Fibroblast Heterogeneity And Its Implications

Monali Shah*, Ankit Patel, Sunit Patel***, Jalpesh Surani******

*Ahmadabad Dental College And Hospital, Gandhinagar, Gujarat, India -382115.

Abstract: After acute inflammation fibroblasts participate transiently in tissue repair by regulating the structure and function of healthy tissues. They also assume an aberrant stimulatory role during chronic inflammatory states including cancer. Heterogeneity of fibroblast applies to functional and phenotypic properties within or across tissues. Fibroblasts are heterogeneous with respect to functional properties, and that certain subpopulations of these cells may be clonally selected and expanded in diseased tissues. These pleiotropic functions highlight the inherent plasticity of fibroblasts and may provide new pathways to understand and therapeutically intervene in diseases.

[Monali S NJIRM 2016; 7(5):92-94]

Key Word: Fibroblast Heterogeneity And Its Implications

Author For Correspondence: Ankit Patel, Ahmedabad Dental College And Hospital,Gandhinagar,Gujarat, India - 382115 **Email:** ankit.patel68@yahoo.com

Introduction: Fibroblasts are the most abundant cell type within the connective tissues, and are the major source of the ECM. In different parts of the body fibroblasts arise from different embryonic origins like those in the face are derived from the neural crest, dorsal skin from the dermato-myotome, and ventral skin comes from the lateral plate mesoderm. Relative proportion of fibroblast subpopulations and tissue distribution has a great impact on the regulation of connective tissue function in health and disease.[1]

Role In Oral Wound Healing: In wound healing, specific subpopulation of circulating fibroblast-like cells enter the wound site from the vasculature. Oral mucosa appears to be a favorable site in the adult in that it tends to display a 'fetal like' pattern of regenerative and scar less wound healing. It produce different amounts of extracellular matrix components such as proteoglycans, collagens, and matrix metalloproteinases (MMPs); respond differently to inflammatory cytokines and drugs; and express different amounts of integrin-type surface-receptors thus they contribute to the formation of the Granulation tissue during chronic inflammation, wound healing, and certain pathological conditions.[2]

Fibroblast Heterogeneity In Pathogenesis Periodontal Disease Clonal Selection Hypothesis: Fibroblast-derived pro inflammatory mediators and cytokines such as PGE2, IL-1b, IL- 6, or IL-8 may be directly or indirectly responsible for periodontal tissue destruction by promoting fibrosis, granuloma formation or bone resorption. Irreversible changes have been observed in various phenotypic characteristics of fibroblasts which may be attributed to a positive selection process which results in the predominance of a certain subset (s) of fibroblasts with a unique proliferative and/or synthetic phenotype also known as clonal selection hypothesis.[3,4]

Phagocytosis: Under physiologic conditions, fibroblasts degrade the collagen matrix by which they are surrounded by a phagocytic pathway. [5]

Nitric Oxide Release: Van der Paw et al (2000) studied that fibroblasts respond to very weak forces with the release of Nitric oxide thus they has been proposed to play a role in tissue remodeling. Though the exert mechanism is not known, it might play a role in collagen phagocytosis. [6]

Collagen Remodeling & Collagen Synthesis: Recent studies shows that synthetic activity (total protein and collagenase digestible protein) of fibroblast conforms to the reported rapid turnover of collagen Effects of Mechanical Force Primary fibroblasts derived from human periodontium are more resistant to mechanical load. An identical pattern of mRNA encoded for MMPs and TIMPS was found in stretched human gingival and PDL fibroblasts. [7]

Fibroblast Heterogeneity Of Signal Transduction Mechanisms To Complement-C1q: C1q may play a role in compositional change of oral granulation tissues by regulating activities of specific fibroblast subsets. C1q accelerate fibroblast growth, shape, attachment, and movement. Recent observation show that the cC1qR and gC1qR fibroblast subsets responded to purified C1q with a differential generation of [Ca2+] signals that was coupled to a differential formation of IP3 and redistribution of cPKCs.[8]

Roll Of Fibroblast Heterogeneity In The Cancer: **Fibroblast as a tumor-inhibitor :** Stoker et al.

demonstrated that normal quiescent fibroblasts inhibit the growth of polyoma transformed cells by direct contact between the two cell types. Later it has been shown that normal tissue-associated fibroblasts (NAFs) isolated from different organs can inhibit the growth of neoplastic cells (Flaberg et al., 2011), because of the ability of fibroblasts to maintain epithelial homeostasis and proliferative quiescence. That is why certain tumors found in autopsy studies appear dormant and non progressing [9],[10],

Fibroblast as a tumor-promoter: Fibroblasts also acquire an aberrant stimulatory role during chronic inflammatory states including cancer. Such cancer-associated fibroblasts (CAFs) modulate the tumor microenvironment, modify tumor metabolism, remodel the ECM, trigger tumor initiation and progression, modulate the immune response, promote cancer cell migration and metastasis, and can also alter therapeutic responses.[11]

Thus the fibroblast can influence the behavior of neoplastic cells in both tumor-promoting or tumor-inhibiting manner.[12]

Fibroblast Heterogeneity And Its Implications For Engineering Organotypic Skin Models: Recent advances in cell culture methods, multidisciplinary research, clinical need to replace lost skin tissues have led to development of three dimensional models of human skin. Thus in vitro models of skin consist of keratinocytes cultured over fibroblast-populated dermal matrices. Collective evidences indicate that mesenchymal-derived signals are required for epidermal morphogenesis, homeostasis and differentiation. Various studies show that fibroblasts isolated from different tissues in the body are dynamic in nature and are morphologically and functionally heterogeneous subpopulations. Further, these differences seem to be dictated by the local biological and physical microenvironment the fibroblasts reside resulting in “posi-tional identity or memory”. Furthermore, the heterogeneity among the fibroblasts play a critical role in scar less wound healing and complete restoration of native tissue architecture in fetus and oral mucosa; and excessive scar formation in diseased states like keloids and hypertrophic scars.

In this review, we summarize current concepts about the heterogeneity among fibroblasts and their role in various physiological and pathological conditions. Further, we contemplate how the insights on fibroblast heterogeneity could be applied for the development of therapy of cancer and periodontal diseases and next generation organotypic skin models.[13]

References:

1. D. Öhlund, E. Elyada, and D. Tuveson. Fibroblast heterogeneity in the cancer wound..The Journal of Experimental Medicine 2014; 1503- 23
2. Archana1, Srikanth V,Sasireka, Kurien B, Ebenezer. Fibroblast Heterogeneity in Periodontium – a Review. International Journal of Dental Sciences and Research 2014; 2(3): 50-54.
3. Lekic PC, Pender N, McCulloch CA. Is fibroblast heterogeneity relevant to the health, diseases and treatments of periodontal tissues? Crit Rev Oral Biol Med.1997; 8: 253-68.
4. Irwin CR, Picardo M, Ellis I, Sloan P, Grey A, McGurk M, Schor SL. Inter- and intra-site heterogeneity in the expression of fetal-like phenotypic characteristics by gingival fibroblasts: potential significance for wound healing. J Cell Sci.1994; 107 (5):1333-46.
5. McCulloch CA, Bordin S. Role of fibroblast subpopulations in periodontal physiology and pathology. J Periodontal Res. 1991;26 (3):144-54.
6. McCulloch CA, Knowles G. Discrimination of two fibroblast progenitor populations in early explant cultures of hamster gingiva. Cell Tissue Res.1991;264 (1): 87-94.
7. Ko SD, Page RC, Narayanan AS. Fibroblast heterogeneity and prostaglandin regulation of subpopulations. Proc Natl Acad Sci U S A. 1977; 74 (8): 3429-32.
8. Hakkinen L, Larjava H. Characterization of fibroblast clones from periodontal granulation tissue in vitro. J Dent Res. 1992; 71 (12): 1901-7.
9. Barcellos-Hoff, M.H., and S.A. Ravani.. Irradiated mammary gland stroma promotes the expression of tumorigenic potential by un irradiated epithelial cells. Cancer Res. 60:1254–1260.
10. Gopu Srirama,1, Paul Lorenz Bigliardi a,b,c, Mei Bigliardi-Qi a, Fibroblast heterogeneity and its implications for engineering organotypic skin models in vitro. European Journal of Cell Biology.2015; 94: 483–512.
11. Hassell TM, Stanek EJ 3rd. Evidence that healthy human gingiva contains functionally heterogeneous fibroblast subpopulations. Arch Oral Biol. 1983; 28 (7): 617-25.

12. El Ghalbzouri et al. Fibroblasts facilitate re-epithelialization in wounded human skinequivalents. a journal of technical methods and pathology. 2004; 84:102–112.
13. Bordin S, Costa LG, Tan X. Fibroblast heterogeneity of signal transduction mechanisms to complement-C1q. Analyses of calcium mobilization, inositol phosphate accumulation, and protein kinases-C redistribution. J Periodontol. 1998; 69 (6): 642-9.

Conflict of interest: None
Funding: None
Cite this Article as: Monali S, Ankit P, Sunit P, Jalpesh S Fibroblast Heterogeneity And Its Implications. Natl J Integr Res Med 2016; 7(5): 92-94