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Distinct phenotype and therapeutic potential of gingival fibroblasts

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Abstract

Gingiva of the oral mucosa provides a practical source to isolate fibroblasts for therapeutic purposes because the tissue is easily accessible, tissue discards are common during routine clinical procedures and wound healing after biopsy is fast and results in complete wound regeneration with very little morbidity or scarring. In addition, gingival fibroblasts have unique traits, including neural crest origin, distinct gene expression and synthetic properties and potent immunomodulatory functions. These characteristics may provide advantages for certain therapeutic approaches over other more commonly used cells, including skin fibroblasts, both in intraoral and extra-oral sites. However, identity and phenotype of gingival fibroblasts, like other fibroblasts, are still not completely understood. Gingival fibroblasts are phenotypically heterogeneous, and these…fibroblast subpopulations may play different roles in tissue maintenance, regeneration and pathologies. The purpose of this review is to summarize what is currently known about gingival fibroblasts, their distinct potential for tissue regeneration and their potential therapeutic uses in the future.

Key Words: *fibroblast, gingiva, phenotype, therapy, tissue regeneration*

Introduction

Fibroblasts are the most abundant cells present in connective tissues, where they regulate tissue development, organogenesis, homeostasis and maintenance. They are also key cells in various physiological and pathological situations, including wound healing, inflammation, fibrosis and cancer (1–3). One of their primary functions is to deposit and remodel the extracellular matrix (ECM), which provides structural integrity for the tissues and creates the cellular microenvironment (niche) also for other cells, including vascular, inflammatory, epithelial and tissue-specific stem cells. This ECM niche guides and modulates the function of cells directly through receptor-ligand interactions, storing and releasing growth factors and transmitting mechanosensory signals (3). Fibroblasts also communicate with other cells by secreting growth factors and cytokines or releasing them from the ECM, and they develop cell-cell contacts with each other and other cells, creating complex cellular communication networks (Figure 1) (3). This versatility and relatively easy isolation and expansion in culture make fibroblasts an attractive source of cells for various cell-based therapeutic modalities. However, regardless of the wealth of information about the identity and function of fibroblasts in the literature to date, these cells still remain surprisingly poorly defined. There are no markers that are only present in fibroblasts that can be used to specifically identify them *in vivo* (4,5). Therefore, fibroblasts are still defined by morphological and functional criteria that are not unique to fibroblasts and are partially shared by other cells, including epithelial, inflammatory and vasculature-associated cells and tissue-specific stem cells (5–8). It is also evident that fibroblasts are a heterogeneous group of cells with distinct properties and functions. This may be in part because of the presence of different fibroblast-like cells, including myofibroblasts, fibrocytes, pericytes and mesenchymal stem cells (MSCs), in connective tissues and fibroblast cultures. In addition, fibroblasts may undergo changes related to aging and/or differentiation (9,10), or their phenotype is modulated by other factors, including developmental origin (eg, mesodermal versus neural crest origin) or the local tissue niche (4) (Figures 2, 3). Different methods to isolate

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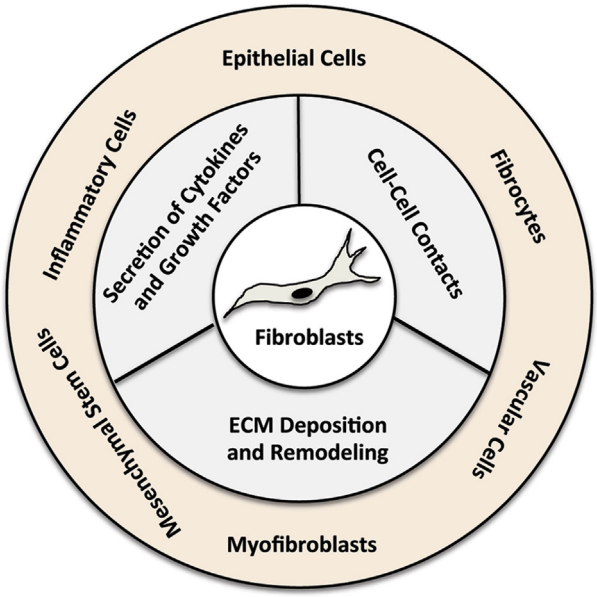

Figure 1. Schematic presentation of fibroblast functions and interactions with other cells. Key functions of fibroblasts include secretion of cytokines and growth factors, establishing cell-cell contacts with other cells and deposition and remodeling of the ECM. These functions create a specific tissue niche for fibroblasts and other cells in the tissue (epithelial cells, vascular cells, MSCs, inflammatory cells, myofibroblasts and fibrocytes). This tissue niche and reciprocal interactions of different cells with each other ultimately determine their phenotype, differentiation, function and fate.

and propagate cells from the tissue biopsy may also result in selection of functionally distinct fibroblast populations (4). Therefore, finding out the tissue-specific properties of fibroblasts and their subpopulations that support a specific therapeutic goal may help to improve current treatment modalities.

Specific features of gingiva in vivo

Several studies have indicated that fibroblasts from oral mucosal gingiva, although being functionally heterogeneous (Figure 2) (11–30), have in general a high regeneration potential, fetal-like phenotype and can regulate inflammation; thus they may have distinct therapeutic potential (see below). The distinct properties of gingival fibroblasts, among similar cells in other locations in the body, may depend on specific tissue anatomy and function, ECM niche, developmental origin or other factors present in gingiva. For example, whereas various oral tissues derive from the neural crest (31), they are not identical, and the structure and composition of the stratified squamous epithelium covering the oral cavity varies regionally. Sophisticated tissue and cell recombination experiments have shown that the oral epithelial phenotypes are determined by the underlying connective tissue and fibroblasts (32,33), which indicates that gingival fibroblasts and the connective tissue niche that they produce are functionally distinct.

Gingival connective tissue cells have also other specific functions in the oral cavity. Gingiva seals the interface between teeth and oral mucosa, actively participates in immune defense and is highly dynamic, having one of the fastest tissue turnover rates in body (34,35). One of the key characteristics of gingiva that relates to its possible utility in therapeutic applications is its wound-healing response. Experimental wounds created in the keratinized masticatory mucosa of the palate and gingiva resulted in a significantly reduced clinical and histological scar formation as compared with similar skin wounds that developed hypertrophy-like scars within 2 months (36–38). Although systematic research data are missing, clinical experience suggests that the scarless wound healing is a specific property of gingiva, because in oral lining mucosa scar formation after surgical procedures appears to be a more common clinical finding. Nevertheless, wound-healing speed is accelerated in both gingiva and other parts of the oral mucosa compared with that in skin (13,36–40). The reason for this preferential wound healing in oral mucosa is not completely understood but may depend on local factors. For example, saliva that bathes oral wounds contains molecules that promote wound healing, including growth factors (eg, transforming growth factor [TGF]-α, TGF-β, insulin-like growth factor, nerve growth factor, epidermal growth factor and fibroblast growth factor), histatins and secretory leukocyte protease inhibitor (41–45). Other local factors that may be involved include distinct mechanosignaling from the ECM to the cells. Mechanical signals transmitted from the ECM to the cells are powerful modulators of cell function. Skin contains an elastic, more loosely organized connective tissue, whereas the masticatory mucosa of the gingiva and hard palate contain a dense connective tissue that directly attaches to the underlying bone (46,47). This leads to a high tensile strength and stiffness of the gingiva that may accelerate cell migration and reduce wound contraction (48). At cellular and molecular levels, similar to that in fetal skin wounds that display fast and scarless wound healing, oral mucosal wounds have a mild and short inflammatory reaction that includes reduced recruitment of neutrophils, mast cells, macrophages and T cells. They also contain elevated levels of immunomodulatory and anti-fibrotic TGF-β3 relative to pro-fibrotic TGF-β1 as compared with similar skin wounds (13,36,39,40,49,50). Interestingly, accumulating evidence has suggested that the gingival wound-healing response may also depend on a distinct phenotype of gingival fibroblasts (11,13,38,51).