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Review

Tissue engineering technology and its possible applications in oral and maxillofacial surgery

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Abstract

Tissue engineering is a rapidly advancing discipline that combines the attributes of biochemical and biomaterial engineering with cell transplantation to create bio-artificial tissues and organs. For the oral and maxillofacial surgeon, the reconstruction of maxillofacial defects in hard and soft tissues is an ongoing challenge. While autologous grafts and vascularised free flaps are the current gold standard, they are not without complications at both the donor and reconstructed sites. Tissue engineering, which aims to create tissue-matched, prefabricated, prevascularised bony or soft tissue composite grafts, or both, therefore has the potential to revolutionise practice in maxillofacial surgery. We review the technology of tissue engineering and its current and future applications within the specialty, and discuss contemporary obstacles yet to be overcome.

Keywords: Tissue engineering; Maxillofacial surgery; Reconstructive surgery; Head and neck surgery

Introduction

The reconstruction of large tissue defects is one of the main challenges to face the modern oral and maxillofacial surgeon. Being either iatrogenic in origin after serious operations for head and neck cancer or caused by traumatic injury or congenital deformity, the need to reconstruct multi-layered defects is growing as surgical techniques advance.[1] While the transfer of autologous tissue such as bone grafts or tissue free flaps are well described, they are not without complications.[2] With this in mind, the prospect of using principles of tissue engineering to reconstruct defects in soft and hard tissues of the head and neck continues to gain the attention of the reconstructive surgeon.[1,3]

Over the last 2 decades tissue engineering has emerged as an alternative technique to repair and restore function of damaged or diseased tissue. Tissue engineering is "the application of the principles and methods of engineering and the life sciences towards the fundamental understanding of structure–function relationships in normal and pathologic mammalian tissues and the development of biologic substitutes that restore, maintain, or improve tissue function".[4] Fundamentally this involves combining biochemical and biomaterial engineering with cell transplantation to create bio-artificial tissues and organs.[5] From a surgical standpoint, it is important to view tissue engineering not as a new concept, but as a step on the continuum of research in biomaterials (Table 1). Current research makes use of previous

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Table 1
Ages of biomaterials: the continuum of research in biomaterials and tissue engineering.

1920–1970	bioMATERIALS age of device	Fracture fixation, joint replacement, spine instrumentation
1970–2000	BIOMATERIALS age of biomaterials	Hydroxyapatite coatings, bioactive materials, bone graft substitutes
2000 onwards	BIOmaterials age of biomimetic scaffolds and beginning of tissue engineering	Cell-seeded scaffolds, bioactive factors with or without cells, porous absorbable materials
2010 onwards	Age of tissue engineering and gene therapy	Tissue engineered vascularised grafts, materials as delivery systems for genes

(Adapted from Anderson[6])

biotechnology and focuses on the repair, replacement, and ultimately on the regeneration of tissue.

We review the technology in tissue engineering and its current and future applications within oral and maxillofacial surgery (OMFS) based on organ or tissue type, and discuss contemporary obstacles yet to be overcome.

Basic principles

The basic principle of tissue engineering involves a "triad" wherein a combination of cells in a suitably engineered material scaffold with appropriate biochemical signals is used to provide viable therapeutic options for clinical applications. Advances in research have shown that the engineering and design of the scaffold matrices, and the mechanical signals that regulate engineered tissues, have an important role.

A scaffold is a "permanently placed, or temporary three-dimensional porous and permeable natural or synthetic biomaterial that is biocompatible".[7] It is of pivotal importance as it allows the attachment, migration, and differentiation of progenitor cells.[8] Readers should be aware that the physical characteristics of scaffolds (such as biodegradability, porosity, stiffness, and strength) can greatly influence cell adhesion, migration, and proliferation (such as osteoconduction), which signals the delivery of molecules and therefore the subsequent overall clinical success of the graft (Fig. 1). Perhaps of greater importance to maxillofacial surgeons than to other surgical counterparts, is the need for precise, anatomically correct bony scaffolds for the reconstruction of facial skeletal defects. Research has shown promising results using image-based computer-aided design and manufacture to create biomimetic scaffolds[9] – for example, the complex three-dimensional shape of the mandibular condyle.[10] A favourable approach, although challenging, in maxillofacial surgery would be the injection into complex anatomical defects of a substitute that would exhibit adequate mechanical properties and porosity on hardening, which is challenging.

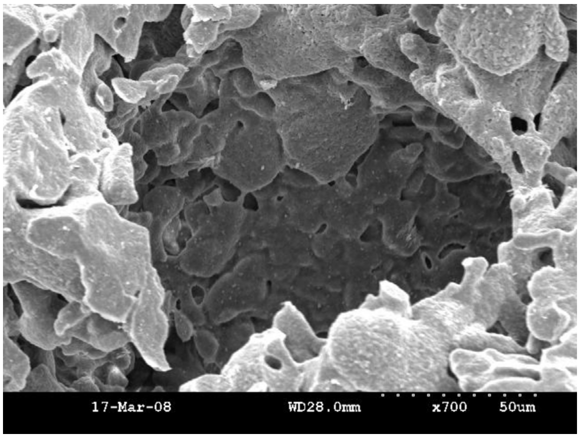

Fig. 1. A bioactive glass scaffold with an interpenetrating porous structure. A "pores within pores" structure supports the flow of nutrients and ingress of cells within the core of the scaffold.

To complete the triad, tissue engineering requires cell lines that have "ease of access and availability, a capacity for differentiation, and a lack of immunogenic or tumourigenic ability".[11] Choices of cell line within engineered tissues are discussed below. A promising new development is the use of stem cells and gene therapy with viral vectors to express growth factors in cultured cell lines,[12] but further discussion of stem cell research lies outside the scope of this article.

Ex-vivo engineering of living tissues is a concept that has potential to make a great impact on future treatment therapies. One of the major obstacles in creating viable functional tissues outside the body is, understanding the way in which cells are regulated in their specific physicochemical *niches*. In this respect, bioreactors provide a means of controlling these conditions and mimicking the natural physiological conditions.A bioreactor is a "device(s) in which biological or biochemical process, or both, are re-enacted under controlled conditions".[13] As tissue engineering has advanced from constructs of single cell thickness to three-dimensional cell-seeded scaffolds, the need to maintain a controlled microenvironment for ex vivo growth of tissue has emerged. Mathematical modelling can now be used to calculate the flow rates of scaffold fluid (to supply nutrients and remove waste) and diffusion of oxygen, together with other variables such as the external mechanical forces needed to stimulate the proliferation of osteoblasts.[13] An alternative approach is in vivo cultivation of grafts using animal models or man as a "living bioreactor" to provide the already present homeostatic environment needed for cells to grow (Fig. 1).[14,15]

Bone

The discovery that demineralised bony matrix is capable of ectopic ossification led to the discovery of several signalling molecules for osteogenic protein.[16] Named "bone morphogenetic proteins" (BMP), these growth factors are capable of osseoinduction and osteogenesis, and are used extensively in