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

Mohammed E Grawish

Gingival-derived mesenchymal stem cells (GMSCs) are a stem cell population within the lamina propria of the gingival tissue, which can be isolated from attached and free gingiva, inflamed gingival tissues, and from hyperplastic gingiva. Compared to other dental-derived mesenchymal stem cells, GMSCs are more easily accessible and available. 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

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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 implanta-
tion. 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 Pol-
yethylene fiber (ribbon) 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 ma-
chineryes that use the ER:Yag laser, which is a more
conservative alternative to conventional acid-etching
for aesthetic brackets[2]. The second field of investi-
gation involves research about new features, such as
biomimetic materials that use fiber reinforced composi-
tive 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 composi-
tive that are polymerized with light-curing and
additional postcuring or in animal models,

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[5].

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[6]. The gingiva
represents the most accessible, abundant, conserva-
tive and minimally-invasive source for stem/progeni-
tor cell isolation from the oral cavity[7]. GMSCs can be
isolated from normal or inflamed gingiva, from the atta-
ched 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[8]. 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 hypersensitivi-
ty. In addition, they are also known to have antitumor
effects[9].

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[10]. They could also be used as a strategy
to treat accidental or surgery trauma, especially for cranial
bones[11], as well as to treat gingival defects with a safe
and effective innovative treatment method[12]. They
also may help ameliorate the regeneration of partially-
dissected submandibular salivary gland, especially when
combined with fibrin glue[13], and have shown significant
potential for periodontal tissue regeneration[14]. 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 prop-
ties 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 immune-modulatory 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. 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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