DHR International Journal Of Medical Sciences (DHR-IJMS)
ISSN: 2278-831X, Vol. 5(1), Special Issue 2014
Available online http://www.doublehelixresearch.com/DHRIJMS

Original article

Periodontal tissue engineering: A new paradigm for periodontal regeneration

Awadhesh K. Singh

Reader, Department of Periodontology & Implantology, Chandra Dental College & Hospital, Safedabad, Barabanki, Uttar Pradesh, India
*Corresponding Author: Awadhesh K. Singh

Abstract

Regenerative treatment of periodontal defects with an agent, or procedure, requires that each functional stage of reconstruction be grounded in a biologically directed process. With this paradigm, we contended the way of periodontal regeneration through the application of current knowledge in the fields of molecular and cell biology, developmental biology and tissue engineering principles as applicable to tissue engineering. Through a combination of transplanted biomaterials containing appropriately selected and primed cells, together with an appropriate mix of regulatory factors to allow growth and specialization of the cells and matrix, we envision a new vista for periodontal regeneration becoming possible.

Keywords: Stem cells, scaffolds, signaling molecules.

Introduction

The term" Tissue Engineering" was coined at a National Science Foundation (NSF) bioengineering meeting in Washington D.C., in 1987. Tissue engineering is defined as "the reconstruction of living tissues to be used for the replacement of damaged or lost tissue/organs of living organisms and is founded on the principles of cell biology, developmental biology and biomaterials science" [1]. Distinction between tissue engineering and guided tissue regeneration (GTR) is that tissue engineering is the implantation of *in vitro*-seeded cells and matrices whereas GTR involves the use of acellular matrices that are spontaneously repopulated by host cells after implantation. The management of periodontal defects, including destruction of the periodontal ligament, cementum and alveolar bone with the formation of intrabony defects, has always been a challenge in clinical periodontics. Today, attention appears to focus on techniques that being developed to guide and instruct specialized cellular components of the periodontium to participate in the regenerative

process. This approach to reconstruction makes use of understanding of the development of the periodontium and the cellular processes that involved.

Current understanding of periodontal regeneration:

For periodontal regeneration, at least four criteria must be met which include all the features of the normal dentogingival complex that would equate the restoration of these tissues to their original form, function and consistency. First- a functional epithelial seal must be re-established at the most coronal portion of the tissues and be no more than 2 mm in length. Second- new connective tissue fibers i.e. sharpey's fibers must be inserted into the previously exposed root surface to reproduce both the periodontal ligament (PDL) and the dentogingival fiber complex. Third- new acellular, extrinsic fiber cementum must be reformed on the previously exposed root surface. Fourth- alveolar bone height must be restored to within the cementoenamel junction. Events and processes associated with periodontal regeneration are:

Cell selection, differentiation and maturation:

The cells require for periodontal regeneration are epithelial cells to seal the wound area, fibroblastic cells for soft connective tissue of gingiva and periodontal ligament, mineralized tissue forming cells i.e. osteoblasts for bone formation, cementoblasts for cementum formation, and endothelial cells for blood vessels formation [2].

Soluble mediators and regulators of cell function:

Molecules necessary for periodontal regeneration can be grouped into three categories- polypeptide growth factors, adhesion molecules and structural proteins.

Growth factors include FGF-1 & FGF-2 (acidic & basic FGF), IGF-1 & IGF-2, EGF, PDGF, BMP and chlorella growth factor. Adhesion molecules include FN, OP, BSP, laminin, collagen and cementum attachment protein. Structural proteins include type I, III, V, XII, XIV collagens, proteoglycans, hyaluronan, osteocalcin, noncollagenous proteins, tenascin, osteonectin, dentin/enamel matix proteins [3] .

Role of evolving and developing extracellular matrix (ECM):

ECM does not directly promote regeneration but plays prominent role in regulating the events for regeneration. Temporal and spatial sequence of ECM deposition during tissue regeneration is coordinated through a similar sequence of synthesis and sequestration of soluble mediators, both of which result in homeostatic feedback mechanism [4].

Periodontal tissue engineering:

A tissue-engineering approach for periodontal regeneration will need to utilize the regenerative capacity of cells residing within the periodontium and would involve the isolation of these cells and their proliferation within a 3D framework with implantation into the defect. The use of prefabricated 3D scaffold with appropriate cells and instructive messages incorporated into it, may overcome many limitations associated with current regenerative technologies. With the success reported for other system, a tissue engineering approach to regenerate periodontal defects seems reasonable [5].

Requirements for successful periodontal tissue engineering:

The two main areas for successful periodontal tissue engineering are biomechanical/ design features of synthetic matrix/scaffold for cell culture as space maintenance & barrier/ exclusionary features, and second is the biological functions of engineered matrix produced by cells in scaffold as biocompatibility, incorporation of cells & incorporation of instructive messages.

Space maintenance within defect site, & barrier/ exclusionary feature:

Bone will grow into adjacent tissue space if space can be maintained & soft tissue ingrowth prevented [6] which led to the principle of GTR, provides a fundamental concept of tissue engineering. The engineered material should be appropriate form & sufficient strength to allow placement into defect & subsequent collapse of the overlying tissues into the defect site in a manner consistent with principle of GTR & have similar design features [7]. The necessary design features to maintain space are ease of handling to desired shape, sufficient rigidity to withstand soft tissue collapse into the defect [8] & internal structure compatible with attachment & colonization by cells of desired phenotype, as well as ingrowth of tissue compatible with those to be regenerated [9].

Biocompatibility: The tissue engineering scaffold material should be either biocompatible with the tissues to be regenerated or biodegradable, allowing for gradual replacement with regenerated tissues [10].

Incorporation of cells with appropriate phenotype for ongoing periodontal regeneration: It is possible to culture & subsequent incorporation of 'Periodontal regenerative phenotype cells & adult mesenchymal stem cells of PDL' into a suitable biodegradable scaffold for immediate introduction into periodontal defect [11].

Incorporation and bioavailability of instructive messages: The synthetic scaffold used for tissue engineering should have affinity for adsorption of appropriate growth/ differentiation factors as

well as integrins, cell receptors & other instructive molecules normally found in regenerating tissues [12].

CELL-DELIVERY DEVICES/ CELL SEEDING SCAFFOLDS IN PERIODONTICS:

They are fabricated from either non-resorbable or resorbable materials-

Non-resorbable materials: Expanded polytetrafluoroethylene have been used as GTR membrane, could also be used to nurture specific cells that are expanded ex vivo & then delivered to defect site. Several porous ceramic scaffolds have been developed & investigated with regard to bone tissue engineering [13].

Hydroxyapatite (HA) scaffolds cultured with bone cells have good osteogenic potential [14]. Biodegradable porous ceramic materials as beta-tricalcium phosphate (β-TCP) undergo rapid degradation with little bone formation. The hybrid materials as β-TCP & HA or β-TCP & polymers appear to be reliable vehicles cell delivery showing good tissue formation with implanted cells [15].

Titanium mesh can be beneficial for management of large osseous defects through various surface treatment as fibronectin (FN), collagen or β-TCP with bone marrow cells (16).

Resorbable materials: Alpha-hydroxyacids polymers as polylactic acid, polyglycolic acid & their co-polymer polylactic-co-glycolic acid have been extensively used for cell seeding in tissue engineering (17). Alginate beads incorporating cells have been developed as drug-delivery devices than cell-delivery devices for tissue engineering (18). Amino-acid based polymers as collagen, elastin etc. have been used as scaffold for cell seeding (19).

Scaffolds derived from natural products: Chitosan is a carbohydrate biopolymer, extracted from chitin, structurally similar to glycosaminoglycan have been used as tissue engineering scaffold (20). Synthetic hydrogels as polyethylene glycol & polyethylene oxide are used as a 3D scaffold for cell delivery (21). Extracellular matrix scaffolds as Dermagraft, Matrigel, Alpigraf, Epidex, PV702 & Allograft have been developed to allow incorporation of ex vivo-expanded cells.

CELLS FOR TISSUE ENGINEERING IN PERIODONTICS:

Periodontal-regenerative phenotype cells and mesenchymal stem cells of PDL are used for periodontal tissue engineering by two modes: incorporation into scaffolds which ensure their localization at defect site- the concept being referred as cell seeding, & injection of cell suspension into a sealed compartment containing defect.

SIGNALLING MOLECULES/ BIOLOGICAL MODIFIERS/ MORPHOGENS IN PERIODONTICS:

They can be divided into 3 groups-

Growth/ differentiation factors: The growth factors play important role in periodontal tissue engineering are PDGF, IGF-1 & IGF-2, TGF, FGF-1 & FGF-2 (acidic & basic FGF), EGF, BMPs, chlorella growth factor, Wingless & int-related proteins (Wnts) and Hedgehog proteins (Hhs). BMP4 from epithelium induces mesenchyme to be odontogenic. BMP2, BMP4 & BMP7 are expressed in enamel knot responsible for morphogenesis of epithelium. BMP2, BMP4, BMP6 & BMP7 for odontoblast differentiation & BMP4, BMP5 for ameloblast differentiation. rh-BMP7 also known as osteogenic protein-1 for osteogenesis.

Extracellular matrix proteins and attachment factors: Enamel matrix derivative (EMD) as EMDOGAIN coated surfaces improved attachment of PDL fibroblasts but had no effect on gingival fibroblasts & epithelial cells indicating a selective advantageous in periodontal regeneration [22]. FN functions as attachment of cells to ECM, which lead to increase in PDL and bone formation.

Mediators of bone metabolism: Prostaglandins increase periosteal & endosteal formation suggesting the possibility of augmentation of bone formation with this agent (23). Glucocorticoids as dexamethasone chronic administration augment activity of some growth factors & synergistically increase differentiation of osteoblastic cells, and hence bone formation. Bisphosphonate, structurally similar to pyrophosphate has calcium chelating property, binds to HA crystals of bone and prevent both their growth & dissolution. Bisphosphonates are classified into 3 generations: First generation bisphosphonates are characterized by alkyl side chains, e.g. Etidionate. Second generation bisphosphonates are characterized by amino terminal groups, e.g. Alendionate & pamidionate. Third generation bisphosphonate are characterized by having cyclic side chains, e.g. Risidionate. The anti-resorptive property of bisphosphonates increases approximately 10 folds between generations.

Both systemic and topical application of bisphosphonate inhibits bone resorption. Alendionate can inhibit bone resorption induced as a result of flap elevation & attendant regional accelerated phenomenon (RAP) [24]. Etidionate can be used to accelerate bone formation (osteoacceleration) if used in a pulsatile fashion [25]. The rationale behind this is that etidionate was capable of inhibiting mineralization reversibly, consequently stimulating osteoid matrix formation, and upon removal, mineralization would ensure with a net result in total bone volume, which would be more densely mineralized.

Periodontal tissue engineering in future: To understand the rational basis of regenerative procedures, more information is needed on the variety of molecular and cellular processes associated with the formation of each periodontal component. Continuing efforts should be made to explore means of attaining true regeneration of all periodontal connective tissues i.e. cementum, ligament & bone to a

level consistent with health and thus restore original form and function to the dentition with a resultant improved tooth retention rate.

Conclusion

At present, there is no good evidence to suggest that current regenerative technologies will enhance tooth retention or lead to improved oral health. However, this does not preclude ongoing search for regenerative technologies.

References

1. R. Narem, A. Sambanis, Tissue Eng., 1995, 1, 3-13.
2. CAG. McCulloch, Anat. Rec., 1987, 219, 233-252.
3. AS. Narayanan, PM. Bartold, Connect. Tissue Res., 1996, 34, 191-201.
4. RAF. Clark, In: 2nd edn, The molecular and cellular biology of wound repair (Plenum Press, New Yark; 1996).
5. PM. Bartold, CAG. McCulloch, Periodontol. 2000, 2000, 24, 253-269.
6. LA. Hurley, FE. Stinchfield, AL. Bassett, WH Lyon, J. Bone Joint Surg., 1959, 41A, 1243-1254.
7. TV, Scantlebury, J. Periodontol., 1993, 64, 1129-1137.
8. JH. Brekke, JM. Toth, J. Biomed. Mater Res., 1998, 43, 380-398.
9. K. Whang, KE. Healy, DR. Elenz, EK. Nam, DC. Tsai, CH. Thomus et al., Tissue Eng., 1999, 5, 35-51.
10. BS. Kim, DJ. Mooney, Trends. Biotechnol., 1998, 16, 24-230.
11. S. Ivanovski, HR. Haase, PM. Bartold, J. Dent. Res., 2001, 80, 1665-1671.
12. Y. Tabata, Tissue Eng., 2003, 9(Suppl.), S1-S15.
13. T. Uemura, J. Dong, Y, Yang, H. Kojima, T. Sato, D. Iejima et al., Biomaterials., 2003, 24, 2277-2286.
14. J. Dong, T. Uemura, Y. Shriraski, T. Tateishi, Biomaterials., 2002, 23, 4493-4502.
15. S. Gronthos, S. Chen, CY. Wang, PG. Robey, S. Shi, J. Bone. Miner. Res.,2003, 18, 716-722.
16. J. van den Dolder, Jw. Vehof, PH. Spauwen, JA. Jansen, J. Biomend. Mater. Res., 2002, 62, 350-358.
17. RC. Thoson, MC. Wake, MJ. Yaszemski, AG. Mikos, Adv. Polym. Sci., 1995, 122, 245-275.
18. PA. Tresco, R. Biran, MD. Noble, Adv. Drug Deliv. Rev., 2000, 42, 3027.

19. JA. Hubbell, Biotechnology, 1995, 13, 565-576.
20. A. Fakhary, GB. Schneider, R. Zaharias, S. Senel, Biomaterials, 2004, 25, 2075-2079.
21. SJ. Briyant, RJ. Bender, KL. Durand, KS. Anseth, Biotechnol. Bioeng., 2004, 86, 747-755.
22. SE. Lynch, J. Periodontol., 1992, 63, 1085-1092.
23. SC. Marks Jr, S. Miller, J. Oral. Pathol., 1988, 17, 500-505.
24. Yang Mong Lee et al., J. Periodontol., 2000, 71, 410-417.
25. AR. Ten Cate, Periodontol. 2000, 1997, 13, 9-19.