Prospectivity of studying fibroblasts for improving the quality of therapeutic, prophylactic and rehabilitation measures for patients with cardiovascular diseases and lung pathology

Prospectividad del estudio de fibroblastos para mejorar la calidad de medidas terapéuticas, profilácticas y de rehabilitación para pacientes con enfermedades cardiovasculares y patología pulmón

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Abstract

In this paper, the authors aim to study different methods, analyses of proliferative activity and morphometric indices of fibroblasts as a key link in in vitro experiments for the possibility of enhancement reparative regeneration processes to improve the quality of prevention and treatment in cardiovascular and pulmonary diseases. In the process of research the authors conduct an analysis of publications in peer-reviewed journals, performed using electronic databases PUBMED.com, RINC (Russian Science Citation Index), as well as scientific electronic library eLIBRARY.RU analysed publications and studies on the topic of scientific work. Based on the study of published literature data on the study of proliferative activity of fibroblasts morphometric indices changes, the authors come to conclusions about their significance, identifying the most evidence-based techniques for use in in vitro experiments to improve the regenerative processes in various organs and systems of the human body (including pathologies of the pulmonary, cardiovascular systems).

Purpose: studying different techniques used to analyse proliferative activity and changes in morphometric indices of fibroblasts as a key link in in vitro experiments enhancement of reparative regeneration processes to improve the quality of prevention and treatment in cardiovascular and pulmonary diseases.

Keywords: fibroblasts, rehabilitation, polymorphisms, wounds, traumatology, cardiovascular pathology, fibrosis, pulmonary pathology.

Resumen

En este artículo, los autores pretenden estudiar diferentes métodos, análisis de la actividad proliferativa e índices morfométricos de los fibroblastos como eslabón clave en experimentos in vitro para la posibilidad de mejorar los procesos de regeneración reparadora para mejorar la calidad de la prevención y el tratamiento en enfermedades cardiovasculares y pulmonares. En el proceso de investigación, los autores realizan un análisis de publicaciones en revistas revisadas por pares, utilizando las bases de datos electrónicas PUBMED.com, RINC (Russian Science Citation Index), así como la biblioteca científica electrónica eLIBRARY.RU, analizaron publicaciones y estudios sobre el tema. del trabajo científico. Basándose en el estudio de los datos publicados en la literatura sobre el estudio de la actividad proliferativa de los cambios en los índices morfométricos de los fibroblastos, los autores llegan a conclusiones sobre su importancia, identificando las técnicas más basadas en evidencia para su uso en experimentos in vitro para mejorar los procesos regenerativos en varios órganos. y sistemas del cuerpo humano (incluidas patologías de los sistemas pulmonar y cardiovascular).

Propósito: estudiar diferentes técnicas utilizadas para analizar la actividad proliferativa y los cambios en los índices morfométricos de los fibroblastos como eslabón clave en experimentos in vitro de mejora de los procesos de regeneración reparadora para mejorar la calidad de la prevención y el tratamiento en enfermedades cardiovasculares y pulmonares.

Palabras clave: fibroblastos, rehabilitación, polimorfismos, heridas, traumatología, patología cardiovascular, fibrosis, patología pulmonar.

Introduction

The search for new therapies related to the enhancement of the efficiency of regenerative and reparative properties of the living organism is the most urgent topic of modern preventive medicine. It is especially important to study the topic within the framework of the influence of the microbiota in innovative prevention and therapy research, where advanced research on the internal systems of the body plays an increasingly important role[26]. Regeneration is dependent on fibroblasts, caused by the secretion of metabolites, extracellular matrix elements (ECM), and signalling factors regulating tissue metabolism. Fibrosis, characterised by excessive accumulation of extracellular matrix, can develop in almost any organ, in response to injury or chronic process, leading to death in 45% of all fatal cases[1,2]. Pulmonary fibrosis is the most dangerous form of fibrosis, and therefore it has received special emphasis in the last two decades of fibrosis research [3]. Particular attention has been paid to the so-called idiopathic form, i.e. the form of indeterminate development, which affects about 5 million people annually worldwide, corresponding to 20% of all cases of interstitial lung disease[3,4,5]. The causes of the development of this form are most often considered to be environmental or occupational factors, leading to varying degrees of fibrosis and inflammation. The difficulty of diagnosis is that diagnosis is often delayed due to the fact that fibrosis is detected only in the case of scar tissue formation, which can only be detected by chest CT[6]. Therefore, the main method of investigation of interstitial lung diseases is histopathological examination of surgical biopsy specimens, which cannot be widely used due to the relative complexity of the procedure, as well as the potential for deterioration of the patient's condition due to its performance[7]. Therefore, molecular markers determined in vitro, without the use of invasive methods, are beginning to play an increasingly important role in the diagnosis of lung diseases.

It should be noted that the accumulation of extracellular matrix leading to tissue fibrosis also leads to chronic overloading of atrial volume and pressure, which further leads to atrial fibrillation, which is a major clinical problem. Fibrosis in this case is a consequence of stretching of cells due to excessive strain on them.

It should be noted that cardiac fibroblasts are the main cellular regulators of VSM homeostasis. According to modern data, proliferation, migration and differentiation into myofibroblasts are potentiated by the load of haemodynamic factors, which leads to massive secretion of intracellular matrix proteins. The resulting fibrosis impedes the coupling of myocardial excitation and contraction and disrupts VSMC-dependent impulse propagation and signalling pathways[12]. The common molecular mecha-

nisms and signalling pathways involved in fibroblast dysregulation and cellular mechanotransduction have been described in detail elsewhere[20]. Fibroblast activation can also be stimulated by mechanical processes, which include neurohumoral changes, release of paracrine factors, as well as interaction with leukocytes and cytokines and direct effect of mechanical stretching on fibroblasts.

In fact, fibroblasts play a key role at all stages of the regenerative process, which goes through a complex sequence of regenerative stages that includes three main phases: inflammation, proliferation, and remodelling[8]. During development, fibroblasts undergo differentiation from spindle-shaped progenitor cells to postmyotic polygonal fibrocytes and myofibroblasts, and different types of fibroblasts are closely related in the regeneration process, performing different functions, from the deposition of intracellular matrix components to wound contraction and scarring[9,10].

Differentiated groups of fibroblasts lead to the release of cytokines, which plays a crucial role in the regeneration process[12,14-17]. Therefore, this area of research is promising from different aspects, both from theoretical and practical points of view, leading to the study and discovery of new techniques and methods of healing wounds, injuries and diseases with the development of fibrosis.

Materials and methods: In the course of the study, publications in peer-reviewed journals were analysed using the electronic databases PUBMED.com, RSCI (Russian Science Citation Index) and scientific electronic library eLIBRARY.RU. The authors analysed publications and studies on the topic of scientific work. The data were analysed only in the framework of scientific research officially published in the public domain.

Results

The 3 phases of regeneration are described as inflammatory phase, proliferative phase and remodelling phase. Fibroblasts come into their own in the proliferative phase, which most often begins on day 3 of the healing process, overlapping with the inflammatory phase. Fibroblasts reach peak development on day 7 after activation and are responsible for initiating angiogenesis, epithelialization and collagen formation. In addition, fibroblasts are responsible for the production of type III collagen during this phase. The granulation tissue formed during this phase is particularly important in secondary tension wound healing. When collagen synthesis and breakdown become equal, the next phase of wound healing begins.

During the remodelling phase, fibroblasts differentiate into myofibroblasts, causing tissue contraction during this phase of wound healing. Eventually strength approaches 80% of that of intact tissue. Vascularisation decreases, creating a less hyperaemic and more constricted wound as this phase progresses.

It should be noted that some authors, for example, in the article «Fibroblasts - cell choreographers of wound healing» note the fact that despite the fact that fibroblast cells are vital for a full-fledged regeneration process, they can lead to fibrosis, and with it to increased scarring or, in some cases, inhibit the process of wound healing, for example: diabetic and ulcer wounds[24].

It is therefore not surprising, given the importance of the role played by fibroblasts in regeneration processes, that the role of fibroblasts in the treatment and prevention of diseases not only of surgical, but also of pulmonary and vascular pathologies is currently being discussed by many authors.

Thus, in the article «Comprehensive Analysis of Fibroblast Activation Protein Expression in Interstitial Lung Diseases» protein and mRNA expression of fibroblast activation protein (FAP) in lung tissue grafts from patients with and without idiopathic pulmonary fibrosis (IPF) was studied. Frozen lung tissues from both healthy donors and patients with ILF or non-ILF interstitial lung disease were used to assess FAP expression by Western blotting. FAP mRNA expression was analysed by real-time PCR. As a result, the authors of the current study note, for example, that the distribution pattern of FAP-positive cells in lungs with ILF tended to be quite scattered, in contrast to the aggregated pattern observed in the non-ILF group. As a result of the study, the authors conclude that fibroblast activation protein may be a relatively sensitive surrogate marker of the early phase of lung fibroblast activation[23]. Following this logic, the researchers note that the FAP monitoring approach can be a bench-

mark for antifibrotic activity, as it directly detects effector cells of fibrosis.

The authors of the paper suggest that targeting FAP with non-invasive imaging can potentially predict with reasonable certainty increased fibrotic responses, which may lead to early intervention and prevention.

It should be noted that many authors point out the stress effect on the state of fibroblasts that physical, chemical and biological factors have on them. Thus, recently, a wide interest arises in connection with studies of the influence of microbiota associations with B. bifidum[28]. Bifidum[28]. Among others, the effects on fibroblasts have been studied. In such studies, it is noted that the products of B. Bifidum metabolism, enhancing the production of proteins and cytokines of different functionality, leading to the enhancement of tissue regeneration processes. In this case, adult human fibroblasts (LHR-4(81) cell line) were cultured in DMEM/F12 medium, then seeded on Petri dishes at a density of 1x106 cells/cm2 and placed in CO2 incubator conditions[22]. The authors conclude that the products of the secondary metabolism of B. bifidum affect the morphofunctional state of fibroblasts during the initial 24 hours of co-cultivation, enhance proliferation in culture, leading to stimulation of the production of extracellular matrix proteins and cytokines, resulting in accelerated tissue repair and regeneration.

These studies are not the only ones that point to the ability of probiotics, namely the genus Bifidobacterium bifidum, to stimulate the proliferative ability of fibroblasts, which leads to the formation of new blood vessels in the process of wound healing, for example, the article «Probiotics or pro-healers: The role of beneficial bacteria in tissue repair»[18].

However, not all authors note the importance of studying fibroblasts in the context of pathologies of functional systems of the organism. For example, the authors of the article «Effects of cardiac stretch on atrial fibroblasts: review of the evidence and potential role in atrial fibrillation» note that fibrosis occurs in many paradigms of cardiac pressure and/or volume overload. In atria exposed to chronic pressure/volume loading conditions, fibrosis is common and appears to play an important role in FP. However, contrary to widely held assumptions, evidence regarding direct activation of cardiac fibroblasts by mechanical forces is weak and unclear, with key responses such as fibroblast proliferation, collagen production, and indices of differentiation into myofibroblasts showing divergent and sometimes directionally opposite changes among studies in response to stretch. The authors note that further studies are needed to obtain reproducible results that will answer the question of whether and how mechanical stretch directly activates fibroblasts[21].

The authors of the article «Fibroblast growth factors: biology, function, and application for tissue regeneration» note the need for further research not only on fibroblasts but also on related biomaterials[28]. The paper states that fibroblast growth factors (FGF), which transmit signals through FGF receptors (FGFR), are responsible for the regulation of an extensive number of biological functions, including cell proliferation, migration, and differentiation. However, the authors note that although the biological functions of FGF are involved in the life cycle of a significant number of cell types in vitro through this signalling pathway, the maintenance of stability and half-life in vivo must be taken into account. The authors conclude that future clinical applications of FGFs in tissue regeneration, including skin, muscle, ligamentous apparatus, as well as bone, teeth and nervous tissues, may be realised if their biological functions are maximised through the appropriate use of biomaterials and stem cells[27].

Equally important are the conclusions reached by the researchers in the article «The Role of Fibroblast Growth Factor (FGF) Signalling in Tissue Repair and Regeneration». According to this article, there is growing evidence not just that FGFs are involved in the regulation of repair and regeneration processes. While in invertebrates and lower vertebrates FGF is crucial for regeneration, in the case of higher vertebrates it is FGF that mediates the mechanisms of wound healing and tissue repair. According to modern data, FGF is the main stimulator of tissue repair, participating in the support of pluripotency, which consequently promotes self-renewal. And due to strengthening of proliferation processes FGF leads to suppression of cell aging and, as a result, apoptosis. FGF also induces angiogenesis by increasing protease expression, confirming its role in tissue repair and wound healing[30]. Thus, the authors found that the growth factors FGF1, FGF2, FGF4, FGF7, FGF16, FGF21 and FGF23 have promising therapeutic results in diabetic foot ulcers[31]. From the literature reviewed above, it is evident that FGF may serve as a very promising therapy for tissue repair. At the same time, no data on adverse effects of FGF on tissues have been reported by the authors.

It is indicated that inflammatory cells such as T-lymphocytes and macrophages infiltrate tissues upon FGF2 stimulation[25]. At the moment it has been demonstrated that transgenic overexpression of FGF2 in cardiomyocytes increases T-lymphocyte infiltration in the heart, but under the condition of isoproterenol treatment[33].

Fibroblast growth factors also play a role in other diseases. Thus, according to the study published by Yanucil et al, FGFR4 blockade may be a safe alternative in the fight against chronic inflammation in patients with chronic kidney disease[32].

Thus, the problem of using fibroblasts as a key link in regeneration in pulmonary, cardiovascular and surgical pathologies is a burning issue at the moment, and their importance in the prevention of diseases of physiological systems of the body is beyond doubt.

Conclusions

Based on the conducted study of literature data devoted to the study of proliferative activity and changes in morphometric indices of fibroblasts under the influence of various factors, their effectiveness and significance were proved. Also the most proved methods for their application in experiments in vitro were revealed in order to substantiate the possibility of improvement of regenerative processes in various organs and systems of human organism, including pathologies of pulmonary, cardiovascular systems.

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