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Growth Factor Technologies in Cartilage Tissue Engineering (Review)

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Abstract. The article presents a systematic review of literature analyzing the prevalence, base technologies, and perspective directions of growth factor usage in cartilage tissue engineering. The main attention is given to problems of combinations of growth factors in modern scaffolds for cellular settlement and options for mechanical and physical-chemical stimulation of chondrogenesis, including the use of bioreactors.

Keywords: cartilage; tissue engineering; scaffolds; transforming growth factor β; bone morphogenetic proteins; insulin-like growth factor-1; platelet-derived growth factor.

Introduction. The restoration of damaged and lost tissue in articular cartilage refers to serious problems of modern regenerative medicine. This is based on well defined complex of biological and social reasons [1, 2]: initially low capacity of the articular cartilage to regeneration (1); the increase of duration and quality of life resulting in rapid growth of the elderly person number with the need for an active lifestyle (2); the «traumatic» epidemic due to expansion of technologies in all spheres of professional activity and everyday life, as well as calls to extremism (3). As a result, we have a huge volume of recovery procedures on the joints – more than 6 million a year in the USA alone, about the same in the EU, about 250 thousand in Russia [3].

In current situation, the classical approaches, based on autologous chodrocyte transplantation (ACT) or the stimulation of regenerating potential of own cartilage, cannot satisfy the experts. These methods have a number of serious limitations and imrairments, and they do not provide an adequate restoration of joint function for a long time [2, 4, 5]. The new «gold standard» in this area aims to become the tissue engineering. To realize this approach anyone must perform the selection, managed proliferation, and differentiation of the most promising cellular pool for tissue reconstruction, and develop the design of the most effective conditions for the subsequent remodeling of the implant into authentic tissue with valuable functional abilities [4, 6, 7].

Despite certain difficulties in situ, and the relatively high cost, the use of growth factors as stimulators for remodeling tissue-engineering constucts is considered to be one of the key moments of providing clinical success of cartilage tissue engineering [8, 9]. Based on the systematization of current world literature we considered it appropriate to conduct a comparative analysis of the growth factors usage in tissue-engineered technologies for the articular cartilage restoration and show the main trends in development of this direction of regenerative biomedicine.

Materials and Methods. The main sources for systematization and synthesis of information, were accepted from the open database Pubmedcentral (NCBI, NIH, USA), mainly for the period of the last five years. In some cases we used the key monographs on the problem, data from resource Elibrary.ru (Russia), as well as the results of our research in collaboration with prof. D.A. Malanin

(Volgograd State Medical Universiry, Russia). In the end, we tested and annotated research on the application of transforming growth factor (TGF 1, TGF (2), bone morphogenetic protein (BMP-2, BMP-7), basic fibroblast growth factor (FGF-2), insulin-like growth factor (IGF-1), platelet-derived growth factor (PDGF), and some other signal molecules.

Cocepts and common approaches to cartilage tissue engineering. Modern tissue engineering (in conjunction with cellular technologies in regenerative medicine), is the interdisciplinary scientific area, which has behind it a little more than 20 years of development. It is based on the principles, methods, advanced achievements of engineering, materials science, chemistry, biology, and bioinformatics to restore, support, and enhancing the functions of damaged tissues by applying biomimetic agents in it [9, 10].

Fundamental work in cartilage tissue engineering belong J.Vacanti and colleagues from Boston (USA), who grow the chondrocytes on polyclactic scaffold for the closure of osteochondral defects in flopping joint of pigeons [11]. The ability to organothypical reimbursement of large defects, particularly of difficalt shape and varying in depth of the lesion, are the most valuable for the Clinicians using the tissue engineering approaches. This approach can provide earlier, reliable and lasting recovery of the articular surface [2, 7]

The concept of cartilage tissue engineering is based on the idea about the healing of cartilage defects to be constructed on the principles of ensuring sufficient number of phenotypically complete chondrocytes, capable of remodeling temporary artificial media (scaffold) to a natural matrix of hyaline cartilage. Optimal management of this process should combine the stimuli including of the structural properties of scaffold, signalling molecules, and physical and chemical impacts [7, 8].

Ultimately, we need to correctly seed the active chondrocytes into three-dimensional structures and gradually replace scaffold matter with natural cartilage matrix. Such implants (tissue endineering construct) may be precultured in a bioreactor before setting into a joint (fig. 1).

To compare and discuss in detail different sources of cells for cartilage tissue engineering is not a goal of this review, therefore, we confine ourselves to the facts, which are crucial for understanding the action of growth factors to cells in tissue-engineered constructs.

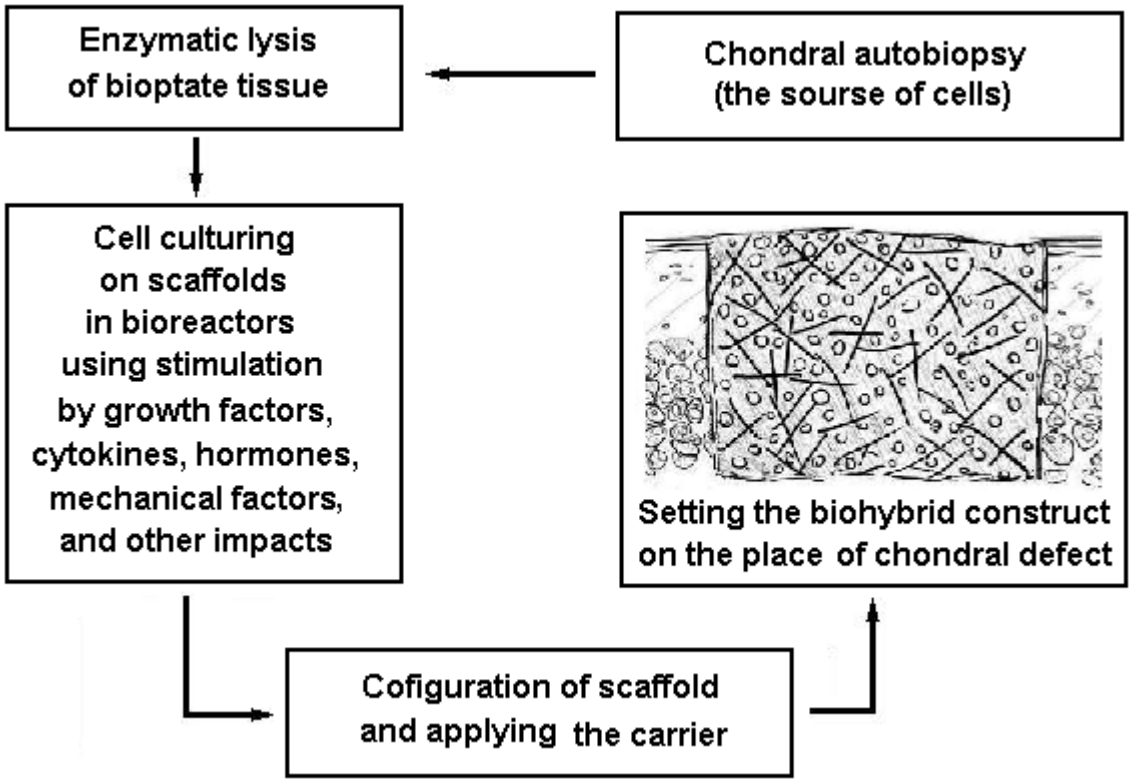

Fig. 1. Common scheme of tissue engineering, shown on the example of autologous chondrocyte pre-culturing in vitro

To date, of the many cell sources for cartilage tissue engineering, the ACI technology was mostly used in clinical practice. It based on transfer of own chondrocytes from the same joint or other chondral tissues of person to place of chondral defect [2, 12]. The ability to product collagen type II, proteoglycans, sulfated glycosaminoglycans, matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP) seems to be a key phenotypic signs of chondrocytes that determined their successful participation in the tissue-engineered constructs. Unfortunately, there are a number of objective limitations, as a relatively small number of chondrocytes in donor material (about 5% in the volume of tissue), fast dedifferentiation with the production of collagen type I, integrins and other signal molecules (SHC, Erk1/2), typical connective tissue [12, 13]. Just to prevent this phenomenon one applyes the main components of bioengineering technologies: the use of growth factors, scaffolds, and physico-chemical stimuli in a bioreactor or in vivo [2, 14].

With the same purpose a various stem cells derived from embryonic tissue, autologous mesenchymal tissues (MeSC), like bone marrow, synovial membrane, periosteum, fat, muscles, connective tissue, can be directed to chondrogenic differentiation [8, 15, 16]. The data about transdifferentiation of some mature cells of mesodermal origin (fibroblasts, adipocytes) into chongral phenotype due to culturing in the three-dimensional bioactive scaffolds were published [9, 17].

The key moment for the use of stem cells is their ability to be directed on chondral way of differentiation under the action of TGF-1, some other growth factors (BMP-2, FGF, IGF-1, PDGF) or protein components of synovial fluid [6, 9]. At the present time, the convincing results of cartilage matrix production by seated stem cells after differentiation were shown at use of practically all known scaffolds for cartilage tissue engineering [7].

Three-dimensional matrices (scaffolds) for cartilage tissue engineering must have biomimetic properties, it has to be biocompatible, have adequate physical and chemical characteristics and, ideally, completely replaced by auto-self chongral tissues in time. Extracellular matrix (ECM) of cartilage is difficult three-dimensional network for the growth, proliferation and differentiation of cells with nanofibers amd nanopores, which formed different local microenvironment [6, 8]. The three-dimentional porous structure of acellular scaffolds is required by the metabolic needs in the neoformed tissue [7, 18]. The attention to cartilage ECM properties was actualized, once molecular signaling pathways between the mechanical effects on the cells and regulation of their differentiation with the participation of TGF-β had been disclosed. This led to the development of technologies that met the chemical signaling management in cells due to the variation of ECM mechanical properties [19].

Scaffolds can be used for the culturing of a complete composite in bioreactors, but this approach refers to very expensive technologies, still having no broad prospects in the real sector of biomedicine. The more useful technology for scaffolds application concludes in settlement by the cells immediately before implantation, or during it [20]. Both these approaches are combined by the mechanism of the cartilage formation. It starts from the migration and setting stem and progenitor cells in scaffold matter, subsequent differentiation and synthesis of matrix de novo, as well as partial biodegradation of tempopary matrix followed this.

Today, a wide range of materials used for the fabrication of scaffolds in cartilage tissue engineering, they can be divided into natural and synthetic polymers, and their hybrids. Accoring to the structural properties all scaffolds one may distinguish hydrogels, sponges and porous [6, 21, 22]. The most widely used products, annotated according to the materials of recent surveys in this area, are presented in table. 1.

Although the use of nanomaterials for scaffolds fabrication is, rather, in their infancy, they have already recognized by almost ideal imitators of cartilage ECM. Nanofibrous or nanoporous structures are formed using the procedures of electrospinning, phase separation, freeze-drying, chemical corrosion or 3D printing [7, 23]. Nanofibres are very similar in structure to most of molecules in cartilage ECM (matrix proteins and proteoglycans), therefore, they have the ability to improve the adhesion, proliferation and differentiation in implant.

To optimize these properties, several methods have been proposed, including the accession of functional groups (thiolate, acrylate, and tyramine) and the use of composites (collagen-polyacrylamide, alginate-polyacrylamide, agarose-polyethylene glycol etc) [20].

General characteristics of the growth factors in cartilage tissue engineering. Hormones and growth factors regulating the adhesion and aggregation of chondrocytes, their growth and

metabolism, were well researched since the late 60th and 70th. The use of growth factors in cartilage tissue engineering coincided with the development of scaffold technologies. As the technologies applied for different scaffolds and molecular stimulators are unique in themselves, it is impossible to imagine any complete list of these methods.

All types of connective tissue, including cartilage, are regulated by fairly stable set of growth factors, and other mediators for differentiation of cells and intercellular signaling.

Table

Characteristics of the main materials for the scaffolds fabrication in cartilage tissue engineering

Material	Application for tissue engineering of cartilage	
	Cells	Clinical application
Natural polysaccharides [21, 24-27]*		
Alginate, agarose	Chondrocytes MeSC, embryonic stem cells	Cartipatch® (TBF Banque de tissues, France)
Hyaluronate		HyalograftC (Fidia Advanced Biopolymers, Italy) - benzyl ether
Chitosan		BST-CarGel (Bio-Orthopaedics, Canada)
The natural proteins [6, 10, 23, 28]*		
Collagen	Autologous chondrocytes, MeSC	MACI® (Genzyme Biosurgery, США) ChondroGide (Geistlich Biomaterilas, Switserland). Novocart 3D (TETEC AG, Germany) - copolymer with chitosan CaReS® (Ars Arthro®, Germany) Sphero®Gel (Russia) - copolymer with hexosamines и uronic acide
Fibrin	Autologous chondrocytes	Tissuecol® (Baxter International Inc.)
Synthetic materials [6, 8, 24, 25]*		
Polyorganic acid and its copolymers	Almost all sources of cells	BioSeedC (Biotissue Technologies, Freiburg, Германия) - copolymer with fibrin
Polycaprolactonean d polyethylene glycols		Experiments in vivo
Nanostructured materials [7, 20, 23, 29]*		
Modified polymers: gels, nanofibers or nanoporous sponges	Autologous chondrocytes, MeSC	Experiments in vivo

* - the only elected final reports and reviews.

They collectively regulate cell proliferation, adhesion, chemotaxis, differentiation, and ECM synthesis. Growth factors are used for stimulation of transplanted chondrocytes, and (less frequently) to manage auto-self cells when acellular scaffold technologies have been applied (Fig. 2).

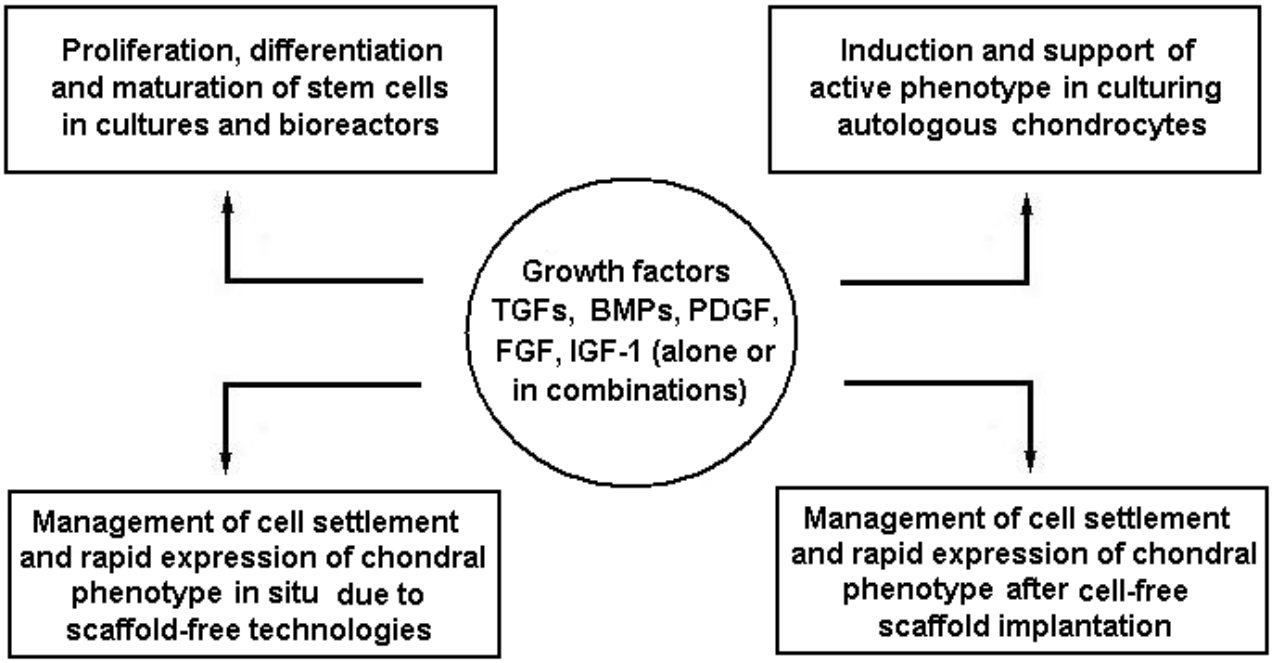

Fig. 2. Common scheme of growth factor application due to cartilage tissue engineering

General effect we achieve applying growth factors in tissue engineering, as in cell culturing for ACT, to induct and support phenotypic expression on chondral phenotype. For chondrocytes it looks like a rise of anabolic activity, an increase in the size, intensive synthesis of cartilage ECM components, and successful adhesion of cells in lamellar or three-dimensional structures [30, 31]. Transforming growth factor 1β, TGF 2 [32, 33, 34], BMP-2 and BMP-7 [31, 35, 36], FGF-2 [37], IGF-1 [30, 38], and PDGF [30, 39, 40] have been successfully used for chondral differentiation of MeSC, as well as for redifferentiation of autologous chondrocytes. Vascular endothelial growth factor VEGF, epidermal growth factor EGF, and hepatic growth factor HGF were investigated, but their application to the stimulation of chondrogenesis was proved unsuccessful [31].

To stimulate a culture, as a rule, it is applied not alone stimulating factor, and their combination with the optimal effect, of TGF-1 and IGF-1, TGF-1 and BMP-2, for example [41]. In vitro a variety of microspheres and microparticles have used to delivery growth factors to cells. In vivo the use of alone growth factor are more efficient, and it may be delivered as a part of hydrogels of polyethylene glycols, polilactide or soluble fibrin [32]. These approaches provide dose- and time-controlled release of growth factors in the culture medium.

From the beginning a few patterns was discovered. First, the effects of growth factors pre-adminisrated in a cultural medium are better than the same during their direct application in the place of transplantation. Secondly, pre-incubation with by growth factors in bulk cultures (semi-liquid and gel environment) is more effective, in comparison with their influence on single-layer cultures of chondrocytes. In addition, very low concentrations of growth factors are sufficient, the order of a few nmol/L. Any attempts to increase these concentrations in the culture medium not only do not lead to rise of chondral phenotype, but they even depress it, contributing to the formation of connective tissue matrix or cell death [15, 31].

Transforming growth factor superfamily. TGF-β is the most studied factor used in cartilage tissue engineering. It increases the phenotypic expression of chondral cells, chondrogenic differentiation of MeSC, resulting in production of cartilage ECM nacromolecules [31, 33].

Proinflammatory cytokines are strong natural antagonists of TGF-β, therefore, in cases of their high content in tissues of active arthritis the adequate chondrogenic stimulation with TGF-β is not expected. Approximately two-fold increase of density and elastic modulus of the matrix was shown in scaffold-free constructs, administrated by local TGF-1-containing gel, in comparison to healing without growth factor application. TGF-1 and TGF-β3 were successfully used in conjunction with mechanical stimuli of chondrogenesis [33, 42].

Some other activation mechanisms of TGF-β are also interest. Metalloproteinase ADAMTS1 and Granzyme B have recently been described as new mediators for the TGF-β activation. Granzyme B requires the presence of small amounts of leucine-rich proteoglycans (biglycan or decorin) for the liberation of TGF-β [43] while ADAMTS1 needed thrombospondin 1 type. This activation goes through non-proteolytic displacement mechanism [19]. Today TGF-β is the only growth factor, which is connected through the activation of mitogen-activated protein kinases with other molecular ways of chondrogenic stimulation.

BMP are also part of the TGF superfamily. Increased synthesis of ECM and proliferation of cells were recorded using BMP-2, BMP-4, BMP-7 BMP-12, and BMP-13, it was established for BMP-2 and BMP-7 to be maximally efficient [35]. In the culture in vitro the activity of BMP-7 gave it possibility to resist the catabolic effects of interleukin 1, fibronectin, or collagen fragments. This gives the possibility of BMP-7 stimulate healing of cartilage defects in vivo. As TGF-β, BMPs were also investigated in combination with the use of mechanical forces for induction of chondogenesis [34, 44].

In the work by Che et al. [36] have been analyzed the results of BMP-7 application for cartilage tissue engineering on rabbits with full-thickness defects in articular cartilage. About 5 x 106 chondrocytes with BMP-7 transfection were placed in a sterile collagen-fibrin gel and were grown within 14 days. At 12 weeks after implantation the surface of the neoformed cartilage did not differ macroscopically from the surrounding tissues and did not have visible borders with them, unlike zone of spontaneous regeneration or replacement only by gel scaffolds. Immune histochemical study has revealed clear expression of BMP-7 and its m-RNA in chondrocytes of implants from experimental group. Tissue regenerates contained significantly more specific glycosamineglycans and DNA. Aggregates of chondrocytes resembling isogenic groups in native cartilage were formed. Data of semiquantitative analysis on O'Driskoll scale testified to the relatively higher density of chondrocytes, the regularity of the articular surface, and better integration with the surrounding tissues.

The use of platelet-derived growth factor (PDGF) is of interest because platelet-rich plasma of the same patient may be an available source of it. Platelets contain two types PDGF (1 and 2), differing by their molecular masses, both have a positive impact on the regeneration of bone and cartilage tissues [30, 45]. Purified PDGF increases migration of chondrocytes and expression of the surface zone protein (lubricin), but usually unstable fibrocartilage is formed after remodeling, so the application of PDGF alone to cartilage tissue engineering have recognized as ineffective [46].

The efficiency of platelet-rich plasma application as a source of PDGF, as well as proof of his participation in the chondoreparation was published by Kon et al. [40]. The study summarizes the treatment of 100 patients with osteoarthritis (115 knee joints). Platelet-rich plasma obtained from 150 mL of venous blood of the same patient used to stimulation of chondrogegnesis by intraarticular instillations. The results of 91patients (57 men and 34 women) from this group were fully traced within 12 months. Distribution by severity of osteoarthritis (Kellgren) was as 0 from 58 knee joints, I-III from 33 jonts, and IV from 24 ones. The authors do not describe any adverse effects after this procedure, except for a slight swelling in the joints, and single cases of weak pain within 2-3 days after the injection. About 80% (73 of 91) patients were satisfied with the treatment results. The IKDS indicators have shifted in the direction to normal and subnormal data more than 70% of patients, the average values on a IKDS scale increased with 40.5±10.4 to 62.5±18.6 to 6 months, and 60.6±18.9 to the year of observation. Similar data were obtained using a Visual Analogue Scale.

Other growth factors. IGF-1 is an important anabolic factor for chondrocytes; it is able to potentiate the action of many other growth factors in respect of these cells. The level of IGF-1 increases in vivo on the place of cartilage defect immediately after the injury that became as the primary basis for discussion about its participation in the healing of cartilage. Growth factor IGF-I, as it was shown, allows to reduce lesion of the cartilage at the loss of the ECM volume. The application of IGF-I was accompanied by the increase in production of collagen and proteoglycans by chondrocytes, but its effectiveness was sharply different between zones of cartilage [2, 30, 31].

The new factor described like factor of growth and differentiation (GDF-5) is promising, because it can stimulate chondrogenesis at an early stage and be used both separately and in combination with gene therapy [11].

The use of mechanical stimuli and bioreactors. Growth factors have been successfully used in cobination with mechanical and chemical impacts, such as drifting, compression, and variable hydrostatic over-pressure. So, sharing, BMP-2 and IGF-I applied together have increased the functional properties of tissue-engineered construct [31]. The mechanical drifting, combined with BMP-2 in the culture of dedifferentiated chondrocytes, let to expression of chonroblastic genes and synthesis of relevant proteins [47]. TGF-β3 combined with the immediate compression [33], as TGF-1 with hydrostatic water loads [31] increased ECM construction to the values in the normal cartilage; the growth factor and mechanical stimulation had a synergistic effect.

The main task of bioreactors is the ensuring delivery of nutrients and removing waste products from cell culture, and also the required safety in the growth and phenotypic differentiation, including the necessary hydrodynamic loads. In addition to high productivity, each bioreactor should control and maintain pH, temperature, pressure, and concentration of necessary nutrients in the cell culture due to whole operating cycle. According their structure bioreactors for cartilage tissue engineering can be arranged in the form of parallel plates or concentrically placed cylinders, with rotating walls [47, 48, 49]. These structures are designed to provide the maximal square for the diffusion from perfused medium into scaffold matter and back. In comparison with traditional grow containers, bioreactors can minimize the necessary concentrations of growth factors, nutrients and cell-protecting agents.

Although the properties of cartilaginous structures grown in bioreactors are higher than tissue construct cultured statically, they have certain difficulties in engraftment after implantation in vivo. Apparently, a cartilage with a high content of aggrecanes is not only resistant to vascular invasion, but it disrupts remodeling in the subchondral bone [48].

Discussion. Despite the fact that autologous chondroplasty is the «gold standard» to recover damaged cartilage today, most specialists in regenerative medicine assume about tissue engineering to become the leader in this field in the nearest decade [3, 7]. Today the spectrum of cell sources and materials for the fabrication of its temporary media (scaffolds) were well outlined.

The research vector in cell-based technologies for cartilage tissue engineering aimes to the gradual transition from the low differenciated stem cells to more mature sources, with the possibility of pointwise change the gene expression to induct chondral phenotype. The work of researchers and developers in this area are focused on optimizing the conditions for the cell culturing (1), management mechanisms of their chondrogenic differentiation including growth factors (2), remodeling of biomimetic structures in authentic cartilage (3), and getting a good evidence in clinical trials (4).

Now it is established, and clinically used the sufficient arsenal of materials with high biocompatibility and mechanical properties. They are more similar to own cartilage ECM and may stimulate its formation in vivo. The use of nanostructured materials and composites, already approbated for the fabrication of scaffolds in classical micro-size structure, open new additional opportunities. Next tasks consist in the creation of “smart” biologically functional polymer structures, capable to control the behavior of cells due to all stages of remodeling tissue-engineered constucts [50]. At the same time Iwasa et al. [21] based on the analysis of refereed literature sources of past five years came to a conclusion about the absence of evidence-based arguments to give preference methods of tissue engineering and bioengineering before classical ACT technique or simple cell-free scaffold implantation. We see, near future will show a real place of these innovative technologies in the restoration of cartilage lesions.

The key problem is to ensure a coherent complete remodeling this constucts into native-like cartilage, that required predictable control impacts on the processes of settlement, proliferation, differentiation and adequate phenotypic expression of cells in the scaffold matter remodeling in autologous cartilage ECM. Fundamentally three control moments should be allocated: the structure of scaffolds (1), the use of growth factors (2) and mechanical stimulation (3), which shall be used only in the complex [4, 29].

Key-points of this development are concentrated around a further understanding the molecular biology and pathophysiology of the cartilage, use of nanotechnology in the scaffold fabrication with preset functions of management, problems of parallel control of the various molecular regulatory pathways. The application of several growth factors, as well as growth factors with non-chemical stimuli remains poorly understood area of research for cartilage tissue

engineering. Technical and legal problems of tissue engineering in connection with the advent of new technological trends are still a problem and needs to discuss.

In the nearest future the whole-cycle development of tissue engineered constructs de novo based on bioinformatics analysis will come one of the promising approaches to achive significant progress in the optimal control of the cell population and their subsequent phenotypic expression on chondral phenotype. To realize this approach, one need to create consistently a database of cartilage metabolomics mapping (1); hold a virtual simulation of biomimetic cartilage structures on the basis of nanomaterials with necessary biocompatibility, biodegradation and chondroinduction (2), develop the technologies to fabricate this biohybrid scaffold (3), and test its capabilities in model experiments (4) and in vivo (5). Eventually this can lead to the creation of new tissue-engineered solutions allowing to successfully remodel biohybrid constructs in functionally complete cartilage.

Conclusion and perspectives. Tissue engineering of cartilage is certainly perspective field in regenerative biomedicine; its short progressive development already returned many thousands of people to active life and movement. This practical field of molecular biotechnology deserves to subsequent steps of its development, was not less rapidly and successfully, based on the key findings in molecular biology and epigenetics of cartilage. The whole-cycle development of new three-dimensional and real-time-managed structures, fully remodeling within a few weeks after implantation in natural hyaline cartilage beeng functionally complete and stable to subsequent injuries, are presented the most successful in this way.

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Использование факторов роста в тканевой инженерии суставного хряща (обзор литературы)

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Аннотация. В статье представлен систематизированный обзор, анализирующий распространенность, основные технологии и перспективные направления использования факторов роста в тканевой инженерии суставного хряща. Наибольшее внимание уделено проблемам сочетания факторов роста между собой, с современными скаффолдами для клеточного заселения и вариантами механической и физико-химической стимуляции хондрогенеза, в том числе – в условиях использования биореакторов.

Ключевые слова: суставной хрящ; тканевая инженерия; скаффолды; транформирующий фактор ростаβ ; костные морфогентические белки; инсулиноподобный фактор роста-1; тромбоцитарный фактор роста.