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Review Article

Current Concept for Periodontal Regeneration with New Materials

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The purpose of this review was to consider the history and future of periodontal surgical treatment and regenerative treatment. In the past two decades, periodontal surgery has changed radically, with resective periodontal surgery turning to regenerative therapies. The concept of treatment has also changed toward regeneration with a return to natural periodontal apparatus. New materials and techniques are being developed every day. Ideal regeneration requires a complex of stem cells, growth factor and scaffold. Recently, the study of stem cells has seen great breakthroughs, and any cell can be a stem cell. A huge number of growth factors have been discovered and studied for their functions and treatment abilities. Scaffolds for cells and growth factors are also developing for individual organs, containing periodontal tissue. This review may help to clarify periodontal treatment from the past to future.

Key words: GTR, enamel matrix derivative, growth factor, scaffold, regeneration

Introduction

The goal of periodontal therapy is to maintain natural dentition and functional periodontal apparatus for a lifetime by creating an easy oral environment for patients' oral hygiene. The resective surgical approach and mucogingival surgery (MGS) were major periodontal therapies in periodontics until the1970s[1)]; however, problems with esthetics, root sensitivity and root caries resulting from resective therapy for severe periodontitis were eventually pointed out. Also, resective therapy was admitted to be "Repair" not "Regeneration" after evaluations of animal and human studies. Since then, a variety of periodontal tissue regenerative techniques and devices have been developed. Guided tissue regeneration (GTR) utilizing a barrier membrane was advocated by Nyman et al. as a new treatment approach for periodontal tissue regeneration in the1980s[1)].

In the1990s, Emdogain® (EMD) was developed as a biological regeneration approach and has been utilized for regenerative therapy. EMD seems to mimic the development of attachment apparatus during nascent tooth development. Alveolar bone formation is induced de novo by EMD and/or triggered by early cementum formation. The regenerative potential of EMD in intrabony defects is at least equal to or better than other "regenerative" therapies based on clinical parameters[1)].

Platelet-rich plasma (PRP) has a high concentration of platelet-derived growth factor. In particular, PRP including various cytokines is in clinical use for periodontal regenerative therapy[2)].

Recently, it has been attempted to use growth factors, such as BMP or PDGF, in periodontal tissue regenerative therapy. This review concludes by surveying periodontal regenerative therapy from the past to the future in Japan.

GTR

Guided bone regeneration or GBR, and guided tissue regeneration or GTR are surgical procedures that utilize barrier membranes to direct the growth of new bone and soft tissue at sites having insufficient volumes or dimensions for proper function, esthetics or prosthetic restoration.

GBR is similar to guided tissue regeneration (GTR) but is focused on the development of hard tissues instead of soft tissues for periodontal attachment. At present, guided bone regeneration is predominantly applied in the oral cavity to support new hard tissue growth on an alveolar ridge to allow stable placement of dental implants. Used in conjunction with sound surgical technique, GBR is a reliable and validated procedure.

The theoretical principles basic to guided tissue regeneration were developed by Melcher in 1976[3)], who outlined the necessity of excluding unwanted cell lines from healing sites to allow the growth of desired tissues.

Based on the positive clinical results of regeneration in periodontology, researched in the1980s[4)], research began to focus on the potential for re-building alveolar bone defects using guided bone regeneration[5)].

Technically, primary closure of the wound promotes undisturbed and uninterrupted healing. Angiogenesis provides the necessary blood supply and undifferentiated mesenchymal cells. Space creation and maintenance facilitate space for bone in-growth. Stability of the wound induces

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blood clot formation and allows uneventful healing. Soft tissue control prevents membrane exposure and infection, which is the key to successful results. The resorbable membrane improves problems with the non-resorbable membrane, such as frequent exposure of the membrane, and second surgery to remove the membrane[6].

Enamel matrix derivative[7]

Enamel matrix derivative (EMD) or enamel matrix proteins are proteins that have been found to play a key role in the development of tooth-supporting tissues. For clinical use in regenerative periodontal procedures, they are derived from developing porcine teeth. EMD was introduced in 1996 and marketed as Emdogain by a Swedish company, Biora, until Straumann acquired Biora in 2003 and began producing it under the Straumann name.

EMD, and certainly the amelogenin component, has been suggested to induce the formation of acellular cementum and contribute to the regeneration of periodontal tissues by stimulating the proliferation of mesenchymal cells, inhibiting the proliferation of epithelial cells and promoting the secretion of certain growth factors, such as TGF-β1, by periodontal ligament cells.

Application of enamel matrix proteins results in more efficient healing of the periodontal hard tissues with reference to vertical and horizontal defect resolution in conjunction with open flap debridement than open flap debridement alone.

Use of this material has to consider the patients. In particular, informed consent is required because this material originates from pigs; therefore, for religious reasons, some patients reject this treatment.

Platelet-rich plasma[8]

PRP, the first practical application of tissue engineering, has a respectable database of research findings and clinical outcomes in a variety of settings. A concentrated source of autologous platelets, PRP contains and releases (through degranulation) at least seven different growth factors (cytokines) that stimulate bone and soft tissue healing. The separation and concentration of the platelets is an exact science. Extreme care must be taken when blood products are harvested and processed. In addition to the well-known concerns of HIV transfer, other concerns exist. Because of factors involving its availability and cost, PRP has become an increasingly popular clinical tool as an alternative source of growth factors for several types of medical treatments, including wound healing in surgery, tendonitis, cardiac care, cartilage regeneration, disc regeneration, and dental health. The clinical applications of PRP in dentistry, for example, include cosmetic periodontal surgery, aesthetic dental implant reconstruction, and the immediate restoration of dental implants. Most recently, PRP has found popular and effective applications in sports medicine (including treatment of injured tendons and ligaments in joints without surgery). The use of PRP for tendonitis and sports medicine applications has been reported.

Not all PRP is the same. The strict definition of PRP is a platelet concentration above the baseline. PRP may or may not also contain increased concentrations of white blood cells. The data supporting the use of PRP for tendonitis are 5.5x baseline with a similar increase in white blood cells. As more data emerge from clinical trials, the dosage of PRP must be better defined.

Essential for understanding the biologic rational of PRP is understanding the role of platelets in wound healing as well as the clinical effect of PRP in bone regeneration and soft tissue healing. PRP stimulates earlier and more complete revascularization derived from the connective tissue base, which develops a nutrient gradient into which epithelial cells can migrate. For skin repair after wounds or surgery, such early epithelial coverings of exposed granulation tissue and connective tissue, and development of the dermis are thought to be the mechanism that reduces scarring and provides maximum regeneration of normal skin pigmentation. For bone repair, PRP can be added to harvested autogenous bone or to a mixture of autogenous bone and freeze-dried bone/alloplastic material to improve the consistency for handling during surgery and minimizing particulate migration as well as to add more platelets (i.e. increased growth factors) to the area. In the surgery-free repair of joints, tendons, and ligaments, blood taken from the patient is processed into PRP and then injected into the injured area to accelerate healing.

Growth factors

Bone morphogenetic protein (BMP)[9]

BMPs are now produced using recombinant DNA technology. These formulations have found applications in many disciplines of medicine and dentistry. Orthopedic surgery and oral surgery have benefited greatly from commercially available BMP formulations in the last few years. BMPs are also available in an oral form under the commercial name Ostinol, which is being marketed as a supplement for bone and joint health by alternative health care practitioners.

BMPs interact with specific receptors on the cell surface, referred to as bone morphogenetic protein receptors (BMPRs). The biological basis of bone morphogenesis was shown by Marshall R. Urist, who made the key discovery that demineralized, lyophilized segments of bone induced new bone formation when implanted into muscle pouches in rabbits.

Members of the BMP family are potentially useful as therapeutics in areas such as spinal fusion. BMP-2 and BMP-7 have been shown in clinical studies to be beneficial in the treatment of a variety of bone-related conditions, including delayed union and non-union. BMP-2 and BMP-7 have received Food and Drug Administration (FDA) approval for human clinical uses. At between $4000 and $10,000 for a typical treatment, BMPs can be costly compared with other techniques, such as bone grafting; however, this cost is often far lower than required for orthopedic revision in multiple surgeries.

BMP-7 has also recently been used in the treatment of chronic kidney disease (CKD) and has been shown in murine animal models to reverse the loss of glomeruli due to sclerosis. Curis has been in the forefront of developing BMP-7 for this use. In 2002, Curis licensed BMP-7 to Ortho Biotech Products, a subsidiary of Johnson & Johnson.

Platelet-derived growth factor (PDGF)[10]

In molecular biology, platelet-derived growth factor is one of the numerous growth factors, or proteins, that regulate cell growth and division. In particular, it plays a significant role in blood vessel formation (angiogenesis), the growth of blood vessels from already existing blood vessel tissue. Uncontrolled angiogenesis is a characteristic of cancer. Chemically, platelet-derived growth factor is a dimeric glycoprotein composed of two A (-AA) or two B (-BB) chains or a combination of the two (-AB).

The receptor for PDGF, PDGFR is classified as a receptor tyrosine kinase (RTK), a type of cell surface receptor. Two types of PDGFRs have been identified: alpha-type and beta-type PDGFRs. The alpha type binds to PDGF-AA, PDGF-BB and PDGF-AB while beta-type PDGFR binds with high affinity to PDGF-BB and PDGF-AB. PDGF binds to the PDGFR ligand binding pocket located within the second and third immunoglobulin domains. Upon activation by PDGF, these receptors dimerize, and are "switched on" by auto-phosphorylation of several sites on their cytosolic domains, which serve to mediate the binding of cofactors and subsequently activate signal transduction, for example, through the PI3K pathway. The downstream effects of this include the regulation of gene expression and the cell cycle. The role of PI3K has been investigated by several laboratories. Accumulating data suggest that while this molecule is generally part of the growth signaling complex, it plays a more profound role in controlling cell migration. The different ligand isoforms have variable affinities for the receptor isoforms, which may variably form hetero- or homo-dimers. This leads to the specificity of downstream signaling. It has been shown that the *cis* oncogene is derived from the PDGF B-chain gene. PDGF-BB is the highest-affinity ligand for PDGFR-beta, a key marker of hepatic stellate cell activation in the process of fibrogenesis.

PDGF plays a role in embryonic development, cell proliferation, cell migration, and angiogenesis. It has also been linked to several diseases, such as atherosclerosis, fibrosis and malignant diseases. In addition, PDGF is a required element in the cellular division of fibroblasts, a type of connective tissue cell. In essence, PDGFs allow a cell to skip G 1 checkpoints in order to divide.

PDGF is also known to maintain the proliferation of oligodendrocyte progenitor cells. It was one of the first growth factors characterized, and has led to an understanding of the mechanism of many growth factor signaling pathways. Like many other growth factors that have been linked to disease, PDGF is a marker of protein receptor antagonists to treat disease. Such antagonists usually include specific antibodies that target the molecule of interest, which only act in a neutralizing manner; however, recent developments have allowed biotechnology companies to circumvent this problem by creating specialized molecules that not only bind the protein of interest, but also destroy it in an enzymatic fashion. The "c-Sis" oncogene is derived from PDGF.

Basic fibroblast growth factor[11]

In normal tissue, basic fibroblast growth factor is present in basement membranes and in the subendothelial extracellular matrix of blood vessels, and stays membrane-bound as long as there is no signal peptide. It has been hypothesized that, during both wound healing of normal tissues and tumor development, the action of heparan sulfate-degrading enzymes activates bFGF, thus mediating the formation of new blood vessels, a process known as angiogenesis.

Recent evidence has shown that low levels of FGF2 play a key role in the incidence of excessive anxiety. Additionally, bFGF is a critical component of human embryonic stem cell culture medium; the growth factor is necessary for the cells to remain in an undifferentiated state, although the mechanisms by which it does this are poorly defined. It has been demonstrated to induce gremlin expression, which in turn is known to inhibit the induction of differentiation by bone morphogenetic proteins. It is necessary in mouse-feeder cell dependent culture systems, as well as in feeder and serum-free culture systems. Moreover, a recently published paper has been revealed the basic FGF effect for periodontal regeneration[12].

Biological mechanisms governing bone grafting[13]

Bone grafting is possible because bone tissue, unlike most other tissues, has the ability to regenerate completely if provided the space into which to grow. As native bone grows, it will generally replace the graft material completely, resulting in a fully integrated region of new bone. The biologic mechanisms that provide a rationale for bone grafting are osteoconduction, osteoinduction and osteogenesis. The chart on the right reveals which of these properties apply to the different types of bone graft material.

Osteoconduction

Osteoconduction occurs when bone graft material serves as a scaffold for new bone growth that is perpetuated by native bone. Osteoblasts from the margin of the defect that is being grafted utilize the bone graft material as a framework upon which to spread and generate new bone. At the very least, bone graft material should be osteoconductive.

Osteoinduction

Osteoinduction involves the stimulation of osteoprogenitor cells to differentiate into osteoblasts that then begin to form new bone. The most widely studied type of osteoinductive cell mediators are BMPs. Bone graft material that is osteoconductive and osteoinduction will not only serve as a scaffold for currently existing osteoblasts but will also trigger the formation of new osteoblasts, theoretically promoting faster integration of the graft.

Osteogenesis

Osteogenesis occurs when vital osteoblasts originating from bone graft material contribute to new bone growth along with bone growth generated via the other two mechanisms.

Types and tissue sources of bone grafting

Autograft

Autologous (or autogenous) bone grafting utilizes bone obtained from the individual receiving the graft. Bone can

be harvested from non-essential bones, such as from the iliac crest, or more commonly in oral surgery, from the mandibular symphysis (chin area) or anterior mandibular ramus (coronoid process); this is particularly true for *block grafts*, in which a small block of bone is placed whole in the area being grafted. When a block graft os performed, autogenous bone is preferred because there is less risk of graft rejection because the graft originates from the patient's own body. As indicated in the chart above, such a graft would be osteoinductive and osteogenic, as well as osteoconductive. A negative aspect of autologous grafts is that an additional surgical site is required, in effect adding another potential location for post-operative pain and complications.

Autologous bone is typically harvested from intra-oral sources, such as the chin, or extra-oral sources, such as the iliac crest, fibula, ribs, mandible and even parts of the skull.

All bone requires a blood supply at the transplanted site. Depending on the location of the transplant site and the size of the graft, an additional blood supply may be required. For these types of grafts, extraction of part of the periosteum and accompanying blood vessels along with donor bone is required. This kind of graft is known as a free flap graft.

Allografts

Allograft bone, like autogenous bone, is derived from humans; the difference is that an allograft is harvested from an individual other than the person receiving the graft. Allograft bone is taken from cadavers who have donated their bone so that it can be used for medical purposes; it is typically sourced from a bone bank.

Three types of bone allograft are available: Fresh or fresh-frozen bone; freeze-dried bone allograft (FDBA); demineralized freeze-dried bone allograft (DFDBA).

Synthetic variants

Artificial bone can be created from ceramics, such as calcium phosphates (e.g. hydroxyapatite and tricalcium phosphate), Bioglass and calcium sulfate, all of which are biologically active to different degrees depending on their solubility in the physiological environment (Bioceramics). These materials can be added to growth factors, ions such as strontium or mixed with bone marrow aspirate to increase biological activity. Some authors believe that this method is inferior to autogenous bone grafting; however, infection and graft rejection are much less of a risk; mechanical properties, such as Young's modulus, are comparable to bone. The presence of elements such as strontium can result in higher bone mineral density and enhanced osteoblast proliferation in vivo.

Xenografts

Xenograft bone substitute originates from species other than humans, such as cattle. Xenografts are usually only distributed as a calcified matrix.

Alloplastic grafts

Alloplastic grafts may be made from hydroxylapatite, a naturally occurring mineral that is also the main mineral component of bone. They may also be made from bioactive glass. Hydroxylapatite is a synthetic bone graft, which is the most commonly used synthetic due to its osteoconduction, hardness and compatibility by bone. Some synthetic bone grafts are made of calcium carbonate, the use of which is decreasing because it is completely resorbable in a short time, so the bones break easily again. Finally, tricalcium phosphate is used in combination with hydroxylapatite, providing both osteoconduction and resorbability.

Growth Factors

Growth factor-enhanced grafts are produced using recombinant DNA technology. They consist of either human growth factors or morphogens (bone morphogenic proteins in conjunction with a carrier medium, such as collagen).

The most common use of bone grafting is in the application of dental implants to restore the edentulous area of a missing tooth. Dental implants require bones for support and to enable the implant to integrate properly into the mouth. People who have been edentulous (without teeth) for a prolonged period may not have enough bone left in the necessary locations, in which case bone can be taken from the chin or from the pilot holes for the implants or even from the iliac crest of the pelvis and inserted into the mouth underneath the new implant.

In general, bone grafts are either used en block (such as from the chin or the ascending ramus area of the lower jaw) or particulated, for better adaptation to a defect.

Another common bone graft, which is more substantial than those used for dental implants, is of the fibular shaft. After the segment of the fibular shaft has been removed, normal activities, such as running and jumping, are permitted on the leg with the bone deficit. The grafted, vascularized fibulas have been used to restore skeletal integrity to the long bones of limbs in which congenital bone defects exist and to replace segments of bone after trauma or malignant tumor invasion. The periosteum and nutrient artery are generally removed with the piece of bone so that the graft will remain alive and grow when transplanted into the new host site. Once the transplanted bone is secured at its new location it generally restores blood supply to the bone to which it has been attached.

Besides the main use of bone grafting, dental implants, this procedure is used to fuse joints to prevent movement, repair broken bones that have bone loss, and repair broken bone that has not yet healed. Bone grafts are used in hopes that the defective bone will be healed or will regrow with little to no graft rejection.

Depending on where the bone graft is needed, a different doctor may be requested to do the surgery. Doctors that perform bone graft procedures are commonly orthopedic surgeons, otolaryngology head and neck surgeons, neurosurgeons, craniofacial surgeons, oral and maxillofacial surgeons, and periodontists.

As with any procedure, there are risks involved, including reactions to medicine and problems with breathing, bleeding, and infection[5]. Infection is reported to occur in less than 1% of cases and is curable with antibiotics. Overall, patients with a preexisting illness are at a higher risk of

developing an infection as opposed to those who are generally healthy.

Embryonic stem cells[14]

Embryonic stem cells (ES cells) are pluripotent stem cells derived from the inner cell mass of the blastocyst, an early-stage embryo[1]. Human embryos reach the blastocyst stage 4–5 days post-fertilization, at which time they consist of 50–150 cells.

ES cells are distinguished by two distinctive properties: their pluripotency and their capability to self-renew themselves indefinitely[2]. Pluripotency enables ES cells to differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm. These include each of the more than 220 cell types in the adult body. Pluripotency also distinguishes embryonic stem cells from adult stem cells found in adults; while embryonic stem cells can generate all cell types in the body, adult stem cells are multipotent and can only produce a limited number of cell types. Additionally, under defined conditions, embryonic stem cells are capable of propagating indefinitely. This allows embryonic stem cells to be employed as useful tools for both research and regenerative medicine, because they can produce limitless numbers for continued research or clinical use.

Because of their plasticity and potentially unlimited capacity for self-renewal, ES cell therapies have been proposed for regenerative medicine and tissue replacement after injury or disease. Diseases treated by these non-embryonic stem cells include a number of blood and immune system-related genetic diseases, cancers, and disorders; juvenile diabetes; Parkinson's; blindness; and spinal cord injuries. Besides the ethical concerns of stem cell therapy, there is a technical problem of graft-versus-host disease associated with allogeneic stem cell transplantation; however, problems associated with histocompatibility may be solved using autologous donor adult stem cells or via therapeutic cloning.

Induced pluripotent stem cells[15]

Induced pluripotent stem cells, commonly abbreviated as iPS cells, are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing the "forced" expression of certain genes.

iPS cells are believed to be identical to natural pluripotent stem cells, such as embryonic stem cells in many respects, such as the expression of certain stem cell genes and proteins, chromatin methylation patterns, doubling time, embryoid body formation, teratoma formation, viable chimera formation, and potency and differentiability, but the full extent of their relation to natural pluripotent stem cells is still being assessed.

IPSCs were first produced in 2006 from mouse cells and in 2007 from human cells. This has been cited as an important advancement in stem cell research, as it may allow researchers to obtain pluripotent stem cells, which are important in research and potentially have therapeutic uses, without the controversial use of embryos.

Depending on the methods used, reprogramming of adult cells to obtain iPSCs may pose significant risks that could limit their use in humans. For example, if viruses are used to genomically alter cells, the expression of cancer-causing genes or oncogenes may potentially be triggered. In February 2008, in ground-breaking findings published in the journal Cell, scientists announced the discovery of a technique that could remove oncogenes after the induction of pluripotency, thereby increasing the potential use of iPS cells in human diseases. Even more recently, in April 2009, the group of Sheng Ding in La Jolla, California showed that the generation of iPS cells was possible without any genetic alteration of the adult cell. Repeated treatment of the cells with certain proteins channeled into the cells via poly-arginine anchors was sufficient to induce pluripotency. The acronym for these iPS is piPS (protein-induced pluripotent stem cells).

Conclusion

The numerous studies of periodontal regeneration will determine the future therapeutic potential of these growth molecules, such that they may be used to optimally stimulate and direct specific points along tissue formation cascades. In addition, a specific scaffold will be developed for individual bone defects and gingival lesions. Moreover, the next step in periodontal regeneration is expected to employ site-specific stem cells by cell engineering. Regeneration trials will continue into the next generation.

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歯周組織再生療法の最新のコンセプトと最新材料

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本総説の目的は歯周外科療法の歴史と歯周組織再生療法の将来を考察することである．過去20年で歯周外科療法は革命的な変革を呈した．切除療法から再生療法へと移行した．歯周治療の考えも元の歯周組織への回帰を目的とする再生を目標とした変革である．新たな材料や技術は日々開発されている．再生には細胞と成長因子，足場が必要とされている．近年の幹細胞研究は目覚しく，大いなる発展と希望に満ち溢れている．また成長因子の分野でも多大な研究が報告されている．同様に細胞と成長因子のために必要とされるそれぞれの器官のための足場の研究も進められている．

本総説が過去，現在，未来の歯周治療の変遷を理解するために役立つことを期待したい．

キーワード：GTR（歯周組織再生術），エナメルマトリックス蛋白，成長因子，再生療法

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