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INVITED REVIEW

Cells from bone marrow that evolve into oral tissues and their clinical applications

OM Maria[1], R Khosravi[1], E Mezey[2], SD Tran[1]

[1]*Faculty of Dentistry, McGill University, Montreal, Quebec, Canada;* [2]*National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA*

There are two major well-characterized populations of post-natal (adult) stem cells in bone marrow: hematopoietic stem cells which give rise to blood cells of all lineages, and mesenchymal stem cells which give rise to osteoblasts, adipocytes, and fibroblasts. For the past 50 years, strict rules were taught governing developmental biology. However, recently, numerous studies have emerged from researchers in different fields suggesting the unthinkable – that stem cells isolated from a variety of organs are capable of ignoring their cell lineage boundaries and exhibiting more plasticity in their fates. Plasticity is defined as the ability of post-natal (tissue-specific adult) stem cells to differentiate into mature and functional cells of the same or of a different germ layer of origin. There are reports that bone marrow stem cells can evolve into cells of all dermal lineages, such as hepatocytes, skeletal myocytes, cardiomyocytes, neural, endothelial, epithelial, and even endocrine cells. These findings promise significant therapeutic implications for regenerative medicine. This article will review recent reports of bone marrow cells that have the ability to evolve or differentiate into oral and craniofacial tissues, such as the periodontal ligament, alveolar bone, condyle, tooth, bone around dental and facial implants, and oral mucosa.

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Stem cells in bone marrow

Stem cells are defined as clonogenic, self-renewing, and capable of generating one or more specialized cell types (Anderson *et al*, 2001). Developmentally, stem cells are categorized either as embryonic stem cells or as post-natal stem cells (they are also called organ-specific, tissue-specific, or adult stem cells) (Leung and Verfaillie, 2005). Embryonic stem cells are derived from the inner cell mass of a developing blastocyst and are considered as pluripotent cells as they are able to form all the body's cell lineages (endoderm, mesoderm, and ectoderm) (Smith, 2006). Post-natal stem cells (derived from specific tissues or organs) are considered multipotent as they can form multiple lineages that constitute an entire tissue or tissues (Smith, 2006).

According to our present knowledge there are two distinct populations of post-natal stem cells in the bone marrow – the hematopoietic stem cells (HSC) and the mesenchymal stem cells. HSC were recognized more than 40 years ago as they have the ability to reconstitute the hematopoietic system of a lethally irradiated host (Leung and Verfaillie, 2005) as it gives rise to all blood cell lineages. Their unique ability to self-renew continuously permits HSC to sustain blood cell production throughout life. The frequency of HSC is 1 in 10 000–15 000 bone marrow cells (Weissman, 2000a). Under physiologic conditions, quiescent HSC are interspersed with other cells within the bone marrow. However, under stressful conditions such as massive bleeding or acute bacterial infections, HSC rapidly proliferate, differentiate, and migrate from the bone marrow to circulate throughout the body (Domen and Weissman, 1999; Bordignon, 2006). Mesenchymal stem cells originate from the mesodermal layer of the fetus and in the adult they reside in the bone marrow as well as in a variety of tissues. Mesenchymal stem cells constitute only a small portion (1 in 10^4–10^6) of the bone marrow (Friedenstein *et al*, 1974; Pittenger *et al*, 1999). The pivotal characteristic of mesenchymal stem cells is their ability to differentiate *in vitro* into several cell types based on culture conditions (Pittenger *et al*, 1999). It has been demonstrated that these cells possess a multilineage differentiation capability (bone, cartilage, adipose, tendon, and muscle tissues; Ferrari *et al*, 1998; Jones *et al*, 2002). Several studies have reported that mesenchymal stem cell clones comprise a heterogeneous cell population with respect to their self-renewal characteristic (Bianco *et al*, 2001). However, this self-renewal potential is unclear mainly due to the different approaches used to derive populations of mesenchymal stem cells.

Correspondence: SD Tran, Faculty of Dentistry, McGill University, 3640 University Street, Room M-43, Montreal, Quebec, Canada H3A 2B2. Tel: +1 514 398 7203 Ext. 09182, Fax: +1 514 398 8900, E-mail: simon.tran@mcgill.ca
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Plasticity of post-natal stem cells

For the past 50 years, we were taught that post-natal stem cells have a limited developmental repertoire. Once a cell made a commitment to a dermal lineage during development, this was irrevocable (Mezey, 2004; Leung and Verfaillie, 2005). A stem cell residing in a particular tissue (i.e., a tissue-specific stem cell) could only differentiate into cells of that tissue. For example, a hematopoietic stem cell would give rise to new blood cells; a liver stem cell would make new liver cells, etc. However, in the past 7 years, a large number of studies emerged from researchers in different fields suggesting the unthinkable – that post-natal stem cells isolated from a variety of organs may be able to ignore its (dermal lineage) origin and exhibit more *plasticity* in their fate choices. Plasticity is defined as the ability of post-natal (tissue-specific adult) stem cells to differentiate into mature and functional cells of the same or of a different germ layer of origin (Leung and Verfaillie, 2005). There are reports that bone marrow stem cells can differentiate into hepatocytes (Petersen *et al*, 1999), skeletal myocytes (Ferrari *et al*, 1998), cardiomyocytes (Makino *et al*, 1999; Tomita *et al*, 1999), neural cells (Eglitis and Mezey, 1997; Mezey *et al*, 2003), endothelial cells (Tomita *et al*, 1999), epithelial cells (Krause *et al*, 2001), and pancreatic endocrine cells (Ianus *et al*, 2003). These findings on the plasticity of post-natal stem cells carry great hope for regenerative medicine (Weissman, 2000b; Pittenger and Martin, 2004; Kan *et al*, 2005). As an example, because HSC can reconstitute the entire blood system, bone marrow transplantations have long been used in the clinic to treat hematopoietic diseases (Mayhall *et al*, 2004). Several companies are competing to market a variety of cell-based therapies based on post-natal bone marrow-derived stem cells for treating cancers, autoimmune, neurologic, stroke, and heart diseases (Wilan *et al*, 2005).

Four explanations for the phenomenon of plasticity in post-natal stem cells have been proposed (Verfaillie, 2002; Martin-Rendon and Watt, 2003; Grove *et al*, 2004; Kashofer and Bonnet, 2005; Lakshmipathy and Verfaillie, 2005). First, there might be persistent stem cells from embryonic development with broad developmental potentials which are maintained within the adult bone marrow (Dao and Verfaillie, 2005). When transplanted into other organs, these cells are instructed to differentiate into tissue-specific cells under inductive signals from that specific tissue. A second possibility is that true precursors of post-natal stem cells with embryonic stem cell-like properties persist in adult bone marrow, such as the multipotent adult progenitor cells (Jiang *et al*, 2002). A third explanation may be that the nuclei of the transplanted stem cells undergo reprogramming of the existing genetic information, expressing new genes and proteins that are consistent with the novel lineage, and this might be a result of de-differentiation, and re-differentiation (Brockes, 1997; Lakshmipathy and Verfaillie, 2005; Hochedlinger and Jaenisch, 2006). A final explanation is when cell fusion occurs, which is a rare phenomenon reported *in vitro* and *in vivo* in tissues where polyploidy is common, such as hepatocytes, skeletal muscle, cardiac muscle and Purkinje cells of the cerebellum (Priller *et al*, 2001). As a result, the genetic information of both fused donor and host cells is partially changed (Terada *et al*, 2002; Ying *et al*, 2002; Lakshmipathy and Verfaillie, 2005).

The objective of this review was to evaluate recent reports of cells from the bone marrow (HSC and mesenchymal stem cells) that have the ability to evolve or differentiate into orofacial structures and their clinical applications for oral tissue regeneration (Table 1 and Figure 1). The readers are cautioned with the widely used term *mesenchymal stem cells* as the International Society for Cellular Therapy (ISCT) has stated that the current data are insufficient to characterize unfractionated plastic adherent marrow cells as stem cells (Horwitz *et al*, 2005). Therefore, the ISCT suggests the use of the term *multipotent mesenchymal stromal cell* to indicate these unique properties without ascribing homogeneity or stem cell activity; while the term *mesenchymal stem cells* is reserved for long-term self-renewing cells that are capable of differentiation into specific, multiple cell types *in vivo* (Horwitz *et al*, 2005). For both of these cell populations, the acronym MSC may be used, as is the current practice. Therefore, it is crucial that future publications clearly define the acronym that they are describing. The studies reported in this review are derived from experiments using multipotent mesenchymal stromal cells (MSC). It is not the goal of this review to report on the use of MSC from other oral tissues in tissue regeneration. Such MSC populations are from the human exfoliated deciduous teeth (Miura *et al*, 2003), dental pulp (Gronthos *et al*, 2000), and periodontal ligament (Seo *et al*, 2004; Ivanovski *et al*, 2006). These post-natal stem cells have common characteristics with bone marrow MSC in addition to be readily accessible in the oral cavity.

Cell-based therapies for tissue regeneration

Cell encapsulation is an intervention in cell-based regenerative medicine. In brief, cells are delivered to a donor with the goal of improving the regeneration process. Initial reports in the 1970s by WT Green, a pediatric orthopedic surgeon, demonstrated that implanted

Table 1 Reports describing bone marrow stem cells evolving into orofacial tissues

Origin	*Differentiated tissues*	*Reference*
MSC	Periodontium	Kawaguchi *et al* (2004, 2005)
MSC	Condyle	Abukawa *et al* (2003)
MSC	Dental implant	Yamada *et al*, 2004a,b
BM or MSC	Bone	Abukawa *et al* (2004), Warnke *et al* (2004), De Kok *et al* (2005)
BM	Tooth	Ohazama *et al* (2004)
BM or HSC	Buccal mucosa	Tran *et al* (2003), Metaxas *et al* (2005)

BM, bone marrow stem cells; HSC, hematopoietic stem cells; MSC, multipotent mesenchymal stromal cells.

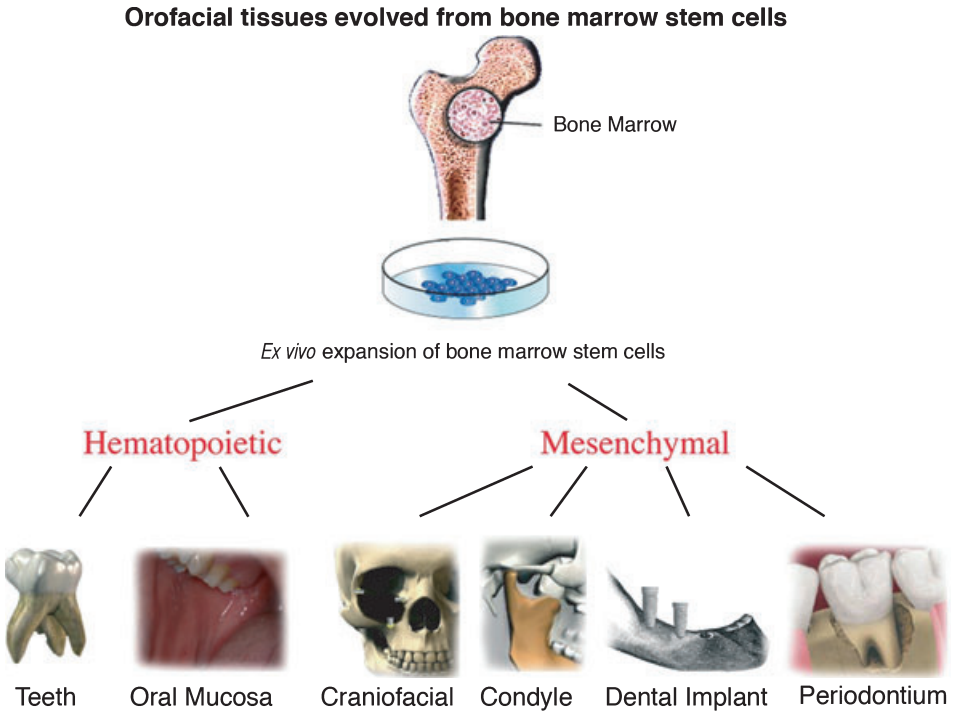

Figure 1 Oral tissues that evolved from bone marrow cells

spicules of bone and cartilage seeded with chondrocytes into animals could generate new cartilage (Green, 1977). Today, the two common methods of cell delivery are intravenous injections (direct delivery of cells) and cell encapsulation systems (indirect delivery of cells using a carrier). The cell encapsulation approach uses a biodegradable material, which is a biocompatible product that is gradually resorbed once implanted in the body, due to enzymatic or hydrolytic degradation. This biodegradable construct is seeded with cells (ideally progenitor cells) and is implanted into defects in order to regenerate lost tissues (Fuchs *et al*, 2005). Bone marrow-derived MSC have a significant but highly variable self-renewal potential during *in vitro* experiments and this property has made them attractive as a source for cell-based therapies aiming at the regeneration of orofacial tissues, especially when the size of the lost tissue is large and that the body can no longer repair this defect (Colter *et al*, 2000; Caplan and Bruder, 2001). Future advancements in stem cell research (either embryonic or post-natal) and in biomaterial science will allow cell encapsulation methods to be utilized in the clinic to regenerate both hard and soft tissues of the craniofacial complex.

Periodontium

Periodontal diseases are highly prevalent worldwide and the main signs are bone tissue destruction and subsequent tooth loss. Regenerating the periodontium has always been a high priority in craniofacial regenerative biology. Due to the complex structure of the periodontium (consisting of hard and soft tissues: cementum, bone, periodontal ligament, and gingiva), its complete regeneration would require a multipotent cell population (Bartold *et al*, 2000; Grezesik and Narayanan, 2002). Kawaguchi *et al* (2004) demonstrated that transplantations of *ex vivo* expanded autologous MSC can regenerate new cementum, alveolar bone, and periodontal ligament in class III periodontal defects in dogs. Morphometric analysis revealed a 20% increase in new cementum length and bone area in animals treated with MSC. In a subsequent study the same group reported a similar approach in humans (Kawaguchi *et al*, 2005) when they transplanted 2×10^7 cells ml^{-1} autologous expanded bone marrow-derived MSC mixed with Atelocollagen into periodontal osseous defects. All patients showed a significant improvement.

Dental implant

A sound and mature bone is an essential factor to achieve successful osseointegration of dental and facial implants. Very frequently, the quality and quantity of the remaining bone (that was destroyed because of trauma or diseases such as an enucleated tumor) are not suitable to allow a complete osseointegration of these implants. In a canine model, Yamada *et al* (2004a) extracted premolars and first molars. After 1 month of healing, they created four 10-mm diameter defects on each side of the mandible. These surgically created defects were filled with (1) platelet-rich plasma (PRP), (2) autologous MSC and PRP (MSC/PRP), (3) autologous particulate cancellous bone and marrow (PCBM), or (4) empty (control defect). After 8 weeks, dental implants were placed in the healed defects. The authors hypothesized that the presence of MSC in the surgical site would enhance wound healing and osseointegration. Higher marginal bone levels were recorded on dental

implants placed in MSC/PRP- or PCBM-filled defects when compared with control defects. Bone-implant contact was significantly increased in MSC/PRP and PCBM groups. Histologic results showed a well-formed lamellar and woven bone and new vascularization around dental implants of the MSC/PRP group. However, PCBM-filled defects exhibited bone resorption. In a similar study, Yamada *et al* (2004b) tested the application of an autologous 'scaffold' for delivering MSC to the surgical site. Using the same study design, they monitored the quality of regenerated bone in each defect. The MSC/PRP and PCBM groups showed a substantial increase in mature regenerated bone tissue. Their findings suggest that the insoluble gel generated from mixing PRP and thrombin–calcium chloride can be a clinically feasible method to deliver MSC to the surgical sites. Other studies have combined progenitor cells with different growth factors such as bone morphogenetic proteins (although not in the orofacial area; Kataoka and Urist, 1993; Higuera *et al*, 2005) or enamel matrix proteins (Murai *et al*, 2005). These growth factors promoted tissue regeneration but the exact role of the MSC alone remains unknown.

Mandible

Autologous bone grafts have been a 'gold standard' in craniofacial reconstruction. However, donor site morbidity and a limited quantity/supply are still substantial hurdles with this method. Bone tissue engineering can fully replace lost bone tissues through the use of three-dimensional biodegradable scaffold materials carrying osseous progenitor cells and bioactive agents (growth factors, hormones, etc.). Abukawa *et al* (2004) used scaffolds to reconstruct bony defects in pig mandibles. They seeded MSC into a biodegradable polymer and incubated for 10 days. Complete bone growth was observed in the experimental group. De Kok *et al* (2005) studied the safety and potential efficacy of utilizing MSC for alveolar bone repair in beagle dogs. They showed that bone marrow MSC seeded on either hydroxyapetite/tricalcium phosphate biomaterials or not can increase bone formation in dental sockets. Improvements in cell encapsulation techniques along with new generations of smart biodegradable scaffolds (Simon *et al*, 2004) will lead to the reconstruction of new and well-differentiated bone.

Human mandibles with major discontinuity defects (more than 5 cm) caused by an ablative tumor surgery can be repaired with autologous vascularized fibula, scapula, iliac crest, or rib bone grafts. However, this approach may create skeletal defects at the donor site which can be associated with serious morbidity. Warnke *et al* (2004) reported the fabrication of a mandibular transplant for a patient who had a large resection of his mandible (from the left paramedian region to the right retromolar region). The transplant was made of a titanium mesh cage filled with bone mineral blocks that were infiltrated with a combination of the patient's own iliac bone marrow and recombinant human bone morphogenetic protein-7. The transplant was implanted into the right latissimus dorsi muscle of the patient for 7 weeks. The skeletal scintigraphy showed bone remodeling and mineralization inside the mandibular transplant both before and after transplantation. Computed tomography provided an evidence of new bone formation. Seven weeks post-transplantation, the transplant was excised with an adjoining part of the latissimus dorsi muscle containing the thoracodorsal artery and vein that had supplied blood for the entire transplant, and transplanted to repair the mandibular defect. The patient had an improved degree of mastication and was satisfied with the esthetic outcome.

Condyle

The cartilaginous and osseous structures of the temporomandibular joint (TMJ) can deteriorate because of injuries, rheumatoid arthritis, and osteoarthritis. Tissue engineering of the TMJ can overcome drawbacks of joint replacement such as immunologic rejection, donor site morbidity, transmission of pathogens, or metal loosening. Abukawa *et al* (2003) fabricated a model of porcine mandibular condyle using porous biodegradable polymer scaffolds. The authors encapsulated differentiated osteoblasts (originating from cultured minipig bone marrow-derived MSC) into polymer scaffolds and incubated the construct in an oxygen-permeable bioreactor system for 6 weeks. Histologic observations revealed uniform new bone formation and densely stained osteoid and osteocytes in lacunae surrounded by bone matrix in deeper layers. Radiographic assessment revealed higher radiodensity of the construct when compared with the control scaffold but lower density than the control minipig cadaver condyle. Alhadlaq *et al* (2004) designed a bi-layer model to engineer cartilage and bone of the mandibular condyle. They harvested rat bone marrow-derived MSC and differentiated them into chondrocytes and osteocytes *ex vivo*. Chondrocytes and osteocytes were then seeded in a two-layer biocompatible poly (ethylene glycol)-based hydrogel. The construct was implanted in the subcutaneous dorsal pockets of immunodeficient mice. Histologic observations of the harvested constructs showed stratified layers of chondrogenesis and osteogenesis.

Tooth

Ohazama *et al* (2004) reported significant progress toward the creation of tissue-engineered embryonic tooth primordia (tooth buds) using cultured cells. In a mouse model, they tested different mixtures of non-dental-derived mesenchymal cells (embryonic stem cells, neural stem cells, and adult bone marrow cells) with embryonic oral epithelium cells. These mesenchymal–epithelial mixtures were transplanted into the renal capsules of adult mice. All mixtures resulted in the development of a tooth structure and bone. They observed that the host tissues make no contribution to the donor tissue. Moreover, transfer of embryonic tooth primordia into the adult jaw resulted in the development of tooth structures, showing that an embryonic

primordium can develop in its adult environment. They concluded that bone marrow-derived cells can form all mesenchymal-derived cells in a tooth structure. *In vitro* control of the shape of the tissue-engineered dental primordia will be a crucial step to bring this therapy to the clinic (Modino and Sharpe, 2005).

Oral mucosa

Tran *et al* (2003) reported an example of transdifferentiation of human bone marrow-derived stem cells into buccal epithelial cells. Using fluorescence *in situ* hybridization and immunohistochemistry, they identified Y-chromosome-positive buccal cells in five female patients who had received either a bone marrow transplant or an allogenic mobilized peripheral blood stem cell transplant from male donors. Y-chromosome-positive cells in these female patients were morphologically distinguishable as buccal epithelial cells and they also expressed cytokeratin 13, a recognized epithelial marker located in the superficial layer of the cheek. These results were confirmed by Metaxas *et al* (2005) who reported the presence of 1.8% donor-derived buccal epithelial cells in cheek scrapings of 12 of the 13 female patients who received a male-to-female hematopoietic cell transplantation 56 to 1964 days ago. The cheek scrapings were made when no oral mucositis or oral graft-*vs*-host disease was present. The donor-derived buccal epithelial cells were identified by epithelial morphologic characteristics, cytokeratin expression, positive Y-chromosome, and negative CD45 (blood lineage marker).

The plasticity of adult bone marrow-derived cells has been questioned by studies suggesting that fusion between donor and host cells gave the appearance of transdifferentiation (Terada *et al*, 2002; Ying *et al*, 2002). However, *in vivo* studies (Tran *et al*, 2003; Metaxas *et al*, 2005) did not observe cell fusion. Tran *et al* (2003) examined more than 9700 buccal cells and reported no evidence of fusion. These findings were also confirmed in the study by Metaxas *et al* (2005) who reported that none of the buccal cells examined had more than one X-chromosome, which excludes fusion as the answer to cell plasticity.

Summary

In this review we have discussed studies reporting successful applications of bone marrow stem cells to reconstruct different craniofacial tissues such as the periodontal ligament, cementum, bone, condyle, tooth, and oral mucosa. Plasticity of adult stem cell is controversial and more research is needed before any safe implementation of these cell-based therapies can be utilized in the clinic.

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