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Expanded View

Preclinical and clinical research on bone and cartilage regenerative medicine in oral and maxillofacial region☆

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ABSTRACT

Recently, there have been remarkable advances in regenerative medicine, and almost all disorders of the oral and maxillofacial region could be research targets of regenerative medicine. Meanwhile, treatment in this region has been well established using biomaterials, prostheses, and microsurgery. Therefore, to surpass such a conventional approach as an alternative, regenerative medicine should take an approach of being less invasive and/or more effective. In this report, we present our preclinical and clinical research on bone and cartilage regenerative medicine in the oral and maxillofacial region.

Regarding bone regenerative medicine, we have tried to develop artificial bone that would maximize bone formation at the transplanted site, but would subsequently be replaced by autologous bone. We have made custom-made artificial bone (CT-Bone) using alpha-tricalcium phosphate (α-TCP) particles and an ink-jet printer, and have conducted clinical research and trials on 30 patients.

To develop tissue-engineered cartilage with proper three-dimensional (3D) morphological form and mechanical strength, we have optimized the culture medium of chondrocytes and the scaffold. Following a preclinical study confirming efficacy and safety, we have conducted clinical research in three patients with nasal deformity associated with cleft lip and palate, and are now starting multicenter clinical research.

Contents

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1. Introduction

The concept of tissue engineering, that is, seeding cells on a scaffold and inducing tissue formation in the presence of growth factors, was proposed by Professor Joseph Vacanti of Harvard University and Professor Robert Langer of the Massachusetts Institute of Technology in 1993 [2]. The photograph of a human ear mounted on the back of a mouse they presented was covered widely by the mass media throughout the world, gaining immediate fame for regenerative medicine. Thereafter, research in the field of regenerative medicine has advanced greatly. Two years ago, Professor Shinya Yamanaka of Kyoto University was awarded the Nobel Prize, and induced pluripotent stem cells (iPS) cells and regenerative medicine have also become hot topics in Japan.

In the maxillofacial region, nearly all disorders have become research subjects of regenerative medicine, including loss of teeth and periodontal tissue due to caries and periodontal disease, hypoplasia or defects of bone and cartilage associated with congenital anomalies, such as cleft lip and palate, defects of bone, cartilage, and soft tissues due to tumors or trauma, and xerostomia. However, the dental field has a long history of knowledge of materials, and treatment using biological materials has been established such as crown prostheses, dentures, dental implants, and epitheses. In addition, with the recent advancements in medical technology, reconstruction of large mandibular defects has become possible by microsurgical operations. Therefore, to surpass such a conventional approach as an alternative, regenerative medicine should take an approach of being less invasive and/or more effective. Particularly, the application of regenerative medicine is considered to be advantageous for the maxillofacial region because the weight load is smaller than in the limb, and the amount of tissue needed for reconstruction is generally small. In this report, we present our preclinical and clinical research on bone and cartilage regenerative medicine in the oral and maxillofacial region.

2. In situ tissue engineering in maxillofacial region

After tumor resection or trauma in the maxillofacial region, bone defects occasionally impair the function of mastication and the facial appearance of patients, worsening their quality of life (QOL). To reconstruct such defects, many surgical procedures have been developed including block bone graft and vascularized bone graft. Especially in mandibular reconstruction, a vascularized free graft of the fibula is preferably chosen because: (1) a sufficiently long bone with vessels can be harvested, (2) it is thick enough for placing dental implants, (3) the bone graft can be harvested during manipulation in the head region, (4) skin grafting can be additionally performed, and (5) complications of the donor site are rare. However, this operation requires intraoperative trimming of the bone graft to adjust its shape to the recipient site, making it difficult to provide satisfactory morphological form. In addition, it is highly invasive at the donor site, and there are limitations in the size and shape of the grafts.

For these reasons, particulate cancellous bone and marrow (PCBM) from the ilium is often transplanted in combination with a titanium mesh tray (Fig. 1) [3]. By appropriate shaping of the tray, this method enables more morphologically natural reconstruction, while restoration of adequate occlusion is also possible with the use of dentures and dental implants. Moreover, mesenchymal cells in PCBM can induce new bone formation and subsequent bone resorption, resulting in bone remodeling that matches the surrounding recipient bone. This is a peculiar property of PCBM, in contrast to the aim of a conventional block bone or vascularized bone graft, which is the survival of the graft bones itself. Due to this osteogenic ability of PCBM, reconstruction using PCBM can be

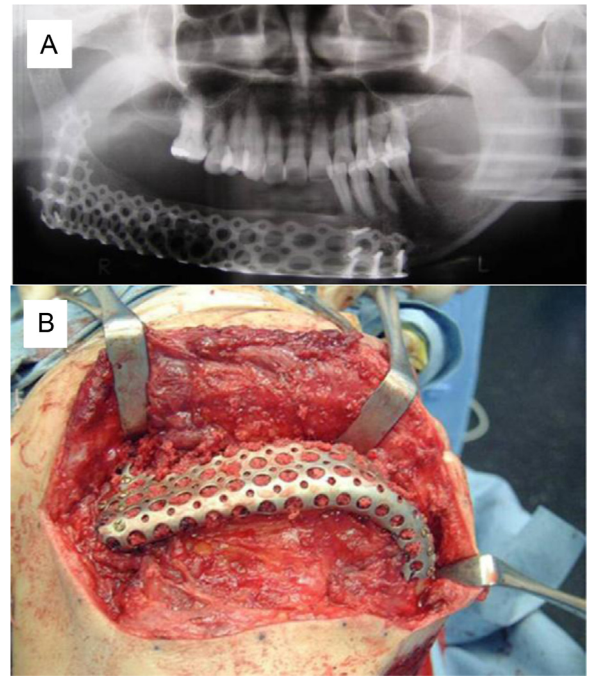

Fig. 1. Bone reconstruction using particulate cancellous bone and marrow (PCBM) in combination with a titanium mesh tray (excerpted from Ref. [3] with permission). (A) A case of reconstruction using PCBM and a titanium mesh tray. Nine-month postoperative panoramic view showing the successfully reconstructed mandible. The occlusal function of this patient is quite good with her remaining natural dentition and removable partial denture. (B) Intraoperative view after PCBM grafting. PCBM was loaded into the mesh and densely condensed as much as possible.

regarded as in situ tissue engineering (it can also be considered "in vivo tissue engineering," because tissue regeneration proceeds after transplantation) [4]. Another example based on in situ tissue engineering in the maxillofacial region is bone lengthening for micrognathia, in which bone formation can be induced by mild traction on the callus of an osteotomy site. It is therefore considered that regenerative medicine may not be such a new approach, as some conventional treatments adopt the concepts of tissue engineering.

3. Preclinical research on bone regenerative medicine

Vascularized bone and block bone are considered to retain the intrinsic properties of bone, because they contain the original cell components and growth factors accumulated in the matrix. Therefore, bone union after grafting of these bones usually progresses smoothly, resulting in a favorable clinical outcome. Transplantation of PCBM with a titanium mesh tray also exhibits excellent results. However, as long as autologous transplantation is used, these operations include the process of harvesting tissues, and the amount obtained for grafts may be limited.

In foreign countries, particularly in the United States, use of allogeneic bone is prevalent. The amount and shape of bone grafts can be managed with allogeneic grafting, and the operation is less invasive with respect to the donor site. While cells in allogeneic bone are not viable and the activity of growth factors in the matrix is suppressed by freezing, the grafts are still natural bone with excellent function. However, the use of allogeneic bone has not been prevalent in Japan because of concerns of infection and ethical issues. Instead, calcium phosphate-based artificial bone has been used as an alternative [5]. The reason why calcium phosphate is preferred is that being a component of bone, it has an excellent biocompatibility and biological safety. Besides, the supply of calcium phosphate is unlimited as it is synthesized from limestone and phosphate rock.