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Local drug delivery and periodontal regeneration: Are we in a dire strait? An original review

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Abstract
There exists an optimum balance between the microbial population adhering the dental structures and host's defense mechanisms. However, the continuous admittance of new colonization, break the homeostasis, promoting dysbiosis and generating inflammatory immune responses, leading to structural breakdown of tissues and disease propagation.

Periodontal therapy aims at reducing the microbial load and to regenerate the lost periodontium to restore its structure and function, hereby preventing disease reoccurrence. This was achieved by SRP (scaling and root planing) and adjunctive use of antimicrobials. Although presence of dental film is responsible for initiation of periodontal disease, individual's host susceptibility plays an important role in production of pro inflammatory cytokines, destructive enzymes, MMP'S (matrix metalloproteinases) etc. Thus, host modulating therapy (HMT) in form of various local and systemic host modulating agents have been used as adjunctive therapy.

However, certain limitation exists with the systemic delivery of the HMT like first pass metabolism, limited availability at the site, side effects as with bisphosphonates i.e. BRONJ (bisphosphonate related osteoradionecrosis of jaw) and thus local drug delivery of HMT has come up as an advantageous therapy mode in delivering the benefits of antimicrobial, anti- inflammatory and periodontal regenerating host modulating agents.

While stage I-III periodontitis can be treated by local drug delivery systems like fibers, strips, gels, nanoparticles etc. Stage IV periodontitis needs true regeneration by help of membranes and scaffolds (stanz et el). But variations in periodontal defect morphology and host response are often challenging for complete regeneration and this necessitate the use of newer adjuncts.

This review highlights the newer periodontal regenerating LDD agents, their mechanism of action, challenges in periodontal regeneration and future avenues of research.

Keywords: Periodontitis, periodontal regeneration, growth factors, new attachment

1. Introduction

Periodontitis is a multifactorial chronic inflammatory disease characterized by slow degradation of alveolar bone and the periodontal tissues. If left untreated, destruction may lead to tooth migration, drifting, mobility and tooth loss [1]. Presence and persistence of dental biofilm and a susceptible host are the key factors in the initiation and progression of periodontitis. Various periodontal therapies have been implied to treat the cases based on the diagnosis, severity, extent, causative factors, impact and association with systemic health.

According to the European federation of periodontology (EFP),S3 level clinical practice guideline for periodontitis [2]. the fundamental cornerstones of periodontal therapy involve 4 sequential steps:

1. Step 1 - Behaviour change and risk factor control.
   This step is therapeutic and preventive in nature and aims to control systemic and local risk factors.
2. Step 2 - Cause-related therapy.
   Aims to eliminate plaque and calculus by non -surgical periodontal therapy, which may include use of adjuncts which maybe:
   a. Based on nature - physical or chemical adjuncts
   b. Based on function-antimicrobials, anti-inflammatory, antioxidant, bone regenerating

or host modulating etc.

c. Based on mode of delivery:
- Local-gels, fibers, strips, nanoparticles, membranes etc.
- Systemic-IV, IM, oral etc.

3. Step 3 - surgical interventions: indications:
- Debridement of inaccessible root surface areas
- To regenerate or resect intra-bony or furcation periodontal defects

4. Step 4 - supportive care

Although NSPT (non-surgical periodontal therapy) and supportive periodontal therapy remains the "gold standard" of periodontal therapy for treatment of stage I-III periodontitis there still exists patients or sites with sustained dysbiosis, microbial recolonisation sites and progression of chronic destructive phase. This substantiates the very need of adjunctive therapy. Another important aspect is unique individual susceptibility profile that reflects the host immunoinflammatory response wherein host immunological factors play a major role in periodontal destruction.
Therefore, various host modulators have been proposed as adjuncts to slow down disease process, improve therapeutic outcomes as well as contribute to periodontal regeneration, which is achieved by the use of GTR/GBR, bone grafts, etc. However, their results are clinically unpredictable and variable due to differences in host response and pre-existing periodontal defect morphology [3-5]. Therefore, newer advance regenerating therapies that could modulate the host immunoinflammatory process, as well as regenerate the lost periodontal tissues is the call of hour.

Host modulatory therapy: Includes systemic and local drug delivery of various host modulating agents.

Classification (Salvi and lang)
1. Modulation of arachidonic acid metabolites.
2. Modulation of MMP's.
3. Modulation of bone remodelling.
4. Modulation of host cell receptors.
5. Modulation of nitric oxide synthase (NOS) activity.

However, there exists various limitations with the systemic delivery of these drugs like low bio-availability, rapid excretion, hepatic metabolism, need for frequent dosing, short biological half- lives, dysbacteriosis, drug resistance etc [6]. Owing to these limitations and complications ,the use of LDD became a popular subject in 1970,introduced by Goodson for the treatment of periodontitis.
This review highlights the newer host modulating agents which are locally delivered to achieve periodontal regeneration.

Locally delivered HMT in periodontal regeneration

1. Enamel Matrix Proteins
- EMD's are mainly comprised of amelogenins.
- These are the proteinous substances that are synthetized during the formation of root and attachment apparatus from hertwig's epithelial root sheath [7]. Commercially, they are available as EMDogain® (Biora AB,Malmö, Sweden) -FDA approved.

Mechanism of action
1. Stimulates the periodontal regeneration by mimicking the events that occurs during root formation [8-11].
2. Act as tissue healing modulators and enhance wound healing.
3. Inhibitors of pathogenic plaque.
4. Reattaches PDL fibers to the newly formed root cementum by the recruiting cementoblasts [12]
5. EMD possesses cell adhesive properties and act as scaffold for PDL cells.
6. Exerts a biological "guided tissue regeneration effect" and exhibit a cytostatic action on epithelial cells.
7. Stimulates the growth of growth factors (TGF-ß1, IL-6, and PDGF-AB) in EMD cultured human PDL cells.

2. Bone morphogenic protein
Belongs to TGF family, and plays a major role in bone induction and maintenance.

Mechanism of action
1. BMP's acts as chemotactic agents and growth differentiation factors.
2. Promotes the migration, proliferation, differentiation and angiogenesis of mesenchymal stem cells into osteoblasts and chondroblasts.
3. BMP's are osteoinductive [13]
   ACS acts as scaffolds over which new bone is laid down [14].

3. Platelet derieved growth factors
- Natural protein found in bone matrix.
- Five isomers of PDGF have been identified-PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD
- Among these PDGF-BB binds to b type receptors and stimulates the proliferation of osteoblasts and fibroblasts. (Nister *et al.*)
- Lynch *et al.* First showed that the PDGF promotes new bone formation around periodontal bony defects in a study done on beagle dogs [15].

Mechanism of action
1. Mature osteoclasts produce factors including the PDGF that attract osteoblasts towards the injured or inflamed sites, promoting new bone regeneration in the target tissues [16].
2. Enhance the proliferation of human gingival fibroblasts thereby promoting and stimulating periodontal soft tissue repair [17-19].
3. Enhances the proliferation and osteogenic differentiation of MSCs [20].
4. Combining PDGF with other GFs such as IGF-1, BMP-2 and EMD augments periodontal tissue regeneration compared to when other GFs are used alone [21].

4. Bisphosphonates (bp's)
BP's were introduced in 1990s first to treat osteolytic tumours and osteoporosis.

Mechanism of Action
1. BP's inhibit development of osteoclasts and induces osteoclast apoptosis through activation of caspase pathway (Hughes *et al.*)
2. Inhibition of MMP's (Teronen *et al.*)
3. BP's have a high affinity for calcium phosphate crystals and this inhibits osteoclast activity.
4. Reduces collagen degradation.
5. At the molecular level-

6. Inhibit mevalonate pathway by reducing post translational prenylation of GTP binding proteins, therefore inhibits osteoclastogenesis.
7. Hydroxy ethylidene bisphosphonate (HEBP) induces matrix formation.
8. Locally administered bisphosphonates are used for achieving post operative bone fills in intrabony defects, reduce bone loss and bone resorption [22-24].

5. Statins

- Statins are lipid-lowering drugs that provide an important and effective approach for the treatment of hyperlipidemia and arteriosclerosis.
- They act as competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which plays a major role in mevalonate pathway, thus stops the production of cholesterol.

Effects and mechanism of action of statins

1. Effect on bone metabolism

There is a continuous bone remodelling going on to maintain the architecture of alveolar bone.

- Statins inhibit bone resorption by inhibiting HMG reductase and subsequent blocking the mevalonate pathway [25].
- Statins stimulate the production of BMP's and increase bone formation [26].
- Enhances collagen synthesis by 60%-70%.
- Statins have been suggested to prevent periodontal tissue breakdown and to have beneficial effects on alveolar bone recovery after ligature-induced alveolar bone resorption [27].
- Statins interfere with generation of isoprenoids that are primarily responsible for the prenylation of GTP-binding proteins, which are responsible for vesicular trafficking, inactivating osteoclasts [28].
- Statins like simvastatin, atorvastatin are involved in the process of endochondral bone formation and stimulates osteoblastic differentiation leading to new bone formation.
- Statins increased bone mineral density in diabetes mellitus patients who were administered statins systemically for the correction of increased cholesterol levels [29].

2. Antioxidant and anti-inflammatory

- Inhibit the ability of macrophages to oxidize low-density lipoproteins [30].
- Decreases production of IL-6 [31].
- Decreases of plasma markers like C reactive protein (CRP).

3. Effect of statins on periodontium

- Statins are responsible for fibrogenesis and fibroclasis, and cementogenesis and cementoclasis [32].
- Statins enhance cell proliferation in human PDL cells and increases alkaline phosphatase activity [33].
- Greater decrease in probing depths, gain in attachment levels and more bone fill was achieved by use of locally delivered simvastatin as adjunctive therapy in treatment of chronic periodontitis [34].

Optimum safety profile and low cost has made statins a good choice in delivering optimum results in treatment of periodontitis [35].

6. Melatonin

The pineal gland, bone marrow, retina, and immune system naturally create melatonin, which is primarily responsible for controlling the circadian rhythm.

Melatonin also has immunomodulatory, anti-inflammatory, and antioxidant properties.

Mechanism of Action

Antioxidant

- Active scavenger of exogenous and endogenous ROS.
- Additionally, superoxide dismutase, glutathione reductase, glutathione peroxidase, and vitamin C are stimulated by melatonin, are essential antioxidant enzymes [36].

1. Stimulate osteoblast proliferation, differentiation, also inactivates osteoclasts [37].
2. Melatonin suppresses proinflammatory mediator's expression, including interleukin-6, prostaglandins, C-reactive protein, and tumour necrosis factor-alpha.
3. Reduces the ratios of receptor activator of nuclear factor kappa beta ligand (RANKL) to osteoprotegerin (OPG), which reduces periodontal inflammation [38].

Additionally, topical Melatonin application in diabetic patients was linked to a rise in salivary OPG concentrations and a decrease in salivary RANKL concentrations, suggesting that melatonin may be able to improve bone quality, slow the advancement of periodontal disease, and lessen bone loss [39, 40].

7. Metformin (MF)

Metformins (MF) are bisguanide compounds that are most often prescribed oral hypoglycemic medications for treating type 2 diabetes mellitus.

Mechanism of Action

Metformin promotes the production of Runx2/Cbfa1, a transcription factor unique to osteoblasts, hence inducing bone lesion regeneration [41].

1% metformin gel are effectively used in treatment of chronic periodontitis to treat intrabony defects [42].

Newer locally delivered host modulating agents for periodontal regeneration

1. Sclerostin

- It is a bone matrix glycoprotein that plays an important role in bone homeostasis.
- Secreted by osteocytes, hypertrophic chondrocytes, osteoclasts, and periodontal ligament cells.

Mechanism of Action

1. Inhibition of sclerostin increases canonical wnt signalling, leading to osteogenesis [43-44].
2. Evenity (romosozumab-aqqg), a humanized anti-sclerostin antibody (Scl-Ab), reduced osteoporotic fractures in post-menopausal women [45].
3. Converts the quiescent lining on osteocytes into active osteoblasts and enhances bone formation.
4. Sclerostin antibody treatment causes greater alveolar crest height and bone mass in an ovariectomized rat model of localized periodontitis [46].
5. Scl-Ab increases osteointegration and bone regeneration around dental implants [47].

6. Scl-Ab prevented alveolar bone loss in a rat model of chronic edentulism [48].
7. Following experimental periodontitis, Scl-Ab treatment also enhanced alveolar bone height, bone volume, and bone mineral density [49-51].

2. Resveratrol

- Natural sources of the polyphenol resveratrol (RES) include red wine, peanuts, cranberries, blueberries, grapes, and peanuts.
- It has anti-inflammatory, anticarcinogenic, cardioprotective, and antibacterial properties [52-53].

Mechanism of Action

1. Antimicrobial

- Disrupts cell membrane disruption causing leakage.
- Blocks cell division.
- Increased ROS causes DNA damage and cell death of microbials

2. Immunomodulatory effects

- Downregulates, nuclear factor kappa β, MAPK and TLR4 pathway. This further reduces production of pro inflammatory cytokines and reduces alveolar bone loss.
- Upregulates Nrf2, SIRT1 pathway, that increases host's antioxidant defence.

3. Resveratrol enhances bone healing and regeneration [54].

3. Galanin (GAL)

(GAL) is one of the peptides involved in maintaining neuroskeletal homeostasis. (Tatemoto *et al.* 1983; Schmidt *et al.* 1991)

Mechanism of Action

1. GAL facilitates bone formation associated with injury by inhibiting excess TNF-α and IL-1β production
2. Additionally, GAL is required for the transcription factor ΔFosB's leptin-independent effects on bone homeostasis via hypothalamic neurons [55].

GAL coated scaffold has shown periodontal regeneration in periodontitis mice model [56].

4. Mineral Trioxide Aggregate-MTA

- MTA is a bioactive substance with various dental application.
- MTA enhances osteogenesis of PDLSCs by NF-κB and MAPK signaling pathways [57].

5. Teriparatide

- It is a biosynthetic parathyroid hormone (PTH) consisting of first 32 amino acids of PTH, which plays an important role in bone metabolism.
- PTH is an anabolic agent.

Mechanism of Action

1. Binding of Teriparatide to osteoclasts via specific, G-protein-dependent, high-affinity membrane cell-surface receptors activates protein kinase-1, cyclic adenosine monophosphate, protein kinase C and phospholipase C,which increases osteoblast numbers and decreases osteoblast apopotosis. This increases bone mass, structural integrity and bone strength [58].
2. Upregulates Basic fibroblast growth factor 2 (bFGF-2) with enhances proliferation and differentiation of osteoblast progenitors and plays an important role in bone formation [59].

   Teriparatide is associated with improved clinical outcomes, greater resolution of alveolar bone defects, and accelerated osseous wound healing in the oral cavity.

6. Erythropoietin (EPO)

Growth factor that enhances angiogenesis and bone regeneration.

Mechanism of Action

1. By binding to the EPO receptor, EPO contributes to the proliferation and osteogenic differentiation of hematopoietic stem cells and mouse bone marrow mesenchymal stem cells (BMMSCs).
2. EPO can directly promote osteoblast differentiation and indirectly suppress osteoclast's ability to resorb material via the ephrinB2-EphB4 signalling pathway [60].

Chitosan (CS)/β-sodium glycerophosphate/gelatin hydrogels loaded with aspirin/erythropoietin (EPO) possessed anti-inflammation and periodontium regeneration properties and was successfully used on treatment of chronic periodontitis. [61].

With so many advances in the periodontal regenerating agents, there still exists a major challenge regarding the success and outcome of these regenerating therapies. This is because of:

1. Differences in the anatomy of defects and the interaction area of the acting drug.
2. Variation in potency of drug.
3. Lack of knowledge about exact mechanism of regeneration.
4. Short follow up periods.
5. Cost considerations and availability.

Some of the limitations of various regenerating agents are:

Limitations of EMD's

- EMD'S lacks exact mechanism of action for periodontal regeneration.
- When used with grafts, EMD-bone causes precipitate formation of different sizes and morphologies which envelop the grafts differently [62].
- Application of EMD alone could be used in well contained defects only [63].
- EMD is more effective in narrow intrabony defects as compared to wide defects [64].
- EMD did not yield satisfactory results when used with β-TCP/HA in augmentation of the maxillary sinus floor [65]
- Even though, EMD was used in vertical root fractures implantations, regeneration of the damaged cementum was not achieved completely. (T.Sugaya *et al.*) and it was effective only for small fractures only [66].

Limitations of Bmp

- Relative short half-life.
- Inductive activity of rhBMP-2 is 10 times less than that of purified BMPs.
- BMP is associated with varying degrees of ankylosis when used for periodontal regeneration [67]
- Difficult to reproduce effective and convincing results in humans, as were obtained in invitro and animal studies

and experiments [68].

- Unsatisfactory mechanical stability.
- Inflammatory tissue reactions.

Limitations of PDGF

Although 0.3 mg/ml rhPDGF-BB is effective in periodontal osseous defect repair, the efficacy to repair and regenerate gingiva is still a challenge [69].

Limitations of teriparatide therapy

1. Occurrence of osteosarcomas.
2. Should not be used in patients with severe, untreated, unresolved hyperparathyroidism.

Conclusion

- Even though newer regenerating agents and therapies have evolved and contributed to better applications and clinical results, the role of correct patient selection, acknowledgment of unique individual susceptible profile, type of selected therapy and adjuncts with appropriate bone augmentation, following the basic surgical principles still remains the critical elements determining the success of any periodontal procedure.
- Despite the current state of knowledge and application future focus on the usage of the newer regenerating agents in clinical implications and longer follow ups could add in the exploration success.

Conflict of Interest

Not available

Financial Support

Not available

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