDGF are degranulating platelets, macrophages and keratinocytes

Role of PDGF in cell division and wound healing is fundamental at cellular level .PDGF serves as a crucial factor that prompts cells to transition from their dormant G0 phase back into active cell cycle, initiating the process of cell division.[22]. This action is pivotal for the regenerative processes that occur during wound healing.PDGF also plays a role in stimulating the influx

of neutrophils to wound site,contributing to the body's defence mechanism.Moreover ,PDGF exhibits a range of beneficial effects on wound healing.It acts as a mitogen,encouraging cell proliferation and supports angiogenesis. Additionally, PDGF upregulates other growth factors and cells, effectively prompting the functions of fibroblast and osteoblasts. It also aids in cellular differentiation and accelerates effects of growth factors on other cell types, including macrophages.[23] Studies conducted by Lynch et al [24], Rutherford et al[25], Cho Moon et al[26] showed that PDGF can stimulate bone growth and periodontal regeneration in vivo, showing that it has potential to serve as a vital adjuvant to periodontal surgery.

2 Insulin like growth factors (IGF) These are a family of single chain of proteins that share 49% homology with pro-insulin. IGF-1 and IGF-2, two members of this group that have been fully defined, are similar in structure and function but are independently regulated. IGF-I and II have molecular weights of 7.7 and 7.5 KDa, respectively, making them relatively tiny proteins. The IGF family has three ligands: insulin, IGF-I and IGF-II; and three cell surface receptors: insulin, IGF-1, and IGF-l-mannose G-phosphate receptors.

Platelets are the major source of IGF's

IGF-I stands as a pivotal cellular progression factor imperative for completing the cell cycle. It appears that growth hormone from the pituitary gland triggers the synthesis of IGF-I in various tissues, primarily the liver. IGF-I takes on the role of mediating several biological processes that were initially attributed to growth hormone. This led to the concept of dual effector action involving both GH and IGF-I, wherein growth hormone initiates cell differentiation and boosts IGF-I production, subsequently fostering cell division.[27] Notably, insulin-like growth factor-I possesses the capability to prevent apoptotic cell death. Han and Amar's study [28] demonstrated that IGF-I significantly enhances cell survival by enhancing antiapoptotic molecules and reducing proapoptotic molecules in periodontal ligament fibroblasts compared to gingival fibroblasts. Additionally, researchers utilizing mandibular molars in primary culture observed the accumulation of various enamel-specific gene products like amelogenin and ameloblast in. This observation suggests the involvement of the IGF system in inducing enamel biomineralization. Moreover, IGF-1 serves as a potent chemotactic agent for vascular endothelial cells, contributing to the process of neovascularization.

3.Transforming Growth factor family: TGFs constitute a protein family found in normal and neoplastic tissues. The two extensively studied growth factors in this category are TGF-α and TGF-β. TGF-α, a single-chain protein of 50 amino acids which weighs around 5600 Da. It competes with EGF for its receptor and has a 42% similarity to EGF. TGF-α primarily stimulates epithelial and endothelial cells. TGF-β, a highly conserved and has three isoforms: TGF-β1, TGF-β2, and TGF-β3.It is mainly synthesized by Platelets and Macrophages.

Transforming Growth Factor-β (TGF-β) plays a pivotal role in wound healing and repair processes.[29,30] It exerts its influence through various mechanisms: firstly, by modulating integrin-mediated cell adhesion and migration, which involves the regulation of integrins, their ligands, and associated proteins.[31] Additionally, TGF-β promotes cell chemotaxis in gingival and periodontal ligament fibroblasts, further facilitating tissue repair.[32,33] TGF-β exhibits a dual nature, possessing both pro-inflammatory and anti-inflammatory properties, in addition to its capacity to stimulate the formation of extracellular matrix while inhibiting

proteolytic matrix degradation during periodontal wound healing.[34] Beyond wound healing, studies on transgenic mice with knocked-out TGF genes have revealed that the absence of TGF leads to a fatal diffuse inflammatory reaction shortly after birth, underscoring its crucial role in immune system regulation.[35] TGF has also been implicated in endochondral bone formation in both animal and human models, emphasizing its significance in the process of regeneration. [36,37]

4.Fibroblastic Growth Factor (FGF)

FGF was discovered in pituitary extracts of cows. Two proteins with different basic and acidic isoelectric points were identified as acidic FGF (aFGF, FGF-1) and basic FGF (bFGF, FGF-2). Since then about 23 different types of FGF have been identified and are subdivided in 7 subfamilies.

The main sources of FGF areMacrophages and Endothelial cells.

Fibroblast Growth Factors (FGFs) exert diverse and crucial actions in cellular processes. Firstly, they promote cellular proliferation in endothelial cells, fibroblasts, neural stem cells, and trophoblast stem cells.[38] Additionally, FGFs are instrumental in cell migration, a vital aspect for wound healing, immune responses, and tissue development. They particularly play a significant role in orchestrating the directional movement of cells.[39] FGF7 emerges as a key player in cell differentiation, specifically in the morphogenesis of suprabasal keratinocytes, and in establishing the normal program of keratinocyte differentiation. This underscores its critical function in the development and maintenance of healthy skin and its appendages.[40] FGF1 and FGF 2 have established roles in angiogenesis.[41] Collectively, FGFs emerge as central regulators in a multitude of cellular activities, ranging from proliferation and migration to differentiation and angiogenesis, highlighting their fundamental importance in various physiological processes.

5. Bone Morphogenetic Proteins (BMPs)

Bone morphogenetic proteins (BMPs) are a collection of growth factors and signaling molecules that hold a crucial role in numerous biological processes, particularly in bone and tissue development and regeneration. These proteins belong to the larger family of transforming growth factor-beta (TGF-β). BMPs are renowned for their capacity to prompt the transformation of mesenchymal stem cells into osteoblasts, pivotal for bone creation. Initially identified for their ability to stimulate new bone tissue formation, hence the name "bone morphogenetic proteins," their functions transcend bone generation. They encompass diverse roles including embryonic development, tissue healing, cell differentiation, and control of cellular growth. BMPs enact their influence by binding to distinct receptors on cell surfaces, triggering internal signaling pathways that ultimately reshape gene expression and cellular behavior. The main action of BMPs is to commit undifferentiated pluripotent cells to differentiate into cartilage and bone forming cells. [42,43]

Characteristics of BMPs: BMPs act as mitogens on undifferentiated mesenchymal cells and precursor osteoblasts and promote bone formation. BMPs exhibit an anabolic impact on periodontal tissue by stimulating osteoblastic differentiation in human periodontal ligament (PDL) cells. BMPs such as BMP 2-12 independently trigger the initiation of de novo endochondral bone formation. [44,45] Moreover BMPs induce the expression of osteoblast phenotype, leading to an increase in alkaline phosphatase activity in bone cells. Additionally, BMPs serve as chemoattractant for

mesenchymal cells and monocytes, while also binding to extracellular matrix collagen type-IV[46]

Categorization of BMPs:

BMPs are grouped into distinct subsets according to their amino acid sequences, facilitating a clearer understanding of their functional diversity:

1. BMP-2 and BMP-4:

- constitute a subset characterized by their shared amino acid sequences. They are renowned for their critical roles in skeletal development and tissue repair.

2. BMP-3 and BMP-3b:

- BMP-3 and BMP-3b form another distinct grouping within the BMP family. These proteins are recognized for their regulatory functions in various cellular processes.

3. BMP-5, BMP-6, BMP-7, and BMP-8:

- This subset encompasses BMP-5, BMP-6, BMP-7, and BMP-8, collectively contributing to a wide array of developmental processes, including organogenesis and tissue differentiation.

4. BMP-9 and BMP-10:

- form a unique pairing known for their roles in liver development and angiogenesis, respectively.

5. BMP-12, BMP-13, and BMP-14:

- constitute a subset with recognized functions in tendon and cartilage development, highlighting their significance in musculoskeletal biology.

6. BMP-11 and Growth/Differentiation Factor 8 (GDF-8):

- also known as GDF-8, is distinguished for its role in muscle development and regeneration, making it a crucial player in the field of myogenesis.BMPs are homodimers, weighing around 30 to 38 KDa,. These BMPs are categorized into distinct subsets based on shared amino acid sequences. The groupings are as follows:

Role of BMPs in periodontal regeneration

BMPs demonstrate distinct characteristics in terms of structure and activity, where BMP-2 predominantly displays osteogenic properties, while BMP-7 primarily exhibits cementogenic activities. The use of recombinant human morphogenic protein-2 (rhBMP-2) has been instrumental in exploring periodontal regeneration. Sigurdsson et al. (1995) and Kinoshita et al. (1997) effectively achieved periodontal regeneration in dogs by employing rhBMP-2 with a systemic carrier. Clinical trials utilizing rhBMP-2 within an absorbable collagen sponge carrier (Howell et al., 1997; Cochran et al., 2000) have yielded promising outcomes, demonstrating favorable tolerance of both the protein and the carrier on local and systemic levels.

Vehicles for Growth Factors

Several matrices and delivery systems have been used and evaluated for their efficacy and biocompatibility as carriers for GFs. Two common types of polymeric materials used in GF delivery strategies are natural collagen-derived materials and synthetic polymers of lactic and glycolic acid (i.e. Poly [lactide-co-glycolide])

Extracellular matrix-derived macromolecules such as collagen have been used for many years in biomaterial application, and it is now possible to create artificial analogues of extracellular matrix proteins using recombinant DNA technology.

Carriers can be of different types such as solids, gels or combinations. A variety of new injectable materials such as hydrogels is also being developed for GF delivery applications and have been of special interest. These injectables are especially attractive because in clinical application they can allow for minimally invasive delivery of inductive molecules. Another area of

increasing attention has been the development of shape-memory materials that have one shape at one temperature and another shape at a different temperature. These materials have the ability to memorize a permanent shape that can be substantially different from an initial temporary shape. As an example, a bulky device could potentially be introduced into a surgical site as a temporary shape (such as a string or freely flowing material), penetrate through a small area of the site, and then be expanded in response to different cues into a permanent shape (i.e., a stent or a sheet). The response signals that stimulate the changes in shape in response to environmental cues are incorporated within the material during its fabrication. These materials have been designated as 'smart' materials, having the capability to appropriately change their structural and functional material properties in response to environmental cues.

Ideal characteristics of delivery agents [47]

• Should be biocompatible
• Should be non-toxic
• Easy to handle
• Release kinetics to be considered
• Characteristics of restorability and retrievability

Agents used for delivery.

• Methyl cellulose
• Osseous grafts
• Collagen gels and collagen-based sutures and hemostatic sponges
• Collagen membranes
• Synthetic polymer material

Discussion

Growth factors are a category of naturally occurring proteins, displaying a range of powerful local features. These proteins play a crucial role in controlling biological processes such cell migration, attachment, and proliferation. IGF and TGF-β serve as progression factors, whilst and FGF and PDGF are competence factors. The growth of the skeleton during embryology depends heavily on PDGF and IGF. PDGF is a crucial activator of cellular chemotaxis, proliferation, and matrix synthesis. It facilitates the entry of fibroblasts into the wound site and boosts the creation of extracellular matrix.

Different growth factors are now on the way to entering clinical practice in dentistry. Hence, it is of utmost importance to assess systematically the effect of the growth factors on the healing of intra-oral bone defects. Current knowledge suggests certain advantages and disadvantages to the use of certain growth factors. Lynch and coworkers and many others have suggested that while the effect of IGF-1 alone had only a slight effect on the PDL cells, a combination of PDGF and IGF caused an increased mitogenesis, migration and metabolism of periodontal ligament cells. Hence, it seems more favorable to use a combination of growth factors to predict better regeneration than experimenting with individual growth factors.

There is no definite answer to the question as to which growth factors will promote regeneration of the periodontium. The study of interaction between multiple growth factors on bone metabolism is important because numerous growth factors are sequestered in bone matrix at high concentration and these bone cells release different growth factors. Also, during repair, temporal expression of many growth factor genes takes place. Hence potential interaction of various growth factors may exist during development and repair of tissues.

Summary

The biology of periodontal connective tissues is important to be understood in terms of development, pathology, regeneration and interrelationship between periodontitis interactions and various systemic diseases.

Although growth factors function as molecular mediators of periodontal tissues, their value as diagnostic biomarkers for periodontal tissue inflammation and/or fibrosis is yet to be elucidated. High-throughput technologies applied for assessment of gingival crevicular fluid and saliva will give new promises for the use of growth factors as objective biomarkers in periodontal disease.

In earlier studies, the application of growth factors provided different degrees of success in stimulating wound healing in the periodontal areas. There is an imperious need to further evaluate the biologic mechanisms that may be responsible for the promotion of tissue regeneration by growth factors. Finally, studies on growth factors delivery and improved stability seek evidence to conclusively support the addition of growth factors strategy to the therapeutic protocol for regeneration of periodontal tissues.

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