

Biological and morphological characteristics of skin fibroblast cells; Current clinical status and future prospects- A review

Safar Ali Amiri Andi¹, Monireh Azizi², Ayoob Rostamzadeh³, Ardeshir Moayeri^{2*}

¹Department of Otolaryngology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran.

²Department of Anatomy, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran.

³Department of Anatomy and Neuroscience, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran.

*Address to corresponding author: Dr. Ardeshir Moayeri, Department of Anatomy, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran. Tel: +988462227136.

*Corresponding author: Email: moayeri46@medilam.ac.ir. Fax: +988432235713.

ABSTRACT

Cell therapy has a possibility to progress wound healing situations short of main surgical approaches and donor-site morbidity. Stem cell investigation has manage to pay for fresh understandings into contingency for organ re-formation . Some first step has been taken to determine stem cells which can cautilization a wholly matured derm. As an achievement, investigation schemes have attend on autologous adult derived stem cell medicine.

KEYWORDS: Fibroblast; Cellular therapy; Skin regeneration; Wound healing; Papilla; Hair follicle.

1. INTRODUCTION

Advantage of stem cell therapy: Each traditional improvement approach has interest and restriction (Slavin, 1998). Newly, the evolution of advanced lesion therapy mechanization has start the utilization of cells to vanquish restrictions of the traditional approaches. Cell therapy has a Possibility to meliorate lesion medicating states without main surgical methods and donor-site morbidity (Lindvall, 2004). Cell therapy could be utilized for both acute and chronic lesions. In the therapy of acute lesions, cell therapy can enhance lesion medicating speed, decrease scar contracture, and minimize donor-site morbidity. This method prepares for us a tissue that has a tendency to the surrounding derm, leaving minimal scars and color mismatch. Whereof the epidermal section can be reformed by epithelialization induced by the migration and proliferation of adjacent epidermal cells inclusive of melanocytes, the density and activity of melanocytes plus precursor melanocytes of the epidermis of the graft become similar to those observed in the adjacent derm. In the remedy of severe injuries, efforts are make up to change the lesion bed to the environment where ultimate lesion medicating can be get by transplanting cells with best wound healing capacity to the wound bed (Asadbegi, 2016, Martin, 1997). Defective cure of cutaneous lesions damage derm role and form owing to scar creation, ulceration that prepare to subsidiary infection, affliction, or bodily changes that intervene with usual obstacle role (Vahabi, 2013, Sayyadi, 2013, Martin, 1997). Modulus ways to promote wound healing may speed re-epithelialization but derm function is often compromised. A recent method to develop common treatment and derm recreation is to change the lesion environs by presenting human cells into the lesion or lesion margin.

A main cellular factor of the dermal layer of derm is the fibroblast. Fibroblasts are inhabitant mesenchymal cells in the dermis that generate collagen and other extracellular matrix proteins. Fibroblasts are noted to have a serious function in derm structure and totality, and cultured autologous dermal fibroblasts are trusted to develop derm recreation and rejuvenation. In the meantime, improvement in the utilization of other cell forms for derm recreation for example keratinocytes, endothelial cells, bone-marrow derived mesenchymal cells, induced pluripotent stem cells, genetically modified fibroblasts, allogeneic cells, and derm substitutes, the point of this work is the utilization of autologous fibroblasts in derm directed Healing. The phrase fibroblast encircle cells with changeable properties observed in derm and other organs. The derm alone has many subtypes with unique properties. Raising perception of variant fibroblast sub-populations has been operated in the improvement of recent treatments created for derm rejuvenation via collagen production. Additionally, there is emerging work to offer that fibroblasts have the capability to “reschedule” the derm for the aim of derm rejuvenation in aging derm. The prior section of this work brief the roles of fibroblasts in typical lesion healing and describes the therapeutic utilization s of fibroblasts in derm regeneration. In the second part, we explore regional and microanatomic properties of fibroblasts for altering derm phenotype (Montagna and Lobitz, 2013).

Papillary and reticular dermal fibroblasts: The papillary dermis is approximately 300-400 mm deep that is variable and depends upon such factors as age and anatomical location. Typically, the superficial portion of the papillary dermis is divided into ridge-like structures, the dermal papillae, which contain microvascular and neuronal parts that withstand the epidermis (Cormack, 1987). Dermal papillae markedly develop the superficial region for epithelial mesenchymal exchanges and transfer of soluble molecules to the epidermis. A vascular plexus, the rete subpapillare, establishes less extent of the papillary dermis. Hair follicles and their associated dermal cells develop into and mostly via the reticular dermis to end in the hypodermis, a tissue affluent in adipocytes. Mechanical segregation of derm (dermatoming) into determined papillary and reticular layers permits formation of explant cultures of cells from each layer. Papillary fibroblasts separate at faster rates than do site-matched reticular

fibroblasts. Reticular dermal fibroblasts seeded into form I collagen lattices contract them quicker than do papillary dermal fibroblasts. When develop to junction in monolayer culture, the papillary cells reach a more cell density partly since they are not entirely connection prevented. The papillary dermis and reticular dermis vary in both the combination and formation of their corresponding extracellular matrices. The papillary dermis is described by thin, weakly formed collagen fiber bundles, including mainly of type I and type III collagens, which compare with the bulky, well-formed fiber bundles in the reticular dermis (Cormack, 1987).

Collagen fiber bundles in the papillary dermis have more type III collagen than do those in the reticular dermis. Other matrix molecules are also variously allocated among the papillary and reticular dermis. Immunohistochemical studies of typical adult derm highlight structural and compositional distinction in proteoglycan deposition. The proteoglycan decorin is severely expressed in the papillary dermis, but is differently diffutilization d among collagen fiber bundles in the reticular dermis. By contrast, versican associates with microfibrils in the papillary dermis, but is more extensively expressed in elastic fibers of the reticular dermis. The non-fibrillar collagen types XII and XVI, besides tenascin-C, are specifically observed in the papillary dermis; whiles, collagen type IV and tenascin-X are primarily limited to the reticular dermis. Experimental studies have tracked the issue of whether cultured papillary and reticular fibroblasts generate distinct contents and types of extracellular matrix molecule that may report for the observed differences in derm. In monolayer cultures, papillary dermal fibroblasts discharge importantly more decorin than did Relating reticular cells, and papillary fibroblasts have more decorin mRNA.

Another research figure out that site-matched papillary and reticular fibroblasts differ in the comparative amounts of the proteoglycans decorin and versican that they generate. In opposite, Tajima and Pinnell appraised the contents of type I and type III collagens generated by monolayer cultures to see whether synthetic differences can report for the detected in vivo differences. They see no differences in the creation of type I and type III collagens by these two gruops of cultured cells, though they cited an increased content of type I procollagen in the medium of papillary fibroblast cultures. Therefore, cultured papillary and reticular fibroblasts represent durable diversity in the creation of some, but not all, extracellular matrix molecules (Tajima and Pinnell, 1981).

Cell structure and morphology: Fibroblasts from other anatomical areas show distinctive phenotypes. Primary research about heterogeneity of fibroblasts accomplished by Castor and co-workers suggest metabolic diversity among mesothelial fibroblasts, fibroblasts of the derm, articular tissues and periosteum. Studies described the gene expression characteristic of fibroblasts due to different anatomical areas of the body with cDNA microarray knowhow (Ahmadi et al., 2013). Data revealed diversity in topographic expression for genes engaged in extracellular matrix synthesis, growth and differentiation, cell migration as well as genes engaged in genetic syndromes. Work by Chipev and Simon (2002) demonstrated that fibroblasts from various body regions distinct in size, with palmar fibroblasts being lesser than non-glabrous derived fibroblasts. Also, growth kinetics and TGF (Transforming Growth Factor) - β 1 Receptor II expression also the capacity to contract collagen lattices were detected to vary with palmoplantar derm derived fibroblasts having minor receptor amounts and an incremented mitotic rate. The authors speculated that this regional diversity may in part account for localized susceptibility to disease manifestation like scarring and keloid formation. Last research on oral mucosal fibroblasts has showed the variation in the ability of these fibroblasts to reconstruct collagen lattices by an incremented matrix metalloproteinase (MMP)-2 expression as compared to derm derived fibroblasts. Furthermore, it was proven that oral mucosa derived fibroblasts multiplied more quickly and had a superior valence for cell doublings. A practical relationship was associated to the reality that cultured oral fibroblasts secrete more hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF) than derm fibroblasts. It was suggested that both effects can chip in a 'fetal' lesion medicating phenotype of oral fibroblasts. Beside the differences in fibroblasts from other anatomical positions fibroblasts disconnected from a one tissue are in the same way not composed of a homogeneous group but rather comprise subsets of Varity of fibroblasts.

Sorrell and Caplan (2004) have checked variation among papillary fibroblasts, which inhabit in the superficial dermis and reticular fibroblasts which are placed in the deeper dermis, highlighting the Varity in matrix molecule creation from these two different cell populations. Versican is created at low amounts by papillary fibroblasts while reticular fibroblasts generate great amounts of this molecule. In conflict, decorin is created in great amounts by papillary fibroblast but just in low contents by reticular fibroblasts. Collagen type I and collagen type III creation and the following proportion of these two dermal collagens were not discover to differ among these populations of fibroblasts. Previous studies revealed the existence of different morphological and biochemical subsets of fibroblasts within the same tissue. Two major populations of fibroblasts have been identified in the dermis; lung and kidney termed mitotically active, i.e. replicative progenitor fibroblasts (MF) and permanent postmitotic fibrocytes (PMF). These two subsets have subsequently been classified by cytomorphological and biochemical characteristics. Founded on in vitro and ex vivo-in vitro experiments it was shown that fibroblasts of human, rat and moutilization derm but also lung as well as renal fibroblasts differentiate in vivo and in vitro along a lineage of replicative progenitor fibroblast cell types and non-replicative, postmitotic functional fibrocytes of man, rodent.

According to their cytomorphology, replicative potential and ability to synthesize specific cytokines and growth factors, like TGF- β and Keratinocyte Growth Factor (KGF), MF-progenitor fibroblasts can be more classified into the cell types MF I, MF II, and MF III. Sub-cloning experiments disclosed that these MF-cell types differentiate along the lineage MF I, MF II, MF III, ere differentiation into irremeable postmitotic fibrocytes (PMF) happens. MF I-type progenitor fibroblasts have the highest replicative capacity. MFI progenitor fibroblasts of human source can go via about cell divisions before differentiating into MF II type cells. This cell type can apportion almost 15–20 times before differentiating into cell type MF III which has the ability for just 5–8 further division cycles before discriminating instinctively into permanent postmitotic fibrocytes. Founded on its biochemical activity the second cell type represent the Practical cell type of the fibroblast-fibrocyte cell system (Yeung et al., 2005).

Cell Marker: Morphological features-e.g., elongated cell bodies, oval nuclei, and linear or bundle like alignment of cellular distribution—serve as conventional markers of fibroblasts in culture. It is vital to stress, though, that fibroblasts change their morphology dramatically depending upon the culture situations, especially the extent of confluency. Regrettably, there is no antibody existing that recognizes fibroblasts selectively. Conversely, the lack of specific markers that are expressed by other dermal components (e.g., cytokeratin in keratinocytes, VCAM-1 on cells, IgE receptor on mast cells, and CD14 on macrophages) serves as a phenotypic Phenotypic marker of fibroblasts. Production of large amounts of type I collagen, as distinguished by immunofluorescence staining, can be utilized as a practical marker.

Differences between fibroblast mesenchymal stem cells and mesenchymal stem cells: Similarities among mesenchymal stem cells and fibroblasts mesenchymal stem cells and fibroblasts represent analogous spindle-like morphology. Besides this, both types of cells adhere to plastic. Flow cytometry is a quick way for segregation of complex cell populations. Nevertheless, MSCs and fibroblasts express the identical external markers. Alt E and colleagues demonstrated that the expression of human adipose tissue-derived MSC external markers CD44, CD90, CD105 was unspecific for these stem cells. Pure human embryonic lung fibroblasts were also positive for these markers. Both hematopoietic cell markers (CD14, CD45) and the endothelial cell marker (CD31) were absent in MSCs and fibroblasts. Halfon and colleagues reported coincidental results. It observed that human bone marrow MSC (BMMSC) external markers CD9, CD29, CD44, CD73, CD90, CD105, CD166 were as well as expressed on human dermal fibroblasts (10). Lorenz K and colleagues (11) showed similar expression patterns for CD14(-), CD29(+), CD31(-), CD34(-), CD44(+), CD45(-), CD71(+), CD73(+), CD90(+), CD105(+), CD133(-) and CD166(+) in human adipose tissue-derived stem cells and human dermal derm-derived fibroblasts. Additionally, fibroblasts regardless of the fact that in the studies reviewed in this article, most of the investigated cell surface markers were nonspecific; CD106, CD146 and ITGA11 have been identified as MSC-specific surface markers and CD10, CD26 as fibroblast-specific surface markers. ITGA11 is a member of integrins that binds to collagen and is engaged in cell attachment, cell migration and collagen reorganization on mesenchymal nonmuscle cells. All fibroblasts were hardly positive for CD26 and CD10 whilst less than 35% of BM-MSCs expressed CD10 (range: 16–35%) and CD26 expression was changeable (range 40–78%). By contrast, more than 70% of BM-MSCs expressed CD106 whereas all fibroblasts were negative. All studies of the MSC and fibroblast surface marker expression reviewed in this article are recapped in Table. Other significant special property of MSCs in which these cells are dissimilar from fibroblasts are the colony-forming valence and differentiation potential (Deans and Moseley, 2000).

The need for separation of mesenchymal stem cells from fibroblasts: Clinical applications require large quantities of MSCs. However, the differentiation potential of MSCs at later passages is often low (Caplan, 2007). This phenomenon could be explained by contamination of MSC cultures with fibroblasts. The few cells that continue to live the “crisis” primary become undying in the culture and then, after further development, can become tumorigenic. Identification and deletion of fibroblasts from MSC cultures could develop the MSC output and differentiation ability and also arrest tumor shaping after MSC transplantation (Ahmadi et al., 2014, Caplan, 2007).

Cell functions: Besides the well-established matrix building effect of fibroblasts, there is experimental evidence for a fibroblast-derived mesenchymal–epithelial crosstalk regulating epithelial growth factors. For example reepithelialisation of cutaneous lesions as a harmony of multiplication and movement of keratinocytes is hardly related to mesenchymal cell- derived factors. Fibroblasts are able to secrete IL-6, IL-8, HGF, and KGF all of which are known to stimulate keratinocyte proliferation and migration. IL-1 alpha stimulated postmitotic fibroblasts depicted lower transcriptional levels (mRNA) of KGF, IL-1 alpha, IL-8, while HGF mRNA was dramatically increased. However, on the protein amount IL-1 alpha- agitated irradiated fibroblasts provided less HGF amounts from proliferating dermal fibroblasts. In prior research by others the growth promoting effect of postmitotic fibroblasts on keratinocytes was clearly demonstrated in vitro. As recently published, non-stimulated subpopulations of dermal derived MF-progenitor fibroblasts or postmitotic fibrocytes constitutively secrete importantly different levels of KGF. When compared to progenitor fibroblasts MF II the amount of KGF produced per cell increases significantly in MF III type progenitor cells by a factor of about 2.2. Postmitotic fibrocytes, however, produce more

than 3-times more KGF than MFII-type progenitors and app. 1.5-times more than MFIII type progenitor fibroblasts. These observations indicate a specific role of the subtypes of progenitor fibroblasts and postmitotic fibrocytes in the mesenchymal–epithelial interaction and specifically in the homeostasis of the epithelial cell system in derm (Lee et al., 2000). As previously described, TGF- β , another important growth factor is secreted by fibroblasts and counteracts the mitotic effect of KGF on keratinocytes. Among the three isoforms of TGF- β , TGF- β 1 is the most prominent regulator. TGF- β 1 was shown to down regulate epithelial growth and induce differentiation and apoptosis in keratinocytes (Hosseini et al., 2014, Corcione et al., 2006).

This cytokine has a vital part in the autocrine regulation of the differentiation process of progenitor fibroblasts to functional fibrocytes through the induction of cell cycle inhibitor proteins like p21 and p27 mediating permanent cell cycle arrest in G0. The significant of fibroblast/fibrocyte interaction with tissue specific epithelia is also demonstrated by the utilization of fibroblasts to construct derm substitutes. Fibroblasts seeded into a collagen-GAG matrix were shown to promote rapid epithelial outgrowth on the collagen-GAG matrix as compared to a non-seeded collagen-GAG. In contrast, the feeder layer system utilization to culture keratinocytes utilizes postmitotic fibrocytes, originally derived from the irradiated transformed moutilization 3T3 cell line for co-culture (Rheinwald and Green, 1975). There is strong evidence from radiobiological research that irradiation does not necessarily kill the feeder cells, but rather induces terminal differentiation with irreversible growth arrest, yet largely preserves physiologic function in producing growth factors and extracellular matrix proteins. So far however, the functional influence of the secreted cocktail of growth factors and cytokines by the various subpopulations of fibroblasts on keratinocyte proliferation remains unclear. Despite the possible qualitative and quantitative differences between the different subpopulations it is well described that a direct cell-cell contact is crucial to promote keratinocyte growth because fibroblast conditioned medium cannot substitute for feeder cells. Besides growth promoting experiments, a novel line of research is focusing on site specific interaction of fibroblast subtypes on development and tissue homeostasis (Corcione et al., 2006). In an elegant set of experiments it was shown that fibroblasts derived from soles and palms are able to induce keratin 9 mRNA in cultured non-palmoplantar keratinocytes. Non-palmoplantar keratinocytes cultured alone or in co-culture with non-palmoplantar fibroblasts failed to express keratin 9, indicating the extrinsic regulation by signals from site specific fibroblasts.

In a comparable set of research site specific regulation of melanocytes and pigmentation was also demonstrated (Jameson and Havran, 2007). In the background of practical epithelialization there is document that fibroblasts have a main function in basement membrane creation either alone or in connection with overlying keratinocytes. These researches have indicated that keratinocytes alone were either unable to or limited in the production of laminin 1, collagen IV and laminin 5. In contrast, human fibroblasts, lonely or in compound with overlying keratinocytes illustrated significant production of laminin 1 and collagen IV, and laminin 5. Subsequently, fibroblasts seeded into a collagen-GAG matrix were demonstrated to improve basement membrane formation and epidermal homeostasis as related to a non-seeded collagen-GAG. Total collagen production by fibroblasts is dependent on the subpopulation of fibroblasts with postmitotic fibroblasts producing 5 to 8 times more collagen type I, III or V as compared to progenitor fibroblasts. Moreover, cultured postmitotic fibrocytes in comparison to progenitor fibroblasts produce the in vivo-like proportion of interstitial collagens I, III and V indicating again the important role of this cell type for tissue and ECM homeostasis (Jameson and Havran, 2007, Lee et al., 2000).

Fibroblast Cells life period: Aging Fibroblasts opposite of Aging Collagen Matrix operations illustrated above confirm the matter of structure, combination, and formation of the collagenous matrix as a firstly determinative of age-related changes resulting in the wrinkled appearance of human derm. This emphasis on cellular environment rather than on genetically inherent age-related/UV-mediated fibroblast alterations is unique (Bodnar et al., 1998). Study about age-related cellular alterations has characterized aging and the free radical opinion of aging. Replicative senescence involves exhausting the genetically-predetermined proliferative capacity of a cell through multiple rounds of cell division. Although aging is easily discernible in cell culture, it has been hard to substantiate aging in human derm in vivo. ROS produced as a result of aerobic energy metabolism, in mitochondria, oxidize cellular constituent's therewith impairing cell function. Accumulation of oxidative damage over time results in irreversible cellular functional impairment and the aged phenotype.

Interestingly, oxidative damage can also lead to functional, oxidative stress-induced senescence. While a large number of investigations convincingly back the free radical theory of aging, especially in simple model organisms, the contribution of irreversible oxidative damage to aging in humans remains an area of intensive research. One way to assess the relative contribution of extracellular environment versus intra-cellular alterations is to determine functional capacities of cells that have been removed from their tissue environment (Vaziri and Benchimol, 1998). Old Fibroblasts Have Substantial Capacity to Produce Collagen Such studies have been conducted on fibroblasts with both photoaged and chronologically aged human derm. Fibroblasts cultured from strictly photoaged forearm derm were detected to be indiscernible from fibroblasts cultured from subject-matched sun- preserved derm, with respect to collagen and MMP-1 production. In opposition, fibroblasts cultured from sun-

preserved derm of People bigger than 80 years of age represented just a simple age- linked decrease in their valence to generate collagen, compared to fibroblasts cultured from sun-protected derm of individuals under the age of 30. Intrinsic differences in fibroblasts could not report for the considerable changes to collagen creation or MMP-1 activity discovered in aged or photoaged derm. These Information emphasize the idea that fragmented collagen in the fibroblast environment is a most important element of decreased collagen output in both photoaged and chronologically aged human derm fibroblasts. Treatments for Aged Derm that Stimulate Collagen Production The detection that fibroblasts in both photoaged and chronologically-aged human derm have fundamental valence to generate new collagen when eliminated from their fragmented extracellular matrix provides a foundation for therapeutic intervention. Even though there be a plenty of therapies that assertion to make better outward of aged derm, few have been strictly measured. Retinoic acid was the first current therapy strictly represent enhance outward of photoaged human derm. Retinoic acid acts through well-characterized intracellular receptors that function to regulate gene expression. Through complex, and not fully understood molecular pathways, retinoic acid or its metabolic precursor's retinol or retinal, are able caulitization deposition of new, undamaged collagen in both photoaged and chronologically aged human derm. Accumulation of new collagen can result in marked improvement in appearance of aged derm. Another well-documented treatment for improving exterior of old derm is CO2 laser reappear. This approach thermally ablates epidermis (with thermal harm to external dermis) and therewith agitates a huge lesion medicating reaction. The natural course of wound healing involves remodeling of dermal collagen and other matrix molecules. This remodeling involves an initial inflammatory phase, described by greatly vast amount of MMPs that breakup the fragmented collagenous matrix, and followed by fundamental and extended output of new healthy collagen. CO2 laser resurfacing regenerates both the epidermis and dermis thereby improving both appearance and health of aged derm. Less invasive laser procedures, employing different types of lasers, have recently been developed. However, these approaches become clear to have the least capacity to change the dermal extracellular matrix. So, it continue to be ambiguous whether these negligible invasive laser procedures can significantly improve the appearance of aged derm. Future work can lustered that to be efficient a laser should result in minimum enough loss to impel MMPs and collagen to change the dermis (Thomson et al., 1998, Lanza et al., 2000).

2. CONCLUSION

To distinguish MSCs from derm fibroblasts and to confirm that our cultured cells were MSCs, we utilization d tissue culture techniques to cultivate derm fibroblasts. After passaging to the fifth generation and inducing differentiation, derm fibroblasts did not have the same characteristics as the MSCs from the derm and did not differentiate into lipocytes, osteoblasts, and chondrocytes. Thus, the derm MSCs and fibroblasts were indeed two different types of cells. In conclusion, the term 'dermal fibroblasts' is an oversimplification of a dynamic, heterogeneous population of cells that exhibit differences in terms of embryological origin, anatomical distribution and functional profiles in health and disease. Stem cell research has afforded new insights into possibilities for organ regeneration. Some initiative has been taken to identify stem cells which can give rise to a fully developed derm. We believe the insights learnt from the diversity and physiology of the fibroblasts in health and diseased states could pave way in the generation of superior derm equivalents. We also revealed that successful culturing of derm MSCs required a minimum sample coverage area. If the area was too small, the number of MSCs after separation was insufficient for effective growth, resulting in culture failure.

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