SCIENTIFIC REVIEWS AND LECTURES

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# THE ASPECTS OF USE OF AUTOLOGOUS DERMAL FIBROBLASTS

**ABSTRACT**

Methods of healing of skin injuries with the use of cell therapy have been approved all over the globe to be safe and effective. Many different cell types are used in clinical applications including keratinocytes, endothelial cells, bone marrow stem cells and iPS cells. However, skin fibroblasts are in the spotlight today due to their efficacy and ease of culturing.

At present, autologous dermal fibroblasts are widely used in cell therapy and have very promising perspectives in healing of skin defects and injuries. It was demonstrated that fibroblasts have high efficacy in healing such injuries as burns, chronic wounds, tendon regeneration and correction of age-related skin changes.

**Keywords:** cell therapy, autologous skin fibroblasts.

## INTRODUCTION

Fibroblasts are mesenchymal cells located on a border of the epidermal and the dermal layers of the skin. Their main function is production of the extracellular matrix (ECM) that play structural role in the skin and also provide morphological and functional organization, as well as homeostasis of the skin in both normal and pathological states. Fibroblasts participate in restoration of skin integrity after damage, interact with other skin and blood cells that migrate to the lesion site, therefore functioning in both physiological and reparative histogenesis in the dermis. Depending on the location there are different subpopulations of fibroblasts each of which have unique features, influencing their regenerating abilities [2]. The deep understanding of differences between these subpopulations was used when developing new methods of treatment aimed for skin rejuvenation with the use of collagen.

The improper skin healing can affect its function and leads to deterioration in its appearance due to formation of scar tissue and ulcers that promotes development of a secondary infection and cause disturbance of the barrier function of the skin. Traditional methods of wound care promote the fastest epithelization, however skin function is not always restored. The new approach to skin regeneration is based on change of a local microenvironment of a wound by introduction to it or to its edges of human cells.

Fibroblasts, interacting with epithelial cells and producing growth factors, regulate epidermal morphgenesis, producing collagens and glycoproteins promote skin regeneration and rejuvenation [29]. Although there were positive results with the use of other cell types for skin regeneration, this review will be focused on the use of autologous fibroblasts in cell therapy.

At present, fibroblasts based cell technologies are established method in regenerative medicine, which not only effectively eliminates visual defects of the skin, but also reorganize it from within. Constantly growing experience in the field cell technology and its use in various medical spheres including treatment of dermal injuries, trophic ulcers, use in orthopedics, healing of wounds of different etiology and use in cosmetology indicate the importance of further research in this area.

*Use of autologous fibroblasts in cell therapy*

The deeper understanding of the role of fibroblasts in skin regeneration and rejuvenation led to extension of their use in cell therapy for treatment such conditions as: chronic wounds, dermal injuries, diabetic and trophic ulcers, age-related changes of face, neck and arms skin (decrease of thickness and elasticity of skin, wrinkles), cicatrixes of various etiology and alopecia. Recently, the use of cultured fibroblasts began to incorporate in medical practice after it was demonstrated that dermal fibroblasts maintain diploid karyotype, have limited life expectancy [2], and don't induce tumorogenesis after injections in laboratory animals [12].

Transplanted autologous dermal fibroblasts showed higher survival rates, faster epithelialization and adhesion to wounds as compared to allogenic skin fibroblasts. It is possibly related, to increased immune response to allogenic fibroblasts, and significant increase in scar tissue formation whereas autogenic dermal fibroblasts caused restoration of dermal function with the minimum formation of a scar tissue. Autologous dermal fibroblasts also improve healing of radiation-caused injuries, increasing the healing rate of wounds, tensile strength analyses also demonstrate higher density of cells as compared to the control group [5].

Dermal fibroblasts were also considered for restoration of other tissues. So, use of skin fibroblasts in combination with Bmp2 (bone morphogenetic protein-2) in gelatin scaffold resulted in complete regeneration of cranial seams in 4 weeks after engraftment. This method has potential as a therapy for patients with congenital disturbances of premature ossification of cranial seams [23]. Also other applications of dermal fibroblasts, such as regeneration of tendons, closing of pleural defects for sealing of respiratory tracts, restoration of a forward crucial ligament were considered.

Various methods are used for isolation of fibroblasts from skin biopsy these methods utilize mechanical or enzymatic treatment of tissue or combination of both. After cultivation isolated cells can be frozen or delivered to a medical institution for immediate use [9].

Fibroblasts based cell technologies have a huge potential and require further studying. Especially such areas as isolation from heterogeneous tissue homogeneous population of fibroblasts, technology of rapid

harvesting of necessary amount of cells with necessary functions, the optimal selection of biopsy site considering desirable medical effect, and also storage and transportation of fibroblasts to medical institutions.

**Indications for use**

*Burns.* The major goal at treatment of burns is restoration of barrier function of skin, prevention of secondary infection and scar tissue formation and disfiguration. Wound care materials and synthetic substitutes provide a temporary barrier to reduce the risks of infection.

The most effective approach for burn treatment is application of fibroblasts containing matrix material on the wound surface. Both synthetic and natural polymers are used for such matrices, as well as combination of two and their derivatives [8]. At present different types of skin substitutes are developed. It is heterogeneous group of therapeutic materials which differ in biological properties and methods of application. Long term storage and usability together with optimum price-effect ratio provided their universal availability [6]. The common principle that such materials all share, is creation of substitute that will mimic the structure of normal skin and have both dermis and epidermis layers. The base of the dermal component is usually represented by a three-dimensional collagen matrix containing mesenchymal cells. The epidermis layer is created on the surface of the dermal layer by growth and differentiation of keratinocytes. The composition of matrix proteins, cellular elements and methods of formation of the epidermis layer varies depending on the model [13]. There are multiple materials that combine cellular components and matrices. Skin equivalents containing autologous fibroblasts and keratinocytes were successfully developed and tested [18].

Quite recently spray system for delivery of cells directly to the wound area was developed. This system developed by Avita Medical (Northridge, LA, California) contains the mixture of patient's own cells and is sprayed directly to the wound area. Such treatment result in accelerated skin regeneration with less expressed scaring [20].

The possibility of use of artificial skin containing autologous fibroblasts and keratinocytes in other applications, except burns, was demonstrated by Llames *et al.* [16]. They used skin equivalents for treatment of patients with big wounds after removal of a giant nevus. These patients experienced epithelization in all cases without formation of bubbles and tightening of wound edges. These studies indicate that fibroblasts based cell therapy alone and in combination with skin equivalents is effective for treatment of burns and other serious injuries.

*Fibroblasts in cosmetology*. In 2011 FDA (Food and Drug Administration) approved the use of autologous skin fibroblasts in the form of injections for correction of nasolabial folds wrinkles of moderate and heavy degree in adults (LaViv technology, Fibrocell Technologies, Exton, PA) [14].

In studies involving therapeutic use of autologous fibroblasts significant improvement of the face contour after injection of autologous cells is shown. In addition to reduction of wrinkles, scaring after acne was also reduced. Side effects were not observed in these studies. Because of the early progress in use of autologous fibroblasts in treatment of nasolabial fold wrinkles and improvements of a face contour after fibroblasts application, the indications were extended also on esthetic medicine. The use of autologous fibroblasts is authorized also for treatment of post-acne scars and reduction of flabbiness of skin in the periorbitary region.

*Fibroblasts in orthopedics*. The Replicel Life Sciences Inc. has developed therapy on the basis of autologous fibroblasts from hair follicles for treatment of a chronic tendinitis. Autologous skin fibroblasts promote the activation of reparative processes in injured tendons [16]. Another orthopedic indication is the use of autologous fibroblasts in osseointegrated prostheses. Autologous fibroblasts reduce chances of skin infection and development of osteomyelitis, the most disturbing complications in the area of a prosthesis attachment [28].

*Wound healing.* Healing of surgical wounds is another sphere of autologous fibroblasts application. The wounds treated with autologous skin equivalents on the basis of hyaluronic acid undergo faster epithelialization and result with lesser scaring increasing the overall satisfaction of patients as compared to use of the skin transplant along. These results were obtained during studying of skin defects after removal of basal cell carcinoma [17].

Apligraf (Organogenesis, Canton, Ohio) is an allogenic skin equivalent consisting of 2 layers of skin obtained from fibroblasts and keratinocytes. This equivalent is approved by FDA for treatment of chronic wounds, such as trophic and diabetic ulcers of foot, so far more than 200 thousand patients were treated with this product [25]. Nevertheless it is an allogenic product and can provoke immune rejection. This problem can be solved by using autologous components of the skin consisting of fibroblasts and keratinocytes for production of individual two-layer equivalents for recovery and regeneration of the skin. The latest discoveries clearly demonstrate that chronic diabetic ulcers treated with a mixture of autologous fibroblasts and keratinocytes in fibrin suspension result in faster healing of ulcers without side effects [26].

Fibroblasts can be used in the form of suspension on a wound or ulcer. In case of a diabetic ulcer the patented mixture of keratinocytes and fibroblasts is suspended in fibrin glue and applied on a wound before applying of a bandage.

One more sphere of autologous skin fibroblasts application is treatment of chronic wounds caused by vascular pathologies (atherosclerosis, thrombosis, varices), or physical impact (decubituses), harmful environmental effects (radiation). The use of skin equivalents promotes full epithelization of such lesions. However, since the main reason preventing wound epithelization is an obstruction of vessels, the complete healing is impossible without elimination of the main reason of a disease.

Also fibroblasts based cell therapy is effective method for treatment such dermatologic diseases as vitiligo, epidermolysis bullosa and pyoderma gangrenosum [24]. Fibrocell Science together with Intrexon Corp. is developing genetically modified skin fibroblasts for treatment of such orphan skin disease as epidermolysis bullosa

– a severe genetic disorder caused by the mutation in gene coding for collagen VII protein (COL7) [21]. The results of laboratory experiments and clinical trials indicate the possibility of collagen VII accumulation at the boundary of the dermis and the epidermis layers of the skin and healing of chronic skin defects in patients with epidermolysis bullosa using the method based on injection of allogenic fibroblasts [15].

**Location-specific properties of fibroblasts**

One of the most fascinating properties of the skin is its regional specificity. It is observed in many species and is an adaptive feature which is strictly followed. In human this phenomenon is represented by the presence of different types of hair. Also such divergence can be seen by the differences between the skin of palms, soles and face.

For studying of the location effect the experiments of substitution of the dermis and the epidermis layers were carried out on animals. This series of experiments showed that fibroblasts can determine a phenotype [19].

Clinical experiments have demonstrated similar results. When fibroblasts taken from hairy part of the head were transplanted to a hand this resulted in growth of a long hair as fibroblasts can "remember" their original location and determine the corresponding phenotype. It was shown that fibroblasts maintain the expression of specific genes (i.e. HOX gene) associated with their localization on the skin. Fibroblasts keep expressing them even after 35 cell divisions in culture. These studies revealed differences in gene expression pattern in fibroblasts taken from different areas of the skin that confirms the theory that fibroblasts shall be taken from sites suitable for further therapeutic application [27].

Thus, fibroblasts not simply play a supporting role. They have a great influence on determination of regional identity of skin. The role of fibroblasts in determination of skin phenotype is of great importance for development of cell therapy, and allows controlling the skin phenotype.

The idea to use autologous fibroblasts to help people with amputated limbs, decubituses and changes in the area of amputation [22]. Considering that skin diseases develop in 48% of cases in amputation area, the purpose of fibroblasts based cell therapy is to change skin phenotype in that area to promote better fixation of an orthopedic device.

Development of the therapy that would utilize autogenic fibroblasts is a very promising area, however there are difficulties related to material logistics, collection and transportation of material and production costs. Solving these issues will result in increase of perspective autologous fibroblasts based developments and products in the field of regenerative medicine.

**Uniqueness of structure**

In addition to regional differences of fibroblasts taken from various skin areas there are also structural and functional differences unique for each separate population. Fibroblasts isolated from reticular dermis and papillary dermis have different genetic markers and functional properties that show their regional uniqueness. Synthesis of collagen is a common feature of all types of fibroblasts, irrespective to their lineage, however reticular fibroblasts produce more procollagen. As for dermal equivalents, it was shown that papillary fibroblasts have higher differentiation and maturation rates and produce various soluble growth factors. Fibroblasts from reticular dermis produce various cytokines, such as keratinocyte grows factor and interleykin-6, and also suppress terminal differentiation of keratinocytes and formation of the basement membrane. Also they produce molecular targets which promote various rearrangements of glycosaminoglycans in collagen of the extracellular matrix. These data demonstrate that papillary and reticular dermis of skin contains different populations of fibroblasts. It was also shown that the upper population of fibroblast play role in formation of a hair follicles [20]. And the lower population is generally responsible for synthesis of the extracellular matrix, promotes wound healing that leads to development of ECM enriched tissue, but deprived of hair follicles. The data obtained in these studies can be used for anti-aging cell therapy based on autologous fibroblasts.

**Domestic research**

During the 1990th clinical trials were conducted at A.V. Vishnevsky Institute of Surgery on effective methods of skin restoration with the use of skin fibroblasts with further developing of these methods. In 1994 for the first time 3-day culture of allogenic skin fibroblasts was used for treatment of wound surfaces alone and in combination with autodermoplastics [11]. Later at the same institute the method of treatment of deep burns was developed, which include preliminary surgical treatment and combined autodermoplastics with the use of perforated dermal mesh and fibroblasts distributed in cell gel [1].

The studies carried out at Naval Clinical Hospital No. 1 (St. Petersburg) in 2008 demonstrated the efficiency of mesotherapy of dystrophic and destructive processes in skin with suspension of allogenic fibroblasts. The data suggests that use of cultured fibroblasts allows optimizing metabolic processes in skin [10].

During three year period of clinical trials of autologous dermal fibroblasts in correction of skin defects, carried-out in Ural State Medical University and Institute of Medical Cell Technologies (Yekaterinburg), all examinees experienced positive cosmetic effect in a problem area after introduction of autologous fibroblasts. Particularly they experienced a decrease of large and small wrinkles, decrease in dermal defects, and also the general improvement of face skin in the area of fibroblasts transplantation [9].

After clinical trials conducted in RGMU and V.N. Orekhovich Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, authors came out with a conclusion on safety and efficiency of cultured dermal autologous fibroblasts for treatment of age changes of a skin [5].

Today one technology that utilizes autologous dermal fibroblasts is officially recognized in Russia. The SPRS (Service for Personal Regeneration of Skin) therapy is personalized complex of diagnostic and therapeutic procedures for skin restoration developed by Human Stem Cells Institute (HSCI). In 2010 HSCI got permission from Federal Service for Supervision of Healthcare (Roszdravnadzor) to use of SPRS therapy for correction of age and cicatricle changes of a skin [2].

Russian researchers from the

Institute of Cytology of RAS developed a collagen-based dermal equivalent applied on a polylactide matrix and allogenic fibroblasts which was successfully tested as treatment of trophic ulcers and burns wounds in St. Petersburg's clinics [7]. It represents gel of the extracellular matrix proteins - collagen type I, or fibrinogen (commercially available substances prepared from plasma of a human blood) with the human dermal fibroblasts embedded in the gel. Toxicological tests have been performed in V.I.Shumakov Institute of Traumatology and Orthopedics and clinical tests were carried out in 3 clinics – Regional Burn Center of I.I. Dzhanelidze ambulance training Institute (St. Petersburg), Department of surgery of Academy of Military Medicine (St. Petersburg) and N.N. Burdenko Main Military Clinical Hospital (Moscow). According to the results of all tests carried out in 2006, Roszdravnadzor issued permission for production and a clinical use of the skin equivalent for a period of five years. Now, with the support of the Federal Agency for Scientific Organizations (FASO Russia), organizational and methodical approaches are being developed to introduce this effective method in clinical practice [3].

**CONCLUSION**

Thanks to their properties fibroblasts play an important role in regeneration processes. They are involved in formation of the extracellular matrix, synthesis of biologically active substances, initiation of migration and proliferation of various cell types after lesions. All these features make fibroblast very promising tool in various fields of medicine including: combustiology, dermatology, cosmetology, orthopedics, endocrinology and surgery. Differences in structural and functional features of fibroblasts depending on their localization and their role in development of a unique skin phenotype, open wide area for research on skin reprogramming, however it is necessary to consider the anatomic location of the biopsy site when locating the area of a skin where cell therapy will be carried out.

Proceeding from the above it is clear that clinical cell therapy develops very rapidly. The main directions were determined, safety and efficiency of this technology has been proved. Cell therapy with the use of autologous dermal fibroblasts has huge potential in the field of regenerative medicine. It offers safe, immunologically acceptable and simple option for tissue regeneration.

At present, in the Republic of Sakha (Yakutia) fibroblasts based cell therapy is not introduced. Though, considering climatic conditions of the region, the problem of treatment of patients with lesions and defects of skin belongs to one of the most urgent areas of medicine. For the last decade cell technologies achieved considerable success in the world. Broad clinical experience in effective and safe application of dermal fibroblasts for treatment of various skin defects has been accumulated. This experience demonstrates the importance of further development of this area.

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