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Review Article

Oral epithelial stem cells—Implications in normal development and cancer metastasis

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ABSTRACT

Oral mucosa is continuously exposed to environmental forces and has to be constantly renewed. Accordingly, the oral mucosa epithelium contains a large reservoir of epithelial stem cells necessary for tissue homeostasis. Despite considerable scientific advances in stem cell behavior in a number of tissues, fewer studies have been devoted to the stem cells in the oral epithelium. Most of oral mucosa stem cells studies are focused on identifying cancer stem cells (CSC) in oral squamous cell carcinomas (OSCCs) among other head and neck cancers. OSCCs are the most prevalent epithelial tumors of the head and neck region, marked by their aggressiveness and invasiveness. Due to their highly tumorigenic properties, it has been suggested that CSC may be the critical population of cancer cells in the development of OSCC metastasis. This review presents a brief overview of epithelium stem cells with implications in oral health, and the clinical implications of the CSC concept in OSCC metastatic dissemination.

Contents

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Introduction

Oral mucosa has a remarkable regenerative potential [1]. Several stem cells markers are known to be expressed, mainly in the basal layers of oral mucosa. It has been proven that the expression of these markers is dysregulated in oral squamous cell carcinomas (OSCC), the most common cancer of the oral cavity [2]. There is a need for a better characterization of the oral stem cells in particularly of their cell behavior, tissue-specific regenerative potential and involvement in carcinogenesis. This review provides an overview of stem cells biological implications in oral mucosa with a special emphasis in OSCC.

Oral mucosa

The epithelium on the inner surface of the lips, floor of the mouth, gingiva, cheeks and hard palate is derived from embryonic ectoderm, whereas the epithelium surrounding the tongue is derived from both endoderm and ectoderm [3–5]. The oral mucosa can be divided into: *masticatory* (hard palate and gingival), *specialized* (dorsal surface of the tongue) and *lining* (buccal mucosa, ventral surface of the tongue, soft palate, intra-oral surfaces of the lips and alveolar mucosa) [5]. Of the total surface of the oral lining, approximately 25% is keratinized resembling that of the epidermis covering the skin in regions subject to mechanical forces (masticatory mucosa of the gingiva and hard palate), 60% is the non-keratinized lining mucosa in the regions requiring flexibility to accommodate chewing, speech or swallowing (floor of the mouth, buccal regions, esophagus, etc.), with the remaining 15% is the specialized mucosa (dorsum of the tongue) which can be represented as a mosaic of keratinized and non-keratinized epithelium [6]. Oral epithelium is a stratified squamous epithelium that consists in various layers: basal, spinous, granular and corneal layers for the keratinized area; basal, spinous, intermediate and superficial layers in the non-keratinized areas. The oral epithelium is in direct contact with an underlying, dense connective tissue (*lamina propria*) containing minor salivary glands, structural fibers, blood vessels, fibroblasts along with other cell types [6–11]. Its histological structure involves undulations of epithelium (*rete ridges*) protruding downwards into the lamina propria, with corresponding upward projections of lamina propria (*dermal papillae*) and thus provides increased surface contact, which prevent separation of the oral epithelium from the underlying lamina propria during mastication [12].

The squamous epithelium covering the oral mucosa relies on epithelial stem cells for tissue renewal [1]. It is unanimously accepted that normal tissue stem cells constitute a life-long reservoir of cells with active mechanisms for self-renewal. Cell division in oral mucosa epithelial cells takes place mainly in the basal layer which contains the stem cells compartment from which the oral mucosa is being regenerated [7]. After dividing, the committed cells undergo differentiation that leads to the expression of structural keratin proteins as cells move superficially, and eventually fall off the surface. In the oral epithelium, it takes 14–24 days for a stem cell to divide and the progeny to traverse through the entire thickness of the epithelium (turnover time) [8]. Expression of several stem cells markers including, CD44, Bmi1, Sox2, Keratin 14, have been described mainly in the basal layer (Fig. 1, Table 1), suggesting that it may contain a reservoir of stem cells [5,9]. However, the mechanism of tissue maintenance and regeneration is still largely unknown for these cells. It is interesting to note that no many studies have focused on transient amplifying (TA) progenitor cells in the oral cavity and on their potential to provide a reservoir for would healing and homeostasis [2,5,8,14]. TA cells are slightly more differentiated than stem cells yet highly proliferative; they are derived from stem cells and continue to divide several times before undergoing terminal differentiation/maturation into the functional cells of the tissue; the size of the dividing transit population differs dramatically from tissue to tissue, the number of generations defining the degree of amplification that the transit population provides for each stem cells division seems to be related inversely to the frequency that stem cells will be found within the proliferating compartment [2,13].

Recent findings derived from various solid malignancies models show that cancer progenitor cells have the capacity to dedifferentiate and acquire a stem-like phenotype in response to either genetic manipulation or environmental cues, via implication of various complex molecular circuitries. These findings highlight the need for a better understanding of the dynamic, contextually regulated, equilibrium between cancer stem cells (CSCs) and cancer progenitor cells as a critical step for the development of therapeutic strategies to deplete tumors of their tumor-propagating and treatment-resistant cell subpopulations [14,15]. Better characterization of the CSCs and progenitor cells will contribute to a better understanding of normal and abnormal epithelial growth and tissues regeneration in the oral cavity.

Challenges to the integrity of the oral mucosa

The mucosal lining of the oral cavity is an environment challenged by a large variety of insults, and functions to protect the underlying tissues and organs against mechanical and chemical insults, including microorganisms and toxins, or ingested antigens and carcinogens [10]. The oral epithelium is constantly replaced