Guest Editorial

In situ vasculogenesis: The potential role of mesenchymal stem cells in craniofacial reconstruction

Many years ago, UCLA orthopedic surgeon Marshall Urist, working on what became recombinant human bone morphogenetic protein 2 (rhBMP-2), envisioned that rhBMP-2 would be destined to bring the control of bone formation into the hands of spine surgeons. His student, Phil Boyne at Loma Linda University extended the use of rhBMP-2 forward in membranous bone defects, the mechanism being a stimulation of periosteal stem cells into an osteogenic lineage. In 2001, an unusual case of multiple facial clefts accompanied by a unilateral absence of the ramus and condyle 2001 was treated by this author and Dr. Martin Chin at the Children's Hospital of Northern California with an implant of rhBMP-2 under Food and Drug Administration approval for compassionate use. The defect was successfully reconstructed; we termed the process *in situ* osteogenesis (ISO) and reported the case in 2005.[1,2] The characteristics of ISO – generated bone were further defined when the operative site was re-explored, osteotomized, and distracted.[3] Larger defects of craniofacial bone have been subsequently reconstructed using ISO.[4]

Full scale implementation of rhBMP-2 in maxillofacial surgery and periodontology (for alveolar ridge augmentation and sinus lift) remained elusive, in part due to the expense of the recombination technology involved. Nonetheless, many lessons remained. First, use of rhBMP-2 implants was accompanied by a rapid vascular response. This is not surprising, given that craniofacial periosteum is derived from neural crest, given that mesenchymal stem cells (MSCs) are related to neural crest and given that MSCs produce vascular endothelial growth factor.[5,6] Second, scars formed in soft tissues overlying these implants were difficult to notice, with little inflammation; this is attributable to the anti-inflammatory properties of MSCs *in vivo*. Third, overlying soft tissues were softer than anticipated; this again is due to the anti-fibrotic properties of MSCs. I came to the conclusion that the effectiveness of rhBMP-2 to create bone was utterly dependent upon the presence of responder MSCs in adequate numbers; furthermore that the soft tissue response seen was due to the paracrine effect of bioactive factors produced by MSCs.[7]

Implantation of MSCs is now a clinical reality.[8,9] MSCs have been shown to occupy a perivascular niche; their cell of origin being the ubiquitous pericyte, perhaps the most important and least understood cell in developmental biology.[10] The pericyte is structurally and chemically related to neural crest; these cells have contractile fibers and are under the control of the sympathetic autonomic nervous system, a system embryologically derived exclusively from the neural crest. Molecular markers on the cell membranes of MSCs called the cluster of differentiation markers (CD) demonstrate the relationship between MSCs and pericytes.[11]

The existence of MSCs in adipose tissue was first reported by Zuk *et al*. in 2001.[12] These cells are essentially identical with those residing in bone marrow, save for their difference in number, adipose-derived stem cells (ASCs) being ×500 more common than bone marrow MSCs. The putative cell leading to the development of white fat is the pericyte – brown fat originates from paraxial mesoderm – and this may explain this phenomenon. The biology of stem cells.

Contemporary technology permits the collection of ASCs in large numbers via conventional liposuction plus enzymatic digestion using collagenases followed by centrifugation.[13] New techniques for the nonenzymatic processing of fat using mechanical disruption have been developed; these will be coming online in the near future as well. When ASCs are processed by current means, they form a part of the so-called stromal vascular fraction (SVF) in combination with pericytes, fibroblasts, and endothelial precursor cells. When SVF is transplanted autologously, it has the following major characteristics: (1) Vascular induction, (2) anti-fibrosis, (3) anti-inflammation, (4) anti-microbial through novel mechanisms, (5) production of multiple paracrine factors, (6) a cell-saving or anti-apoptotic effect, and (7) regenerative effect with MSCs potentially responding to differentiation cues from

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the local environment to develop a given cell line, that is, when implanted into a tendon injury to form tenocytes.

In craniomaxillofacial surgery, the implantation of adipose-derived MSCs lends itself readily to a diverse number of problems. The vascular induction capability combined with an osseous framework could lend itself to bone reconstruction such as alveolar ridge augmentation, sinus lift, protection of failing implants, mandible/craniofacial defects, nonunion, and osteoradionecrosis. Temporomandibular joint problems could benefit from the reduction of existing fibrosis, the prevention of fibrosis in primary surgery, and possibly the regeneration of the disc itself. Finally, the paracrine effects of MSCs on soft tissues can provide for *in situ* revascularization both for the preparation of flaps prior to transfer as well as to flap salvage in cases of ischemia or swelling.

From this perspective, the possibilities for further dental research into the effects of MSCs, be they from fat or bone marrow, are very real, very do-able, involve relatively low levels of technology, and are inexpensive. The payoff from such research efforts is destined to bring the control of soft tissues and bone into the hands of clinicians with untold benefits for patients in the future.

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Conflict of interest
There are no conflict of interest.

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