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BIOMECHANISM OF HEALING AFTER GUIDED BONE REGENERATION THERAPY

[1]Dr. Urvashi Verma MDS, [2]Dr. Syed Owais Ahmed MDS, [3]Dr. Kinjal Kanubhai Desai MDS, [4]Dr. Unnati Oza MDS, [5]Dr. Harsh Parikh MDS, [6*]Dr. Babu Salam MDS

[1]Pediatric Dentist, Senior Lecturer, Department of Pediatric & Preventive Dentistry, ITS CDSR Dental College, Muradnagar, Delhi Meerut Road, Ghaziabad, Uttar Pradesh.
[2]Senior Lecturer, Sri Siddhartha Dental College and Hospital, Tumkur, Karnataka.
[3,5]Consultant Periodontist and Implantologist, Mehsana, Gujarat.
[4]Consultant Periodontist and Implantologist, Ahmedabad, Gujarat.
[6]Consultant Periodontist and Implantologist, Chennai, Tamil Nadu.

***Corresponding Author: Babu Salam C.**
Pediatric Dentist, Senior Lecturer, Department of Pediatric & Preventive Dentistry, ITS CDSR Dental College, Muradnagar, Delhi Meerut Road, Ghaziabad, Uttar Pradesh.

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1. INTRODUCTION

Following GBR procedure, bone regeneration exhibits a specific sequence of events. Within the first 24 hours, the graft material/barrier created space is filled with the blood clot which releases growth factors (e.g.**,** platelet derived growth factor) and cytokines (e.g., IL-8), which in turn attracts neutrophils and macrophages. The clot is gradually absorbed and replaced with granulation tissue which is rich in newly formed blood vessels. Through these blood vessels, nutrients and mesenchymal stem cells capable of osteogenic differentiation can be transported to the defect site, which contribute to osteoid formation. The osteoid mineralizes and forms woven bone, which later serves as a template for the apposition of lamellar bone. This transformation of primary sponge work would eventually constitute both compact and reticular bone with mature bone marrow. These events occur 3 to 4 months postsurgery.

Bone formation and blood vessel formation was seen at the periphery of the defect. The new vascular supply emanated from surgically created perforations in the cortical bone. The woven bone was subsequently replaced by lamellar bone, which resulted in mature bone anatomy. Ultimately, bone remodeling occurred with the new secondary osteons being formed.

During an experimental GBR procedure in a rat tibia defect, the presence of a synthetic PTFE membrane enhanced an earlier and higher level of cbf-1/Runx2 positive osteoprogenitor cells and stronger expression of the bone-formation marker, osteocalcin, in the underlying defect compared with the untreated defect.

1. BIOMECHANISM OF HARD TISSUE HEALING

The presence of PTFE membrane stimulated stronger expression of several bone-formation related genes, including alkaline phosphatase, osteopontin, and bone sialoprotein in the underlying defect in comparison with a defect without membrane. The presence of the PTFE membrane also triggered increased expression of tissue and bone remodeling genes, including receptor activator of nuclear factor kappa-B ligand (RANKL) and matrix metallopeptidases (MMPs) 2 and 9, as well as the inflammatory cytokines, interleukins (ILs) 1 and 6, in the underlying defect.[1,2]

The presence of resorbable, naturally derived, collagen membrane promotes coupled increase in bone formation and bone-remodeling genes (osteocalcin, calcitonin receptor, cathepsin K, and RANKL) in the underlying defect, compared with a similar defect without membrane. The presence of the membrane triggers an early upregulation of two major cell-recruitment factors in the defect: C-X-C chemokine receptor type 4 (CXCR4) and monocyte chemoattractant protein-1 (MCP-1). These two factors are of particular interest as the chemokine receptor CXCR4 plays an important role in the recruitment of mesenchymal stem cells, which differentiate to osteoblasts, the cells responsible for bone formation. The MCP-1 has been described as a major chemokine for recruitment of osteoclast precursors, the key cell type for bone remodeling. Hence the membrane promotes an environment for rapid recruitment of different cell types in the defect, including osteoblastic and osteoclastic phenotypes and more importantly, that the membrane promotes an environment conducive for the molecular cascade of coupled bone formation and remodeling in the underlying defect.[3,4]

The collagen membrane predominantly consists of ECM collagen and also contains inherited growth factor [fibroblast growth factor-2 (FGF-2)]. And the membrane per se hosts different cell phenotypes during GBR and that these cells within the membrane progressively express and secrete major bone-related growth factors, including the potent pro-osteogenic factor, bone morphogenetic protein 2 (BMP-2). Strong links between the pro-osteogenic growth factors expressed in the membrane with the bone-formation and bone-remodeling activities within the underlying defect were demonstrated in the correlation analysis.[5]

Taken together, the results provide strong evidence that the membrane directly promotes the healing processes in the underlying defect by activating the host cells that are recruited into and/or become adherent to the membrane, allowing their signals to be communicated to the different cell populations in the underlying defect. Hitherto, it is not known whether this bioactive role of the membrane compartment is exclusively restricted to naturally derived collagen membrane. Interestingly, when clinically retrieved PTFE membranes were cultured *ex vivo* in osteogenic medium, the membrane adherent cells demonstrated the ability to produce higher levels of ALP osteogenic activity compared with clinically harvested gingival cells. These PTFE membrane-adherent cells were also capable of producing mineralized nodules in a similar set-up after a longer period of *ex vivo* culture in osteogenic medium.[6]

These results indicate that the synthetic PTFE membrane may harbor cells with regenerative potential on its surface, and that the PTFE membrane-adherent cells can at least convey inflammatory signals. The role of the inflammatory cells for vascularization and degradation of the membrane per se is an interesting and yet incompletely answered issue. The recruitment of cells into the collagenous membranes has been suggested to enhance tissue integration and transmembrane vascularization, processes that have been suggested to be influenced by the membrane type.[7]

On the other hand, it is not yet known if different membranes will have different potential to host and activate the membrane-recruited cells, and if this would result in different degrees of bone formation and restitution of the underlying defect.[8]

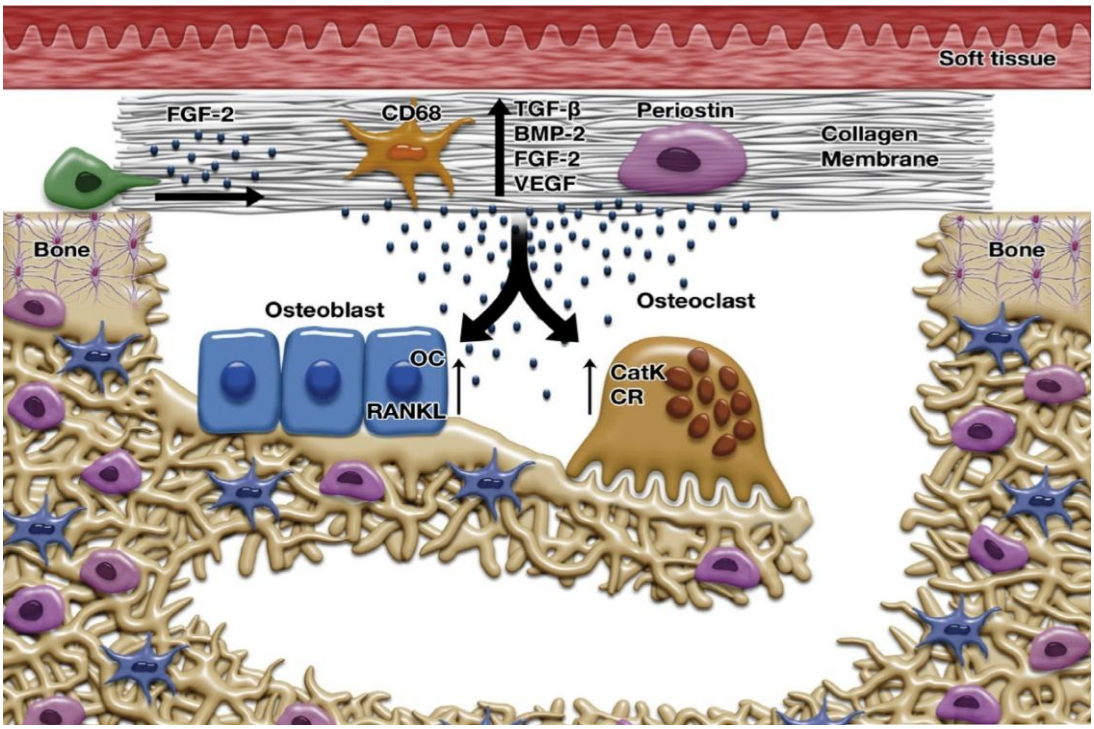

Figure 1: A schematic illustration of the cellular and molecular cascades during guided bone regeneration. The cellular and molecular cascades include: migration of different cells (e.g. CD68-positive monocytes/macrophages and periostin-positive osteoprogenitors) from the surrounding tissue into the membrane. The cells which have migrated into the membrane express and secrete factors pivotal for bone formation and bone remodeling. This promotes the development of mature remodeled bone in the underlying defect, by stimulating the activity of osteoblasts and osteoclasts, the main cells of bone formation and remodeling. BMP-2, bone morphogenetic protein 2; CatK, cathepsin K; CD68, cluster of differentiation 68; CR, calcitonin receptor; FGF-2, fibroblast growth factor 2; OC, osteocalcin; RANKL, receptor activator of nuclear factor kappa-B ligand; TGF-β, transforming growth factor-b; VEGF, vascular endothelial growth factor.

2. BIOMECHANISM OF SOFT TISSUE HEALING

One of the keys to GBR is initial soft tissue coverage and tissue healing. The understanding of the cytokine-mediated processes of connective tissue formation is the basis for the development of new innovative therapeutic strategies. These may include the modulation of chemotaxis, differentiation, proliferation of fibroblasts, synthesis of extracellular matrix proteins, and, as a result, control of soft tissue formation.

Both lack and overexpression of transforming growth factor-β (TGF- β) may be responsible for an impaired healing process. TGF- β attracts fibroblasts, monocytes, and macrophages to the site of inflammation. Furthermore, it provokes a reduced phagocytosis capability of granulocytes and macrophages. During new tissue formation, it induces the expression of integrins, which control the migration of keratinocytes to the wound surface. Additionally, TGF- β stimulates the synthesis of collagen during the wound healing process. In the course of remodeling, the cytokine is believed to influence composition and cross-linking of permanent collagen structures by regulating the pattern of integrin expression in fibroblasts.

Interleukin 1 (IL-1) fulfills a key role within the inflammatory signal transduction processes. IL-1 is produced by monocytes and macrophages and serves as the main stimulus of extracellular matrix catabolism, production of collagenase and proteinase (matrix metal proteinase), and degranulation of neutrophil granulocytes. Implant surrounding soft tissue altered by inflammatory processes expresses noticeably higher levels of IL-1β in comparison to the physiologic mucosa. It can be used as a marker for a proinflammatory cellular response in the peri-implant soft tissue.[9]

Vascular endothelial growth factor (VEGF) is a glycoprotein that induces the microvascular permeability and angiogenesis during the stage of proliferation. The cytokine is activated by hypoxic conditions and furthermore by IL-1 β and TGF-β. The VEGF gene is organized in eight exon subunits separated by seven intron sequences. VEGF is the prevalent molecular type synthesized and secreted by fibroblasts and keratinocytes. Native VEGF is a basic, heparin-binding, homodimeric glycoprotein. Suthin et al described bacterial liposaccharides to be responsible for the stimulation of VEGF secretion. Independent from this involvement in inflammatory processes, VEGF is excreted during every wound healing by keratinocytes.[10]

Whether the surgical implantation itself may cause a potential increase in the expression of inflammatory cytokines such as TGF- β_1, IL-1 β and VEGF in periimplant soft tissue has not yet been investigated in a clinical follow-up. Peri-implant tissues become hemorrhagic and edematous in the course of healing disturbance or periimplantitis. There is little information concerning the biological mechanisms that may produce these alterations. Existing clinical trials have investigated the expression of cytokines in the peri-implant region in inflammatory impaired soft tissues and have reported increased levels of IL-1 β, TGF- β_1, and VEGF in the course of infl ammation. In vitro data show increased values of IL-1 β, IL-6, and TNF α if tissue is incubated with dental implants.[11,12]

In an experimental setting, Shull et al described severe and uncontrollable inflammatory reactions in TGF- β negative mice. High levels of TGF- β_1 can further result in impaired crosslinking of collagen structures and fibrotic transformation of tissue. In experimental models the use of TGF- β neutralizing antibodies results in a reduction of fibrotic processes during wound healing. In contrast, higher levels of TGF-β1 itself seem to have a positive influence on successful implant integration: the synthesis of extracellular matrix and the proliferation of fibroblasts is stimulated while the expression of adhesion molecules in mucosal fibroblasts is enhanced.[13]

In vitro studies also used topical application of TGF-β for enhancement of healing and strength of granulation skin wounds. Lipopolysaccharide adsorption processes on the titanium surface of implants may contribute to this cytokine activation, especially because the use of different implant types results in variable expression levels, as reported by Perala et al. Because elevated levels of IL-1 cause tissue destruction, the application of IL-1 antagonists (IL-1 receptor antagonists or monoclonal antibodies) results in a reduction of tissue damage and limited inflammatory processes during experimentally induced periodontitis. It has further been shown that IL-1 antagonism results in a reduced progression of inflammatory processes and a reduction in loss of attachment and bone destruction.

VEGF is a powerful mitogen for endothelial cells and fulfills an important role in angiogenesis. The differences in terms of stromal cell positivity for VEGF between healthy and peri-implantitis sites have been studied, and higher values were found in peri-implantitis. Other studies proved VEGF to be an important factor in the initiation and progression of gingivitis to periodontitis, promoting expansion of the vascular network that coincides with progression of the inflammation. The demonstration of high expression levels may point to the induction of neoangiogenesis during the periimplant healing processes.[14]

This capability is also underlined by a study in which intramuscular application of recombinant VEGF improved perfusion and formation of vascular structures. TGF- β is composed of a family of multifunctional polypeptide growth factors involved in embryogenesis, inflammation, regulation of immune response, angiogenesis, wound healing, and extracellular matrix formation. TGF- β 1 is the most common isoform found

in human tissues. A role for TGF- β in the pathogenesis of periodontal disease has been suggested. TGF- β 1 may be one of the most important factors in the regulation of the infiltrate and in the production of tissue repair with a stimulation of fibroblasts and endothelial cells.

Successful reconstruction of peri-implant soft tissues is feasible, even in fibrotic conditions when appropriate surgical techniques are selected. The pleiotropic proliferative cytokine TGF- β is involved in the regulation of all phases of wound healing and tissue remodeling. The isoform TGF- β_1 is a cytokine associated with the development of fibrotic tissue. Overexpression of TGF β_1 causes scarring and fibrosis and results in limited clinical success of intraoral soft tissue management.[15]

3. CONCLUSION

Experimental therapeutic approaches with neutralizing antibodies to block TGF-β1 resulted in less scarring and a reduction of fibrosis. Clinical implications of these prolonged tissue remodeling processes may be the development of protocols with extended interim solutions to await the completion of soft tissue remodeling before permanent loading. Inflammatory infiltrate may be important in the evolution of infl ammatory processes involving periimplant tissues. Angiogenesis is an important feature of inflammation and healing, but its role in the development and progression or in the healing of periodontal lesions has not been elucidated. VEGF is a potent inducer of endothelial cell proliferation. Because of its extensive presence, VEGF is probably a factor in both the maintenance of periodontal physiology and in the progression of peri-implant inflammatory disease.

Recombinant human platelet-derived growth factor (rhPDGF-BB) is a bioactive protein that has been combined with bone graft materials in an effort to regenerate the periodontium to its prediseased state more predictably. When using a growth factor such as rhPDGF-BB with broad wound healing activity, an added clinical benefit is the more rapid soft tissue wound healing pattern observed at the surgical site. This also may be seen as a patient-centered benefit because it allows dentists to provide for a patient's prosthetic care on a timely basis, leading to a faster return to normal function.[16]

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