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Published in the Russian Federation  
European Journal of Molecular Biotechnology  
Has been issued since 2013.  
ISSN: 2310-6255  
Vol. 3, No. 1, pp. 4-10, 2014

DOI: 10.13187/issn.2310-6255  
[www.ejournal8.com](http://www.ejournal8.com)



UDC 51-76: 612.751.2

## **The Grouping of Chondrocyte Receptors According to Their Control over Cartilage Tissue Remodeling**

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**Abstract.** To give the empirical space for development of molecular biotechnologies in regenerative medicine the article presents a systematic review of new data for the last 5 years, dedicated to chondrocyte receptor apparatus, connected to physiological and reparative regeneration in articular cartilage. The main attention is given to the receptors of chondrocytes involved in synthesis and degradation extracellular matrix, differentiation and apoptosis of chondrocytes.

**Keywords:** chondrocyte receptors; articular cartilage; extracellular matrix; apoptosis; tissue; engineering.

### **Introduction.**

Progressive damage and loss of tissue in the articular cartilage is major problem of regenerative medicine. This pathology is so widespread that it can be called the multifactorial «disease of civilization». The diseases of joints are important in reducing the quality of life for people of all ages, limiting the working ability of the population, which lead to high costs of prevention and medical care. Low regenerative capacity of the cartilage is serious medical and biological problem resulting in the difficulties in organotypical restoration of articular cartilage after trauma or in severe forms of osteoarthritis [1].

Chondrocytes complete the cellular pool providing regeneration and restoration of the cartilage during all life. Their receptor apparatus is intended to regulate the process of self-renewal and repair of tissue which determine the functional state of the hyaline cartilage. These processes include, as a minimum, synthesis and degradation of extracellular matrix (ECM), differentiation and apoptosis of chondrocytes [2, 3, 4]. The same processes regulate cartilage healing after trauma or osteoarthritis [4, 5].

The aim of this work is to carry out the grouping of chondrocyte receptors, as the regulatory tool of basic molecular processes in cartilage.

### **Material and methods.**

To form the adequate groups of receptors, exhaustive search and analysis of literature was performed using open resources: PubMed, PubMedCentral, PDB and the Russian scientific electronic library (E-library). The search was carried out using the following keywords: receptors chondrocytes, chondrogenesis, matrix cartilage, cartilage, osteoarthritis & molecular biology,

matrix metalloproteinase in Russian and English equivalents. For the detailed analysis we selected more than 300 sources over a 10-year period. Microsoft Office Access was used to create a grouping database. The criteria of adequacy, completeness, and stability characteristics were used for holding groups. In the end following list of information was formed to write the record in the database: the name of the receptor with all synonyms (1), belonging to the family (2); binding ligands (3); secondary messengers and executive intracellular molecules (4); proven involvement in the regulation of synthesis, the collapse of the extracellular matrix, differentiation and apoptosis of chondrocytes (5). Part of the receptor in each of these processes was noted separately. We have selected the key receptors: transforming growth factor beta (TGF $\beta$ R), bone morphogenetic proteins (BMPR), insulin-like growth factor (IGF-1R), toll-like receptor (TLR), tumor necrosis factor (TNFR), interleukin 1 (IL-1R), leptin (LRB), angiotensin (ATR), CD44, and prostaglandins (E2/E4). All of the receptors mentioned above have a direct or indirect impact on the catabolic or anabolic function of chondrocytes, as a result, on the remodeling of the cartilaginous tissue (Fig. 1).

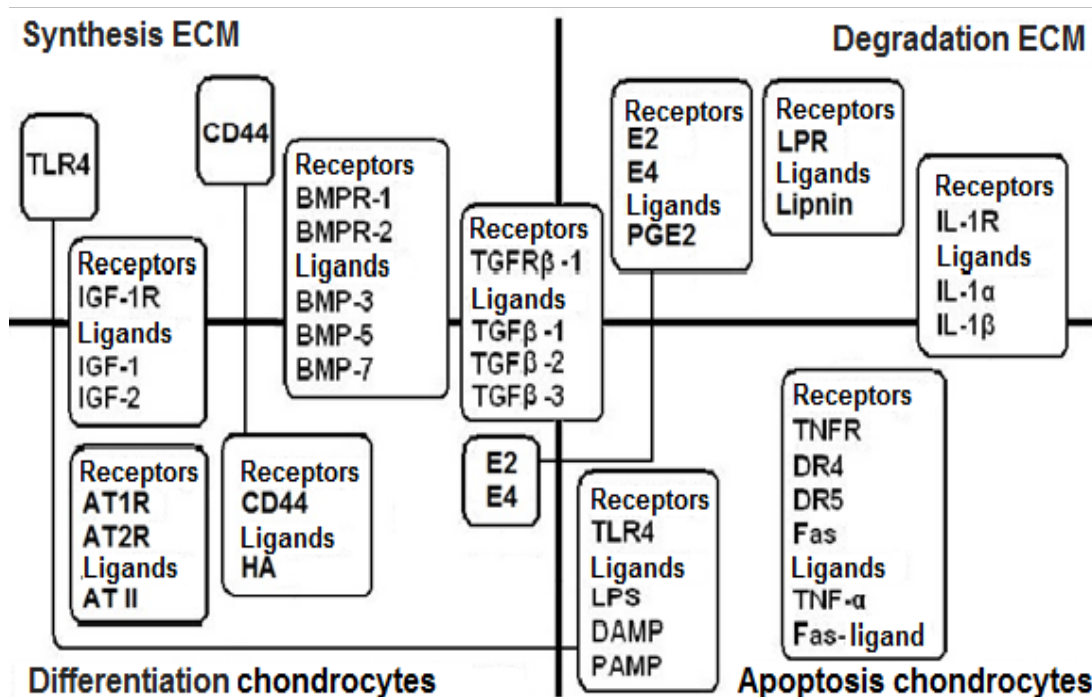


Figure 1. Working groups of chondrocyte receptors in accordance with their participation in the remodeling of the articular cartilage. TLR4, except for the start of apoptosis, takes part in the regulation of proteoglycan synthesis; CD44 in addition to participating in the regulation of ECM synthesis, shows the participation in the differentiation of chondrocytes; PGE2 in addition to running processes of destruction ECM cartilage, shows a possible participation in the differentiation of chondrocytes.

### Results and discussion.

During the analysis and study of the receptor apparatus the main receptors and signaling molecules were detected according to their participation in the remodeling of the articular cartilage under normal and pathological conditions. Their interaction with specific ligands led to the activation of one of the four processes associated with remodeling: differentiation (1) or apoptosis (2) of chondrocytes, ECM synthesis including collagen II, X, and aggrecan (3) or ECM degradation (4) by metalloproteinase (MMP), aggrecanase (ADAMTS) in balance with their inhibitors (TIMP) (Fig. 2).

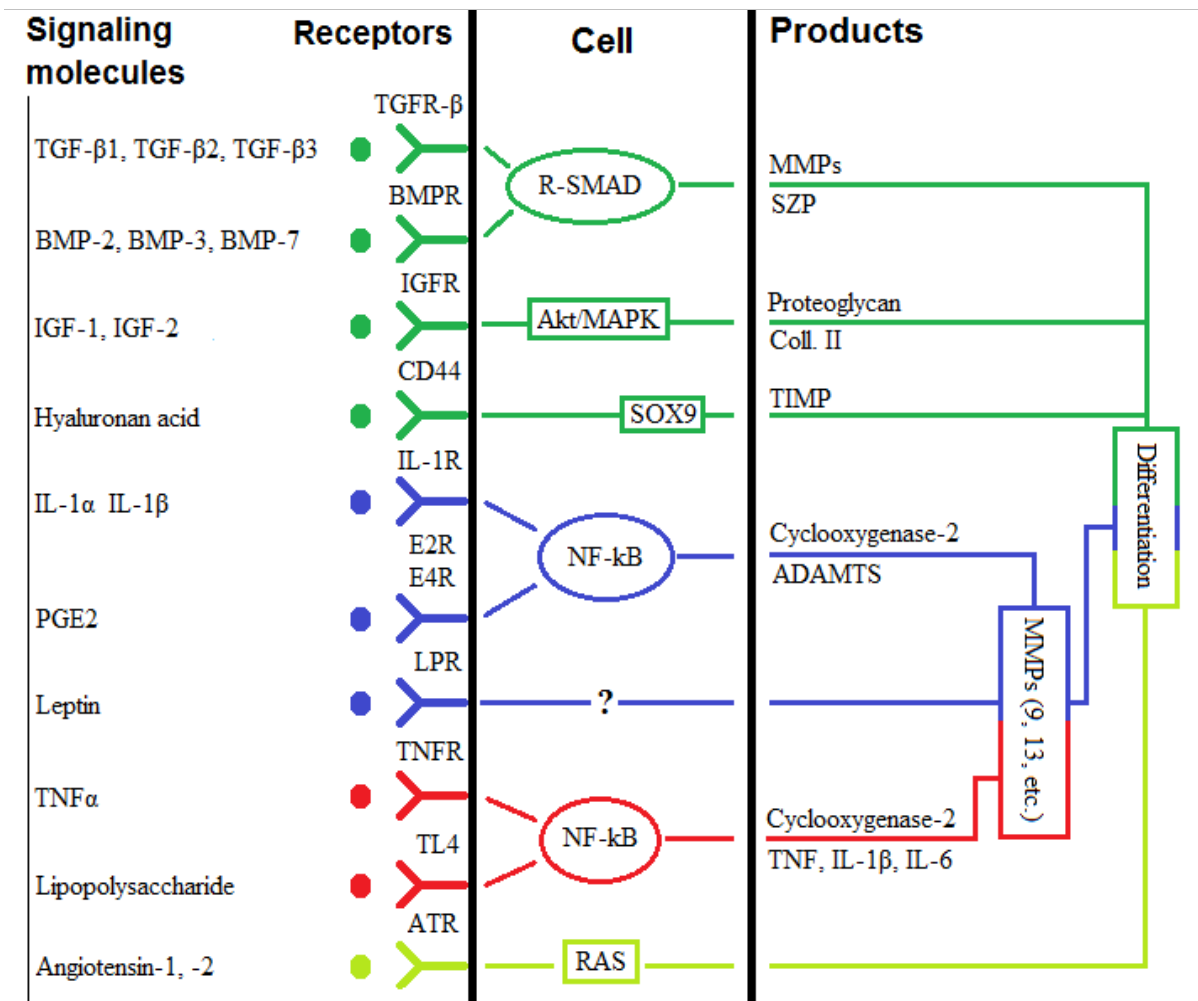


Figure 2. The result of the interaction of chondrocyte receptors with specific ligands, affecting key functions in the cartilage tissue: • – ECM synthesis, differentiation, • – ECM degradation, • – apoptosis, • – differentiation.

Two main families (TFR and BMPR) are crucial in the regulation of ECM synthesis and differentiation of chondrocytes. They include TGFR-1, TGFR-2, TGFR- $\beta$ 3 associated with the relevant molecules of TGF $\beta$  super family, and BMPR, affine to BMP2, BMP4, BMP6 and BMP7 [6, 7]. Intracellular signal transmission from TGFR-beta and BMPR is carried out by phosphorylation of R-Smad (1, 2, 3, 5, 8) with the subsequent activation of the transcription factor and synthesis of matrix metalloproteinases and superficial zone protein (SZP) [4, 8, 9, 10]. Receptor IGF-1R, participating in the regulation of ECM synthesis, can communicate with IGF-1 and IGF-2 ligands. As a result of this interaction the synthesis of proteoglycans and collagen II is activated on the signal pathway Akt/MAPK [11]. Another feature of IGF-1R also takes part in the process of chondrocyte differentiation [12].

CD44 is another receptor, which was expressed on the chondrocyte membrane, with the similar regulatory functions due to its ability to bind with hyaluronic acid. Their interaction activates transmission of a signal by the transcription factor SOX9, which allows the receptor to react to cartilage ECM by the increase of MMP synthesis in chondrocytes [13]. A family of TLR-4 receptors, specifically recognizing bacterial lipopolysaccharide, also affects the ECM synthesis [14]. The TLR-4 activation leads to the increased synthesis of MMP-13 and cyclooxygenase-2, with parallel reduction of collagen II synthesis [15].

Next group of receptors may affect ECM volume by stimulation of its degradation. Thus, IL-1R has similar properties when it started, interaction with the IL-1 $\alpha$  and IL-1 $\beta$  leads to stimulation of MMP synthesis resulting in increased degradation of cartilage matrix proteins [16]. Interaction of IL-1  $\beta$  with IL-1R can also induce apoptosis of chondrocytes with the progressive degenerative

changes in the cartilage [17]. All these processes are regulated by the transcription nuclear factor (NF- $\kappa$ B). In chondrocytes NF- $\kappa$ B is a key regulator of MMP and cyclooxygenase-2 in chondrocytes [11]. Extracellular prostaglandins can get bound to specific receptors E2, E4 which results in slowed synthesis of aggrecans and proteoglycans but in increase of MMP-13 and ADAMTS-5 synthesis. As a result, the progressive decrease of the ECM density has followed. Some data support prostaglandins, in addition to their role in the degradation of ECM, to contribute chondrogenesis and terminal differentiation of chondrocytes [18, 19].

Currently, there is evidence that leptins also had specific receptors (LRB) on the membrane of chondrocytes. The role of these signals in the cartilage is not fully understood, but it is possible that such interactions could regulate the differentiation of chondrocytes and synthesis of collagen X. It is unclear whether this is a direct or indirect effect of leptin [20].

Differentiation of chondrocytes is key to supporting homeostasis in cartilage. As was discussed above, TGFR b BMPR IGF-1R are main receptors in the regulation of differentiation of chondrocytes. In addition to these ones, CD44 can take part in this process. It should be noted that CD44 expression of young chondrocytes is higher than in adult hypertrophic cells [13]. Today there is evidence that renin-angiotensin system takes part in the regulation of chondrocyte differentiation. Angiotensin II molecule interacts with specific receptors AT1R and AT2R. Their interaction results in the differentiation of mesenchyme cells into hypertrophic chondrocytes starts [14].

TNFR1, Fas/apo-1(CD95) and TRAILR-1 (DR4) represent the receptor group regulating the apoptosis of chondrocytes. Fas- and TNF-mediated apoptosis develops in caspase-dependent manner, with the participation of caspase-8. In case of transfer of apoptotic signal through TNFR, the simultaneous anti-apoptotic signal results in gene expression of cytokines TNF, IL-1 $\beta$ , IL-6, and collagenase stromelysin and adhesion molecules. TRAIL-receptors modulate the two different signals: activation of caspases (1), and the expression of nuclear transcription factor gene NF-KB [21].

### Conclusion.

The grouping of chondrocyte receptors (The grouping of chondrocyte receptors) described in this paper is an attempt to make a new step in understanding their role in mediated processes due to natural remodeling and reparative regeneration of articular cartilage. In future it is planned to use this grouping to create a mathematical model, which will more accurately predict the development of various processes in the cartilaginous tissue under the action of different signal molecules. This grouping gives an analytical tool in molecular biology, biotechnology, and regenerative biomedicine.

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UDC 51-76: 612.751.2

**Группировка рецепторов хондроцитов по их участию в управлении  
ремоделированием хрящевой ткани**

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**Аннотация.** В статье, на основании фундаментальных закономерностей молекулярной биологии и биотехнологических потребностей регенеративной медицины, представлен систематический обзор новых данных о рецепторном аппарате хондроцитов за последние 5 лет. Данные сгруппированы так, чтобы показать дифференцированное участие рецепторов в ключевых процессах, связанных с естественным remodelированием и репаративной регенерацией хрящевой ткани: синтезе и деградации экстрацеллюлярного матрикса, дифференцировке и апоптоза хондроцитов.

**Ключевые слова:** рецепторы хондроцитов; суставной хрящ; экстрацеллюлярный матрикс; дифференцировка; апоптоз; тканевая инженерия.