Archives of Oral Biology 60 (2015) 1517–1532

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/aob

Review

Stem cell regenerative therapy in alveolar cleft reconstruction

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ARTICLE INFO

Article history:
Received 15 December 2014
Received in revised form 23 May 2015
Accepted 4 July 2015

Keywords:
Alveolar cleft
Cleft palate
Mesenchymal stem cells
Tissue engineering
Bone regeneration

ABSTRACT

Achieving a successful and well-functioning reconstruction of craniofacial deformities still remains a challenge. As for now, autologous bone grafting remains the gold standard for alveolar cleft reconstruction. However, its aesthetic and functional results often remain unsatisfactory, which carries a long-term psychosocial and medical sequelae. Therefore, searching for novel therapeutic approaches is strongly indicated. With the recent advances in stem cell research, cell-based tissue engineering strategies move from the bench to the patients' bedside. Successful stem cell engineering employs a carefully selected stem cell source, a biodegradable scaffold with osteoconductive and osteoinductive properties, as well as an addition of growth factors or cytokines to enhance osteogenesis. This review highlights recent advances in mesenchymal stem cell tissue engineering, discusses animal models and case reports of stem cell enhanced bone regeneration, as well as ongoing clinical trials.

Contents

1. Introduction

Cleft lip and palate is a congenital defect with the overall prevalence of 7.94 per 10,000 live births (Tanaka, Mahabir, Jupiter, & Menezes, 2012) and wide variability of clinical expression and severity, from orbicularis oris muscle defect to cleft lip, alveolar

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http://dx.doi.org/10.1016/j.archoralbio.2015.07.003
0003-9969/

cleft and cleft palate alone. (Dixon, Marazita, Beaty, & Murray, 2011) Alveolar cleft is a result of an improper fusion of the maxillary prominences around the 5th–6th week of gestation, that is caused by both environmental and genetic factors (Coots, 2012; Molina-Solana et al., 2013 FebMolina-Solana, Yáñez-Vico, Iglesias-Linares, Mendoza-Mendoza, & Solano-Reina, 2013). It comprises a heterogeneous group of defects with large differences in volume and shape (Bugaighis et al., 2010). Affected children suffer from speech and hearing disorders, their academic achievements might be affected as well (Flynn & Lohmander, 2014; Knight, Cassell, Meyer, & Strauss, 2014). The correction procedure is aimed at closing the oronasal fistula and providing adequate support for tooth eruption through restoration of maxillary arch continuity, which provides conditions for proper dentition and occlusion development. (Bajaj et al., 2003 NovBajaj, Wongworawat, & Punjabi, 2003) The repair of the alveolar cleft can be conducted at different phases of dentition. Adequate timing of correction could promote further maxillary growth and reduce future craniofacial abnormalities. (Farronato, Kairyte, Giannini, Galbiati, & Maspero, 2014) Bone grafting is considered to be the gold standard with the cancellous bone harvested from the anterior iliac crest. However, the procedure is invasive and carries a potential risk of complications including pain, bleeding, infection, fracture or even late-occurring problems such as scarring, chronic pain, paresthesia or even gait abnormalities (Gimbel et al., 2007) and (Moreau, Caccamese, Coletti, Sauk, & Fisher, 2007). Moreover, the failure rate is about 15% (Paganelli et al., 2006; Schultze-Mosgau, Nkenke, Schlegel, Hirschfelder, & Wiltfang, 2003). Further orthodontic treatment is a necessity due to malalignment dentition and midfacial retrusion (Toscano, Baciliero, Gracco, & Siciliani, 2012). Bearing in mind all the above-mentioned complications and behavioral implications accompanying cleft palate, alternative approaches to autologous bone grafting are needed (Hunt, Burden, Hepper, & Johnston, 2005). Tissue engineering, a strategy of tissue regeneration employing combined use of biomaterials and biological molecules, arises as a new therapeutic option. It includes use of biodegradable scaffolds, an addition of growth factors and barrier membranes, as well as the use of stem cells. The craniofacial tissue development is closely related to interaction between stem cells and growth factors and thus they represent an interesting field for therapeutic use. Bone regeneration in patients with cleft palate is a challenging task as the newly formed bone must have adequate mechanical properties to endure a significant amount of pressure in the orofacial area.

2. Stem cells

Mesenchymal stem cells (MSC), multipotent stromal cells, are the one considered to be most promising in tissue engineering. Their minimal identifying criteria have been declared by the International Society for Cellular Therapy (Dominici et al., 2006). These cells must be plastic-adherent during culture in standard conditions, express cell surface markers such as CD105, CD73 and CD90 and no CD45, CD34, CD14, CD11b, CD79α, CD19 or HLA-DR. They must be proven to differentiate into osteoblast, adipocyte and chondroblast lineage. MSC are supposed to act not only through direct bone formation, but also due to paracrine effects: releasing cytokines, producing extracellular matrix and promoting angiogenesis. MSC in combination with biomaterials, carry a great potential that has already been proven in animal studies and on first human cases (Yoshioka et al., 2012; Tanimoto et al., 2013; Zhang et al., 2011; Ou, Jian, & Lin, 2007; Pourebrahim et al., 2013; Korn, Schulz, Range, Lauer, & Pradel, 2014; Hibi, Yamada, Ueda, & Endo, 2006; Pradel, Tausche, Gollogly, & Lauer, 2008; Behnia et al., 2009; Behnia, Khojasteh, Soleimani, Tehranchi, & Atashi, 2012; Stanko et al., 2013; Chai et al., 2006). Several aspects have to be taken into consideration when planning stem cell-enhanced bone regeneration.

2.1. Selecting stem cell donor

As for now, autologous stem cell sources are the one being used in tissue engineering, however, their acquisition requires prior harvesting procedure and generates drawbacks in both time and patient comfort. The idea of stem cell tissue-engineered product promptly available for off-the-shelf application is promising. However, an allogeneic source will be needed to fulfill such a concept. MSC can potentially be applied in an allogeneic setting as the mesenchymal stem cell immunophenotype with no major histocompatibility complex (MHC) II and low MHC I expression is said to be weak or non-immunogenic (Law & Chaudhuri, 2013). Host response to autologous, allogeneic and xenogeneic bone marrow-derived MSC (BM-MSC) was evaluated by Pigott, Ishihara, Wellman, Russell, and Bertone (2013). Stem cells were delivered intra-articularly to 6 five-year-old horses. Inflammatory cytokine release was present in all cases, however, host immune response upon re-exposure was detected only with xenogenic material. Further studies are needed to asses MSC immunogenicity, as some of the preclinical experiments show conflicting results. (Knaän-Shanzer, 2014) Third party MSC have been successfully used in a few clinical settings. They are applied to treat Graft-*versus*-Host Disease after hematopoietic stem cell transplantation in immunocompromised patients (Introna et al., 2014). First promising results regarding use of allogeneic umbilical cord blood-derived MSC (UCB-MSC) on 9 patients with bronchopulmonary dysplasia with mean gestational age of 25 weeks and weight of about 800 g have already been published (Chang et al., 2014). In a clinical trial evaluating safety and efficacy of a transendocardial delivery of autologous and allogeneic BM-MSC in treating ischemic cardiomyopathy, no significant alloimmune reactions were reported (Hare et al., 2012). No clinical studies concerning allogeneic MSC and bone regeneration have been carried out, however, a few studies on animal models have been conducted. Tsuchida, Hashimoto, Crawford, Manske, & Lou, (2003) attempted a repair of a rat femoral defect with bone morphogenetic protein 2 (BMP-2) and BM-derived allogeneic stem cells with short-term tacrolimus immunosuppression, and demonstrated equal effectiveness to the autologous source. Dighe, Yang, Madhu, Balian, & Cui (2013) study on a mice model showed that allogeneic MSC could be more efficient in bone regeneration if recipient T-cell and INF-γ production as a host response was inhibited. Another experiment (Liu et al., 2013a) combined allogeneic MSC that were differentiated until forming cell sheet of 6–7 layers with calcined bovine bone to repair critical size bone defect in osteoporosis rat model. No immunosuppression was applied. Osteogenic potential of allogeneic adipose tissue-derived MSC (AT-MSC) was assessed on canine cranial defects and the therapeutic effect was comparable to the one achieved with autologous cells. The study did not include immunosuppression, however, no host immune response was noted (Liu et al., 2013b). Comparative analyses of MSC allogeneic and autologous sources in bone regeneration have been conducted in a few studies. Allogeneic BM-MSC applied in an ovine critical-sized tibial bone defect showed results comparable to the autologous source (Berner et al., 2013). Similar outcome was achieved with allogeneic BM-MSC on a cancellous bone granulate scaffold in a rabbit model of critical-sized radius bone defect. Follow-up with both micro-computed tomography (μCT) and histological evaluation showed no major differences between autologous and allogeneic source (Kang et al., 2014).