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

Grawish ME.GMSCs 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 for the availability and accessibility of the 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 a clinical reality in humans.

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

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**Core tip:** Current therapeutic interventions in dentistry are basically depends on biomaterials such as metals, polymers, ceramics, and composites. These restorative synthetic dental materials can't restore the tissues’ physiological architecture and function. 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. Gingival-derived mesenchymal stem cells with their neural crest origin and with the ease of availability they should be considered as an attractive source for stem cells that can be used in regenerative dentistry.

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**INTRODUCTION**

The 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] or machineries with the use of ER:Yag laser as a more conservative alternative to conventional acid-etching for aesthetic brackets[2]. The second field of investigation involves the research about new features, such as biomimetic materials with the use of fiber reinforced composite and polyethylene fibers with nanohybrid composite as alternates to crown coverage for endodontically treated molars[3], Computer aided design /computer aided manufacturing customized devices to improve the standardization process in the evaluation of cell behavior on different biomaterials for the *in vitro* research on biomedical scaffolds[4], nanomaterials with the use of nanofillers to improve the mechanical properties of fiber-reinforced composites polymerized with light-curing and additional postcuring[5] and the use of stem cells as a source for regenerative therapies in dental research and practice[6].

Gingiva is the band from the masticatory mucosal tissue encircling the necks of erupted teeth, 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 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 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 cells' isolation from the oral cavity[10]. GMSCs can be isolated from normal or inflamed gingiva, from the attached and free gingiva as well as 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 and they have the liability to differentiate towards different mesenchymal lineages and they are also associated with immunomodulatory properties. Therapeutically, these cells were used for skin wound repair, tendon periodontal, and bone defects regeneration, for the treatment of peri-implantitis, oral mucositis, experimental colitis, collagen-induced arthritis and contact hypersensitivity and in addition it has antitumor effect[12].

**STUDY ANALYSIS**

Our and other studies have launched the earliest appraisal on GMSCs and carried out a lot of biological researches. In the head and neck region, GMSCs can be used as the cellular components for 3D bio-printing scaffold-free nerve constructs to meet the increasing clinical demand for peripheral nerve repair and regeneration[13], could be a promising strategy in the treatment of accidental or surgery trauma, especially for cranial bones[14], treating gingival defects with a safe and effective innovative treatment method[15], ameliorates the regeneration of partially dissected submandibular salivary gland especially when combined with fibrin glue[16], showed significant potential for periodontal tissue regeneration[17]. Although biological tooth regeneration as a whole or as apart is not yet achievable but emerging opportunities in stem cell therapy may shift the paradigm in future. The quality of stem cells is extremely important as cells obtained from younger patients are exceptionally of high value than older ones. In addition, the 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 evidences in human clinical research are still scanty. The successful application 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 immune-modulatory properties and fetal like phenotype. These features with the ease of availability, noninvasive access to gingival tissue, 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, periodontitis or to improve regeneration of craniofacial bone[6]. These cells in contrast to bone-marrow-derived mesenchymal stem cells are more closely related to dental tissues. To obtain this goal, experimental animal studies should be accomplished to assure the ability of these cells to form such dental structures and this step should be followed by clinical trials with adequate population number.

**REFERENCES**

1 **Hiremath H**, Kulkarni S, Saikalyan S, Chordhiya R. Use of ribbond and panavia F cement in reattaching fractured tooth fragments of vital maxillary anterior teeth. *Contemp Clin Dent* 2012; **3**: 478-480 [PMID: 23633814 DOI: 10.4103/0976-237X.107446]

2 **Sfondrini MF**, Calderoni G, Vitale MC, Gandini P, Scribante A. Is laser conditioning a valid alternative to conventional etching for aesthetic brackets? *Eur J Paediatr Dent* 2018; **19**: 61-66 [PMID: 29569456 DOI: 10.23804/ejpd.2018.19.01.11]

3 **Hiremath H**, Kulkarni S, Hiremath V, Kotipalli M. Evaluation of different fibers and biodentine as alternates to crown coverage for endodontically treated molars: An in vitro study. *J Conserv Dent* 2017; **20**: 72-75 [PMID: 28855750 DOI: 10.4103/0972-0707.212248]

4 **Marrelli M**, Pujia A, Palmieri F, Gatto R, Falisi G, Gargari M, Caruso S, Apicella D, Rastelli C, Nardi GM, Paduano F, Tatullo M. Innovative approach for the in vitro research on biomedical scaffolds designed and customized with CAD-CAM technology. *Int J Immunopathol Pharmacol* 2016; **29**: 778-783 [PMID: 27106276 DOI: 10.1177/0394632016646121]

5 **Scribante A**, Massironi S, Pieraccini G, Vallittu P, Lassila L, Sfondrini MF, Gandini P. Effects of nanofillers on mechanical properties of fiber-reinforced composites polymerized with light-curing and additional postcuring. *J Appl Biomater Funct Mater* 2015; **13**: e296-e299 [PMID: 26108426 DOI: 10.5301/jabfm.5000226]

6 **Aly LA**. Stem cells: Sources, and regenerative therapies in dental research and practice. *World J Stem Cells* 2015; **7**: 1047-1053 [PMID: 26328020 DOI: 10.4252/wjsc.v7.i7.1047]

7 **Cho MI**, Garant PR. Development and general structure of the periodontium. *Periodontol 2000* 2000; **24**: 9-27 [PMID: 11276876 DOI: 10.1034/j.1600-0757.2000.2240102.x]

8 **Cordero DR**, Brugmann S, Chu Y, Bajpai R, Jame M, Helms JA. Cranial neural crest cells on the move: their roles in craniofacial development. *Am J Med Genet A* 2011; **155A**: 270-279 [PMID: 21271641 DOI: 10.1002/ajmg.a.33702]

9 **Ercal P**, Pekozer GG, Kose GT. Dental Stem Cells in Bone Tissue Engineering: Current Overview and Challenges. *Adv Exp Med Biol* 2018; 1-15 [PMID: 29498025 DOI: 10.1007/5584\_2018\_171]

10 **Fawzy El-Sayed KM**, Dörfer C, Fändrich F, Gieseler F, Moustafa MH, Ungefroren H. Adult mesenchymal stem cells explored in the dental field. *Adv Biochem Eng Biotechnol* 2013; **130**: 89-103 [PMID: 22936399 DOI: 10.1007/10\_2012\_151]

11 **Apatzidou DA**, Nile C, Bakopoulou A, Konstantinidis A, Lappin DF. Stem cell-like populations and immunoregulatory molecules in periodontal granulation tissue. *J Periodontal Res* 2018 [PMID: 29687448 DOI: 10.1111/jre.12551]

12 **Fawzy El-Sayed KM**, Dörfer CE. Gingival Mesenchymal Stem/Progenitor Cells: A Unique Tissue Engineering Gem. *Stem Cells Int* 2016; **2016**: 7154327 [PMID: 27313628 DOI: 10.1155/2016/7154327]

13 **Zhang Q**, Nguyen PD, Shi S, Burrell JC, Cullen DK, Le AD. 3D bio-printed scaffold-free nerve constructs with human gingiva-derived mesenchymal stem cells promote rat facial nerve regeneration. *Sci Rep* 2018; **8**: 6634 [PMID: 29700345 DOI: 10.1038/s41598-018-24888-w]

14 **Diomede F**, Gugliandolo A, Cardelli P, Merciaro I, Ettorre V, Traini T, Bedini R, Scionti D, Bramanti A, Nanci A, Caputi S, Fontana A, Mazzon E, Trubiani O. Three-dimensional printed PLA scaffold and human gingival stem cell-derived extracellular vesicles: a new tool for bone defect repair. *Stem Cell Res Ther* 2018; **9**: 104 [PMID: 29653587 DOI: 10.1186/s13287-018-0850-0]

15 **Li J**, Xu SQ, Zhang K, Zhang WJ, Liu HL, Xu Z, Li H, Lou JN, Ge LH, Xu BH. Treatment of gingival defects with gingival mesenchymal stem cells derived from human fetal gingival tissue in a rat model. *Stem Cell Res Ther* 2018; **9**: 27 [PMID: 29402326 DOI: 10.1186/s13287-017-0751-7]

16 **Abd El-Latif N**, Abdulrahman M, Helal M, Grawish ME. Regenerative capacity of allogenic gingival margin- derived stem cells with fibrin glue on albino rats' partially dissected submandibular salivary glands. *Arch Oral Biol* 2017; **82**: 302-309 [PMID: 28688332 DOI: 10.1016/j.archoralbio.2017.06.030]

17 **Fawzy El-Sayed KM**, Paris S, Becker ST, Neuschl M, De Buhr W, Sälzer S, Wulff A, Elrefai M, Darhous MS, El-Masry M, Wiltfang J, Dörfer CE. Periodontal regeneration employing gingival margin-derived stem/progenitor cells: an animal study. *J Clin Periodontol* 2012; **39**: 861-870 [PMID: 22694281 DOI: 10.1111/j.1600-051X.2012.01904.x]

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