On Novel Options for Oromaxillofacial Functional Restoration

Regenerative medicine seeks to replace or regenerate human cells, tissues, or organs so as to restore or establish normal function. This includes tissue engineering, which was proposed as a specific alternative strategy for tissue grafting and alloplastic tissue repair.[1] Tissue engineering is an emerging interdisciplinary field that applies the principles of biology and engineering to the development of viable tissue substitutes that restore and maintain the function of human tissue. Numerous approaches are currently used for bone tissue engineering; they involve the following key components: seeded cells, growth factors, and three-dimensional biomaterial scaffolds.[2] Tissue engineering and regenerative medicine strategies offer promising and exciting treatment alternatives for patients whose severely compromised bone support precludes predictable treatment outcomes with fixed or removable intra- and extraoral prostheses. This novel approach comprises four compelling considerations: *(1)* cell sources, *(2)* growth/transcription factors and biomaterials, *(3)* animal research, and *(4)* clinical translational research.

Cell Sources

Cell sources for bone regeneration include osteoblasts and stem cells. Osteoblasts possess strong osteogenic potential and can be used as seeded cells for bone regeneration. Despite their lineage commitment to bone formation, osteoblasts derived from autologous bone normally represent a relatively limited source because of their numbers and expansion limits. It was reported recently that osteoblasts derived from mandibular bone chips could be applied for bone regeneration, and more importantly, osteoblasts derived from cryopreserved mandibular bone were comparable to those from fresh bone in terms of their ability to promote osteogenesis in vivo. It appears that fresh/cryopreserved mandibular bone grafts may represent a novel, accessible cell source for bone tissue engineering.[3]

Stem cells are undifferentiated cells with the capability to self-renew and differentiate into different cell lineages. Stem cell sources include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells. ESCs, harvested from the inner cell mass of the blastocyst, are touted as having the only truly totipotent cell lineage. In vitro and in vivo studies have demonstrated the ability of ESCs for bone regeneration. Research on human ESCs has caused controversy with regard to tumorigenicity, immunogenicity, and ethical issues. Originating from cell reprogramming, iPSCs represent a novel cell source for regenerative medicine. Their differentiation into osteoblasts and new bone formation has been described. However, both mechanisms and optimized induction approaches require further study.

Adult stem cells offering promise for bone tissue engineering have also been derived from bone marrow, periosteum, adipose tissue, skeletal muscle, skin, and other sources. More importantly, adult stem cells have been identified from specialized tissues in the cranial and maxillofacial regions, including dental pulp and the periodontal ligament, which may offer advantages for craniomaxillofacial bone regeneration. Among these cells, bone marrow–derived mesenchymal stem cells (BMSCs) and adipose-derived stem cells (ASCs) have received the most attention. Successful repair of bone defects with autologous BMSCs or ASCs has been achieved in various animal models. Further, optimal outcomes have been reported by using autologous BMSCs to repair human bone defects, particularly mandibular defects.[4]

Growth/Transcription Factors and Biomaterials

Bone tissue is composed of a heterogenous mixture of cell types embedded in mineralized extracellular matrix within a three-dimensional structure. Extracellular matrix is a particularly rich source of signaling molecules; acts as a structural support, reservoir of growth factors, transducer of mechanical signals, and source of spatial cues delivered via chemical epitopes; and possesses many related features.[5] Bone tissue–engineering strategies based on growth factors and biomaterials should direct osteoprogenitor/stem cell behavior, with the eventual goal of restoring bone tissue function.

New bone formation is regulated by growth factors, transcription factors, and other cytokines. For bone tissue engineering, growth/transcription factors can improve osteoprogenitor/stem cell chemoattraction, proliferation, and osteogenic differentiation and consequently improve bone regeneration. A large number of growth/transcription factors have been used for bone tissue engineering, such as bone morphogenetic proteins (BMPs), fibroblast growth factors, insulinlike growth factors I and II, platelet-derived growth factor, vascular endothelial growth factor, NEL-like molecule-1, runt-related transcription factor 2, and hypoxia-inducible factor 1α among others. Of particular interest among these growth factors are a subset of BMPs, most notably BMP-2, -4, and -7, since these have been reported to be potent inducers of osteogenic differentiation.

Biomaterial scaffolds play a critical role in bridging the gap between the developmental context of bone tissue engineering and the diverse context of bone regeneration in terms of clinical need. Strategies for designing new biomimetic scaffolds, which account for the hierarchical organization of natural bone, have been investigated. Such scaffold properties, including biomaterial biocompatibility, chemical composition, geometry, porosity, mechanical strength, degradation rate, and incorporation of growth factors/signaling molecules, can be optimized to address the physiologic requirements of tissue-engineered bone.[5] Controlled release for BMP-2 and vascular endothelial growth factor proteins, calcium/magnesium/silicon ions, and certain nanoscale structures have been shown to facilitate the proliferation and differentiation of adult stem cells in vitro and promote new bone formation in vivo. In addition, computer-aided design/computer-assisted manufacturing techniques can be used to fabricate anatomically customized scaffolds. This approach is required for functional restoration of the unique anatomical position and complicated structure of maxillofacial bone and demands customized, hierarchically designed scaffolds for the repair of large and complicated tissue defects.[6]

Animal Research

Animal models provide an important bridge between basic research and clinical translation. They permit the evaluation of tissue-engineered bone and its potential for functional restoration of operated sites. The readily available and common animal models used include nude and SCID mice (for ectopic bone formation with subcutaneous/intramuscular implants), small animals such as rats and rabbits (for in situ bone formation trials), and large animal models that may be closer and more relevant to human subjects such as canines, goats, pigs, and monkeys. The latter group is particularly favorable for the evaluation of mandibular bony defects or bone deficiency regeneration.

For example, vertical ridge augmentation in canines was established to evaluate tissue-engineered bone by combining β–tricalcium phosphate and autologous osteoblasts, which achieved repair effects comparable to autogenous iliac bone grafts at 6 months. Maxillary sinus floor elevation models in both canines and goats have also been created to evaluate the effects of tissue-engineered bone. The complexes of calcium phosphate biomaterials and osteoblasts or BMSCs achieved beneficial effects and suggested the potential for clinical applications as viable alternatives to autologous bone. It was also observed that tissue-engineered bone demonstrated good initial osseointegration with dental implants. Moreover, canine border defect models have been established and optimized, while tissue-engineered bone constructed with BMSCs and apatite-coated silk fibroin scaffolds achieved similar outcomes to that of autogenous bone grafts with respect to bone regeneration at 12 months.

Clinical Translational Research

A preliminary report by Schmelzeisen et al[7] described augmentation of the posterior maxilla in two patients carried out using a bone matrix derived from mandibular periosteal cells on a polymer fleece. The results showed that lamellar bone that formed within 4 months allowed reliable implant insertion, which could be a major benefit for dental prostheses. Furthermore, an alveolar defect resulting from trauma-related loss of a maxillary incisor was reconstructed using tissue-engineering techniques. Successful oral function was restored prosthodontically using implants.[8]

Although there are relatively few published reports, indeed no long-term outcome studies, to support the effectiveness of what appears to be an efficacious technique, there is clearly clinical promise for tissue engineering to address human oromaxillofacial bone deficits. Compelling additional challenges such as limited oxygen and nutrient supply need further investigation, including prevascularized tissue systems and related approaches.[9] Therapies based on tissue-engineered bone are currently predicted to become viable treatment strategies in the near future as widely and safely prescribed clinical alternatives for the restoration of missing bone and associated oral functions. The nature of clinical science and professional ethics demands robust evidence for the long-term safety and efficacy in both animal models and clinical studies.

Conclusion and Future Perspectives

The successful translation to routine and predictable clinical application of tissue-engineered bone for oral functional rehabilitation requires material scientists, biochemical engineers, cell biologists, clinical researchers, and specialist practitioners. The exploration and integration of their skills need to be recruited to create required new approaches to solve key associated constraints such as: *(1)* safe and effective protocols for the isolation of skeletal stem cell populations and their robust ex vivo expansion in chemically defined conditions with particular inclusion of craniofacial stem cell sources; *(2)* biomimetic scaffold designs that include parameters pertinent to stem cell biology, with the latter involving the dynamic transmission and/or attenuation of biologic, chemical, and mechanical signals to be optimized and matched with pertinent clinical application parameters such as easy delivery to the site of bone defects and dynamic and durable/degradable three-dimensional scaffold structures; *(3)* a scaling-up of tissue-engineering constructs to clinically relevant dimensions that address limitations in oxygen and nutrient mass transfer that are met by novel approaches to mimic developmental processes; and *(4)* implant osseointegration with tissue-engineered bone. Apart from the objective enhancement of the quantity and quality of tissue-engineered bone, strategies based on the chemical composition or surface modification of dental implants could also enhance implant osseointegration. The eventual matching of the extraordinary potentials of tissue engineering and the healing phenomenon of osseointegration will inarguably expand the latter's confirmed scope for restoring function and esthetics in patients with both dental and supporting bone deficits. However, it must be realized that scientific prudence and ethical concerns will go on expecting tissue-engineering techniques to first provide conclusive proof that bench research on scaffold biomaterial technology, stem cell science, and related topics can be recruited into safe and predictable clinical therapies.

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References

1. Langer R, Vacanti JP. Tissue engineering. Science. 1993;260:920–926.
2. Crane GM, Ishaug SL, Mikos AG. Bone tissue engineering. Nat Med 1995;1:1322–1324.
3. Wang S, Zhao J, Zhang W, et al. Maintenance of phenotype and function of cryopreserved bone-derived cells. Biomaterials 2011;32:3739–3749.
4. Cancedda R, Giannoni P, Mastrogiacomo M. A tissue engineering approach to bone repair in large animal models and in clinical practice. Biomaterials 2007;28:4240–4250.
5. Sundelacruz S, Kaplan DL. Stem cell- and scaffold-based tissue engineering approaches to osteochondral regenerative medicine. Semin Cell Dev Biol 2009;20:646–655.
6. Hollister SJ. Porous scaffold design for tissue engineering. Nat Mater 2005;4:518–524.
7. Schmelzeisen R, Schimming R, Sittinger M. Making bone: Implant insertion into tissue-engineered bone for maxillary sinus floor augmentation—A preliminary report. J Craniomaxillofac Surg 2003;31:34–39.
8. Meijer GJ, de Bruijn JD, Koole R, van Blitterswijk CA. Cell-based bone tissue engineering. PLoS Med 2007;4:e9.
9. Warnke PH, Springer IN, Wiltfang J, et al. Growth and transplantation of a custom vascularised bone graft in a man. Lancet 2004;364:766–770.

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