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Review Article

Gene Therapy in Perimplantitis Management- A Novel Approach

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Abstract:

Osseointegrated implants are widely used for replacing missing teeth. Despite of reported high success cases, failures during the healing phase of dental implants are still remarkable. Even under strictly controlled cases, sometimes bone tissue does not attach to titanium implant body. The use of osteogenic growth factors such as platelet derived growth factor(PDGF) and bone morphogenic proteins(BMPs) offer significant potential for periodontal regeneration. But drug instability at the site of delivery, is the main shortcoming of the treatment modality. Therefore the utilizations of gene therapy to control the release and the bioavailability of the growth factors(GFs) offers potential for better osteogenesis of failing implants.

Keywords : Gene Therapy, Dental Implants.

Introduction:

Today, dental implant therapy has become the ultimate standard for replacing the missing tooth. Natural aesthetics and optimal functions are established with the utilization of dental implants and the patient satisfaction increases as well. Although the reported success rates of oral implant are high, failures do occur. Failure of dental implant is often related to failure to osseointegrate correctly[1].

Criteria for implant success (Albrektsson et al 1986)[2]:

- An individual unattached implant is immobile when tested clinically
- The radiographs does not demonstrate any evidence of periimplant radiolucency.
- Vertical bone loss is less than 0.9-1.5mm in

the first year and 2.0mm annually after first year of service of implant.

- Individual implant performance is characterized by the absence of persistent or irresistible signs and symptoms such as pain, infection, neuropathies, paraesthesia or violation of the mandibular canal.
- In the context of forgoing, success rates of 85% at the end of 5year observational period and 80% at the end of 10 year observational period is essential for implant success.

Any implant is unable to fulfil these above mentioned criteria is termed as a failed implant.

Pathogenesis of implant failure:

Despite of high success rates reported by various authors, implant failure is still a matter of concern for the clinicians, especially so called early implant failure or implant loss within the healing time. Surgical trauma, acute infections, lack of stability, insufficient biocompatibility of implant body, smoking and host response are considered as possible factors of early implant failure. But beside these important factors , multiple failures seen on same person supports the idea of genetic factors effecting healing mechanisms and probably early implant failure. However ; little is known about genetic susceptibility to osseointegrated implant failure[3] (Kronstrom et al 2001). Till now it is not known why bone will integrate with titanium dental implants or why it rejects the material as a foreign body. Many theory has been postulated over the last five decades. A recent theory argues that rather than being an active biological tissue response, the integration of bone with an implant is the lack of a negative tissue response. In other words for unknown reasons the usual response of the body to reject foreign objects implanted into it does not function correctly with titanium implants. It has been further postulated that an implant rejection occurs in patients whose bone tissues actually react as they naturally should with the foreign body and reject the implant in the same manner that would occur with most other implanted materials.[4]

Available management protocols:

Traditional techniques for enhancing bone formation for oral implant placement include bone autografts , allograft or guided bone regeneration[5]. The use of osteogenic growth factors such as platelet derived growth factors (PDGF) to regenerate tooth supporting structures and peri- implant alveolar bone offers significant potential for periodontal regeneration (seen in preclinical animal models and in early human trails)[6]. However, outcomes of these therapies are limited , in terms of regeneration and predictability, due to drug instability at the site of delivery. Therefore, the utilizations of gene therapy to control the release and bioavailability of osteogenic GFs offers potential for tissue engineering of osseous defects is introduced into this context [7]

Different Approaches of Gene transfer[8]:

A) According to mode of transfer:
- Viral approach
- Non viral approach
  - Direct introduction into the host cell
  - By liposome (artificial lipid sphere in aqua

medium)

- Experimental introduction of 47th chromosome (Artificial Human Techno-chromosome)

B) According to Recipient Tissue:

· Somatic line gene therapy/ Horizontal line gene therapy

· Germ line gene therapy/ vertical line gene therapy

C) According to tissue engineering:

· Protein based approach- through TGF- beta, BMP 2,6,7,12 bFGF, VEGF, PDGF.

· Cell based approach- (eg transferring BMP-2 and other osteoprogenitor mediator through myoblasts)

D) According to Gene delivery approach

· Ex- vivo approach

· In-vivo approach

Viral Approach:

A gene directly inserted into a cell usually does not function, instead a carrier called as vector is used to introduce the therapeutic gene into target cell. The most common vectors are used Retro virus,Adeno virus, HSV, Adeno-associated virus , Lentu virus etc[9]. Retro virus incorporates the genetic material to chromosome of host cell[10]. Adenovirus just delivers the genetic material to nucleus of host cell. Virus an be given I.V or directly into the site[11]

Ex- vivo approach:

In this approach cultured cells are transfected/ transduced with gene construct in-Vitro before they are transplanted into the defect[12, 13]

In vivo approach:

Gene constructed as plasmid DNA or a viral particle are physically entrapped within a scaffold / matrix. When this scaffold/ matrix is implanted into the defect the host tissue take up the gene and start producing the encoded proteins[14,15]

Recent Advancements for Better bone regeneration around implants

Several studies have demonstrated strong potential for the use of

1) PDGF gene
2) BMP 7 gene in bone regeneration.

PDGF and BMP 7 has demonstrated positive effects in regenerating bone around teeth and dental implants. The primary goal of this application is to validate novel gene delivery regenerative medicine strategies and apply them to animal models with a long term goal of human application[16]

BMP 7: BMPs are member of the TGF-h superfamily that are powerful regulators of cartilage and bone formation during embryonic development and regeneration in postnatal life. Recent studies have demonstrated the expression of BMPs during tooth development and periodontal repair[17]. Bone morphogenetic protein 7 (BMP7) also known as osteogenic protein 1, is a multifunctional member of the BMP family with multiple effects on bone formation and regeneration. BMP 7 stimulates bone regeneration around teeth, around endosseous dental implants, and in maxillary sinus floor augmentation procedures[18,]

PDGF: Delivery of PDGF by gene transfer has been shown to stimulate gingival fibroblasts, PDL and tooth lining cell (cementoblast) mitogenesis and proliferation above that of continuous PDGF administration in vitro. PDGF has also demonstrated positive effects in regenerating bone around teeth and dental implants[19].

Experimental studies:

1) Application of BMP 7 gene:

To evaluate the osteogenic potentiality of BMP 7 Dunn,C.A et al (2004) [20]conducted an experimental study on Sprague- Dawley rats. Total of forty four (n=44) 10 weeks old Sprague- Dawley rats (approx…weight 250-300 g) were included in the experimental study. Extraction sockets of maxillary first molars bilaterally were chosen as experimental sites. Where a soft tissues were allowed to heal for 30days , then followed by creation of osteotomy defects and 1 +2 mm titanium oral implants press fit into the position

2) Application of BMP 7 gene by In-vivo Transgene Transduction and Targeting

An adenoviral vector with a collagen matrix is utilized to immobilize the transgene at the dental implant defect site. Experimental dose ranges of 2-200m.o.i. Gene therapy vectors are delivered to implant osteotomy defects just after dental implant placement (fig).

Analytical assessment:

15 animals were assigned to Ad/BMP 7 treatment and 15 animals served as controls with the Ad/Luciferase treatment. The magnitude and targeting of gene delivery are evaluated by using optical imaging , through titanium dental implant fixtures in vivo bioluminescene (n=3). Sustained release of the gene product occurred at a range of 10-35 days. Implant fixtures displayed the localized nature of expression in the near vicinity of the oral implants. The gene product was expressed strongly for the first few days with peak expression at day 4, afterwards steadily declined until it was nearly undetectable by 2-5weeks.

Histomorphometric Analysis :

- At 14 days of post-Gene Transfer- Early bone formation was seen along the defect borders. Several of the Ad/ BMP 7 treated defects displayed tissue consistent with early osteoid formation throughout the defect area
- At 28days of post Gene Transfer – Bone formation was heightened both at the defect margins and along the dental implant surface in the Ad/ BMP-7 treated sites .In addition, the BMP 7 treated implant revealed a more mature lamellar bone formation, lamellar ompaction ND new bone in BMP -7 treated defects beyond the calcein bone label landmark .In addition,osseointegration as shown by SEM could be clearly seen.

Application of PDGF-B GENE:

To evaluate the therapeutic potentiality of PDGF-B gene Zachary R. Abramson et al(2007)[21] conducted an experimental study on Sprague-Daley rats. In an alveolar defect model adenovirus encoding PDGF-B (PDGFB8E11 particles/ml) in 2.6% ollgn gl utiliing AdPDGFB virus, viral copies within the blood and rags were dotted using real time PCR in all four groups: high dose Ad-PDGFB (8E11 particles/ml), low dose Ad-PDGFB (8E10 particles /ml), collagen alone and untreated control. In addition,biodistribution of the virus was evaluated using in vivo bioluminescence.

Results:

By four weeks post surgery, both the Ad PDGF

and collagen only gaps demonstrated more mineralized tissue when compared to the two week time points ($p<0.05$). Viral copies detected in the blood were not significantly different between treated and untreated rats at all time points. Viral copies within the organs were also not significantly different between treated and untreated rats for all time points except for a slightly elevated levels found in the high dose group at 14 days post surgery in the liver and spleen. Bioluminescence results demonstrated the localization of the vector to the defect site , with minimal dissemination to the organs over the course of 70days . Finally, from the set of preliminary micro CT images, representative images were converted to a 3D finite element model for simulated biomechanical testing.

Clinical trials using gene therapy:

1. Jin et al 2004 reported the potential of using gene delivery to regenerate alveolar bone and cementum around teeth and alveolar bone associated with dental implants fixtures [14].
2. W.VGiannobile et l 2001 [19] reported that in vitro delivery of PDGF by gene transfer has been shown to stimulate gingival fibroblasts,PDL and tooth lining cell mitogenesis and proliferation.
3. Anusakahein et al 2006 reported that in an ex-vivo gene transfer experiments,PDGF en was pound upto 10days pot gene transfer [14].
4. Kaigler D et al 2001 discussed upon different methods of gene delivery and the novel approaches for reconstruct oral and tooth supporting structures [22].

Discussion :

Recent studies utilized in vivo gene delivery of BMPs and PDGF to form bone ectopically in immunocompetent and immunocompromised animals. In immunocompetent animals,ectopic bone formation was minimal and noted only after 3 weeks and the quantity and quality of bone were inferior to those of the immunosuppressed groups. In omen studies, animals with intact immune systems showed no bone formation and the suppressed groups did not ow signs of ostogenesis until day 14-21. All groups suggested that the rapid immune response to the viral proteins decreased the expression of the gene in immunocompetent animals. Strategies to circumvent these problems ranged from immunosuppression to the use of AAV (adeno associated virus) and gutted vectors from which viral coat protein genes have been deleted.

Other studies using AAV vectors or gene delivery of bone morphogenetic protein without immunosuppression found impressive results. New bone formation was initiated at 3 weeks, and expression of the protein was noted for 8 weeks. These studies used ex vivo gene delivery to muscle derived stem cells instead of osteoblastic cells, which are known to display different responses.

The use of AAV has the advantage of the minimal elicitation of an immune reponse. However, the longer term gene expression profile may prove a shortcoming once bone heeling has completed.

Rationale for Gene Therapy:

To become a clinical reality for human application in the treatment of periimplantis, safety must be a primary concern. The use of viral vectors for growth factor delivery to bone defects requires evaluation of specific vector biodistribution properties (i.e. dissemination of vectors from the osseous site to other extraorthopic tissues and organs) . Various safety assessment have been performed using growth factor transgenes and for bone sparing agents preclinically demonstrating lack of significant local and systemic toxicity .the continued diligence in carefully evaluating both short term and long term safety of genethrapy vectors will be important if genetherapy is to become a viable treatment alternative for bone repair around implant.

Conclusion .

These preliminary and ongoing data suggest the feasibility of administering and targeting PDGF and BMP-7 genetherapy vectors to oral implant defects and the ability of this model to be assessed In terms of efficacy and safety .finally ,these data confirm the potential of CT imaging of titanium implants for quantification of alveolar bone and stimulated biomechanical testing,before going to human application as treatment modality further preclinical trials are needed.

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