Oral Stem Cells: The Fountain of Youth for Epithelialization and Wound Therapy?

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Significance: The oral cavity represents a novel source of a large number of stem cells.
Recent Advances: Stem cell populations have been identified in dental pulp, gingival epithelium, gingival lamina propria, and the periodontal ligament.
Critical Issues: The utility of using tissues of the oral cavity as a source of stem cells has been only partially explored. Much remains to be learned about the capability of these cells and the differences between cells derived from dissimilar oral locations.
Future Directions: The feasibility of using orally derived stem cells to support tissue regeneration and wound repair is a promising concept that requires additional investigation.

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Abbreviations and Acronyms

COMET = cultivated oral mucosal epithelial cell sheet transplantation
GMSC = gingiva-derived mesenchymal stem cells
hOMSC = human oral mesenchymal stem cells
PDL = periodontal ligament

INTRODUCTION

While Ponce de Leon never actually located the Fountain of Youth, recent studies suggest that we each contain a semblance of this enigmatic structure within our own oral cavity. Several studies and multiple patents now propose that the cells derived from the oral cavity might be important sources of cellular therapeutics for tissue regeneration, including wounds and epithelial restoration. The oral cavity is endowed with multiple rich sources of stem cells, including the mucosal soft tissues, the periodontal ligament (PDL), and the dental pulp, which is the vascularized and innervated tissue found deep within each tooth (Fig. 1). The potential of these cells to regenerate tissue has been explored for both dental and other tissues.[1,2]

DISCUSSION

Stem cells from the dental pulp

Stem cells within the dental pulp are rapidly gaining attention as pluripotent cells that are capable of differentiating into multiple lineages. While the regenerative capability of pulpal stem cells is only beginning to be fully appreciated, patients undergoing dental extractions, including wisdom teeth, can now elect to save and store these cells via commercial entities. Pluripotent stem cells can also be isolated from the pulp of shed deciduous (baby) teeth, a source that might be seen as ideal due to the ease of accessibility.[3] Given the relatively unknown clinical applications and cost, skeptics might reasonably wonder if present-day storage of pulpal stem cells should be discouraged until more is known. Others, of course, consider that the storage of dental pulp cells to be forward thinking and appropriate. Pulpal stem cells have been examined for several bioengineering and regenerative capacities both to regenerate structures found within the oral cavity and elsewhere.[2]

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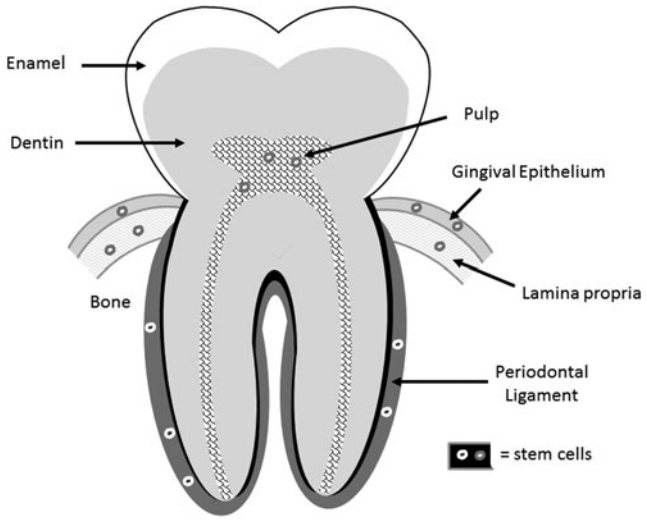

Figure 1. Schematic demonstrating the locations in oral tissue from which stem cells may be derived. Existing hard tissues are labeled on the left-hand side; soft tissues that serve as potential sources of stem cells are labeled on the right-hand side. Stem cells are shown within these tissues.

Stem cells from dental pulp may be useful both for the regeneration of soft tissue components such as those found in dental pulp itself, and for the regeneration of mineralized structures such as dentin and bone.

Stem cells from the oral mucosa

The stem cells found within the dental pulp represent an area of great excitement, yet the cells that are perhaps of most direct interest to the field of re-epithelialization are the abundant and robust epithelial progenitors in the oral mucosa. As compared to skin, oral mucosa is well described to be more highly proliferative, and the concept that oral epithelium has a higher turnover rate than that of skin is well accepted. Another critical difference is the lack of hair follicles and sweat glands. The limited adnexal appendages in oral mucosa suggest that oral mucosa may undergo repair using a more restricted source of progenitors than what has been described in skin. Indeed, multipotent cells that bear stem cell markers have been identified in both the epithelial and connective tissue compartments of gingiva.[4,5]

The lamina propria, which is the connective tissue layer of oral mucosa, harbors a unique stem cell population with multipotency. These unique cells, termed human Oral mesenchymal stem cells (hOMSC), can be readily isolated from small amounts of tissue and have been described to have a primitive neural crest-like phenotype. Compared with MSC from other tissues, hOMSC appear to have a relatively high, self-renewing capacity and cloning efficiency, and to produce growth factors that probably support this ability.[6] hOMSC can be induced to differentiate into the osteoblastic, chondroplastic, adipocytic, and neuronal lineages. Recent studies demonstrate that constructs possessing these oral mesenchymal stem cells can be induced to produce both bone and cementum (the outer mineralized tissue of the tooth root). Importantly, the utility of treating wounds with oral gingival-derived mesenchymal stem cells (GMSCs), again derived from gingival connective tissue, has recently been demonstrated. The systemic infusion of GMSCs cells led to enhanced wound repair in a mouse model.[7] One mechanism by which GMSCs were suggested to improve repair is via the modulation of the inflammatory response, as GMSCs have been proposed to promote polarization of macrophages toward a regenerative phenotype.

Of importance to re-epithelialization, the basal epithelial layer of oral mucosa has also been shown to contain an epithelial progenitor population. Progenitor/stem cell populations have been isolated from oral epithelium using relative cell size fractionation. Such small-sized cells were shown to be stem cells by functional assays and their ability to regenerate an oral mucosal graft.[4] The number of progenitors in oral mucosa is sufficient to easily grow oral keratinocytes in culture, a fact that has been exploited to create constructs suitable for tissue replacement and regeneration. As of yet, the principal clinical advances in the utilization of oral keratinocytes for tissue regeneration have been in the area of corneal restoration. Recently, this technology has been tested as a human therapeutic. Epithelial sheets produced *in vitro* from keratinocytes derived from the oral mucosa (cultivated oral mucosal epithelial cell sheet transplantation, or COMET) have been transplanted into patients to successfully replace the damaged corneal epithelium and provide long-term improvement in visual acuity.[8] While limbal cells can also be employed to create epithelium to replace damaged corneas, limbal cells may be limited in quantity and in severe cases of ocular damage, completely unavailable. In contrast, the gingival material can nearly always be easily obtained and oral epithelial progenitors can be acquired in comparatively large quantities.

Stem cells from the PDL

Another oral source of stem cells is the PDL, which is the structure that attaches the tooth to the

bony socket. Cells with stem-like properties have been isolated from the PDL; these cells have many properties that are similar to bone marrow stem cells. PDL cells have a self-renewing capacity and the ability to differentiate *in vitro* into multiple lineages, including osteoblasts, adipocytes, chondrocytes, and neurocytes.[9] Recent studies have focused primarily on the utilization of these cells to regenerate oral tissues, including cementum and the PDL itself.

CONCLUSIONS

The utilization of mesenchymal stem cells for the treatment of poorly healing and large wounds is a hot topical area with many promising results.[10] Given that the oral cavity has now been shown to be a rich source of both MSCs and epithelial progenitors, a detailed examination of the therapeutic potential of these populations for the treatment of wounds is needed. The utilization of oral MSC and/or epithelial progenitors in the treatment of skin wounds, especially cutaneous ulcers, may provide a promising new therapeutic approach.

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