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EDITORIAL

Gingival-derived mesenchymal stem cells: An endless resource for regenerative dentistry

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Abstract

The gingiva, the masticatory portion of the oral mucosa, is excised and discarded frequently during routine dental treatments and following tooth extraction, dental crown lengthening, gingivectomy and periodontal surgeries. Subsequent to excision, healing eventually happens in a short time period after gingival surgery. Clinically, the gingival tissue can be collected very easily and, in the laboratory, it is also very easy to isolate gingival-derived mesenchymal stem cells (GMSCs) from this discarded gingival tissue. GMSCs, a stem cell population within the lamina propria of the gingival tissue, can be isolated from attached and free gingiva, inflamed gingival tissues, and from hyperplastic gingiva. Comparatively, they constitute more attractive alternatives to other dental-derived mesenchymal stem cells due to the availability and accessibility of gingival tissues. They have unique immunomodulatory functions and well-documented self-renewal and multipotent differentiation properties. They display positive signals for Stro-1, Oct-4 and SSEA-4 pluripotency-associated markers, with some co-expressing Oct4/Stro-1 or Oct-4/SSEA-4. They should be considered as the best stem cell source for cell-based therapies and regenerative dentistry. The clinical use of GMSCs for regenerative dentistry represents an attractive therapeutic modality. However, numerous biological and technical challenges need to be addressed prior to considering transplantation approaches of GMSCs as clinically realistic therapies for humans.

Key words: Gingival-derived mesenchymal stem cells; Regenerative dentistry; Lamina propria of the gingiva; Gingiva; Stem cell therapy

Core tip: Current therapeutic interventions in dentistry depend on biomaterials such as metals, polymers, ceramics, and composites. These restorative synthetic dental materials cannot restore the physiological architecture and function of the tissue. Thus, dentistry should move from restorative to regenerative dentistry, with the ability to regrow damaged or missing teeth with their own dental stem cells. Regenerating an entire tooth or individual parts of the tooth require a suitable number of specific stem cell populations for use and implantation. Considering their neural crest origin and ease of availability, gingival-derived mesenchymal stem cells should be considered as an attractive source for stem cells that can be used in regenerative dentistry.

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INTRODUCTION

New directions for biomaterials research in dentistry is focused mainly on two different aspects. The first field of investigation involves the use of existing technology, such as conventional dental materials with the use Polyethylene fiber (ribbond) and Panavia F cement to give additional strength to the reattached tooth fragment of vital maxillary anterior teeth and obtaining fracture resistance equal to an intact tooth[1]. This involves machineries that use the ER:Yag laser, which is a more conservative alternative to conventional acid-etching for aesthetic brackets[2]. The second field of investigation involves research about new features, such as biomimetic materials that use fiber reinforced composite and polyethylene fibers with nanohybrid composite as alternates to crown coverage for endodontically-treated molars[3]. In addition, computer-aided design/computer-aided manufacturing of customized devices is used to improve the standardization process in the evaluation of cell behavior on different biomaterials for *in vitro* research on biomedical scaffolds[4]. Furthermore, nanomaterials with the use of nanofillers are used to improve the mechanical properties of fiber-reinforced composites that are polymerized with light-curing and additional postcuring[5]. Lastly, stem cells are also used as a source for regenerative therapies in dental research and practice[6].

Gingiva is the band from the masticatory mucosal tissue that encircles the necks of erupted teeth, and is considered as one of the constituents of the periodontium. Anatomically, the gingiva is divided into free, attached and interdental areas. The attached gingiva is tightly bound to the cementum of the root and to the underlying periosteum of the maxillary and mandibular alveolar bone. Histologically, the gingiva is composed of stratified squamous epithelial tissue supported by a matrix of dense fibrous connective tissue stroma termed lamina propria. Developmentally, the connective tissue of the gingiva is derived from both the neural crest and the mesenchyme. In cranial regions, neural crest cells are thought to differentiate into a wide variety of ectomesenchymal and non-ectomesenchymal derivatives[7]. The formed ectomesenchyme plays a pivotal role in the formation of the soft and hard tissues of the head and neck region, such as the majority of facial connective tissues and the facial skeleton, while the non-ectomesenchymal derivatives consist of pigment cells, glia and neurons[8].

Consequently, stem cells have been recognized in different oral tissues, such as stem cells isolated from exfoliated deciduous teeth, bone marrow-derived stem cells isolated from orofacial bones, stem cells from the apical papilla and dental follicle, dental pulp stem cells isolated from dental pulp tissue, periodontal ligament stem cells, progenitor/stem cells from oral epithelium, periosteum-derived stem cells, salivary gland-derived stem cell and gingival-derived mesenchymal stem cells (GMSCs) from gingival lamina propria[9]. The gingiva represents the most accessible, abundant, conservative and minimally-invasive source for stem/progenitor cell isolation from the oral cavity[10]. GMSCs can be isolated from normal or inflamed gingiva, from the attached and free gingiva, and from hyperplastic gingiva. Periodontal lesions, albeit inflamed, retain healing potential as inferred by the presence of MSC-like cells with similar immunophenotypic characteristics to those found in healthy periodontal tissue[11]. These stem cells can be isolated through enzymatic digestion or explant culture, have the liability to differentiate into different mesenchymal lineages, and are also associated with immunomodulatory properties. Therapeutically, these cells were used for skin wound repair, tendon periodontal, and bone defect regeneration. They were also used to treat peri-implantitis, oral mucositis, experimental colitis, collagen-induced arthritis, and contact hypersensitivity. In addition, they also are known to have antitumor effects[12].

STUDY ANALYSIS

Our study, along with others, have launched the earliest appraisal on GMSCs and carried out several biological research investigations. In the head and neck region, GMSCs can be used as the cellular components for 3D bio-printing of scaffold-free nerve constructs to meet the increasing clinical demand for peripheral nerve repair and regeneration[13]. They could also be used as a strategy to treat accidental or surgery trauma, especially for cranial bones[14], as well as to treat gingival defects with a safe and effective innovative treatment method[15]. They also may help ameliorate the regeneration of partially-dissected submandibular salivary gland, especially when combined with fibrin glue[16], and have shown significant potential for periodontal tissue regeneration[17]. Although neither full nor partial biological tooth regeneration has been achievable, emerging opportunities in stem cell therapy may shift the paradigm in the future. The quality of stem cells is extremely important, as cells obtained from younger patients are of exceptionally higher value *vs.* older ones. In addition, their differentiation capacity, accessibility and possible immunomodulatory properties should be considered. Most of the regenerative studies have been done *in vitro* or in animal models, and data from human clinical research remains scarce. The successful application of stem cells in the clinical practice of dentistry remains an elusive and challenging objective.

PERSPECTIVE

Mesenchymal stem cells from adult gingival mucosa retain unique features, including multipotent differentiation capacity, neural crest origin, potent immunemodulatory properties, and fetal-like phenotypes. These features, with their ease of availability, noninvasive access to gingival tissue, and fast tissue regeneration after gingival excision, make gingiva a fascinating source for cell isolation and regenerative dentistry. These cells are attractive to treat diseases like dental caries and periodontitis, or to improve the regeneration of craniofacial bone[6]. In contrast to bone marrow-derived mesenchymal stem cells, these cells are more closely related to dental tissues. To achieve this goal, experimental animal studies should be accomplished to ensure the ability of these cells to form such dental structures. This step should then be followed up with clinical trials that involve an adequate population number.

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