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Protein Receptors on Chondrocytes

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Abstract

Here we reviewed various protein receptors and their roles on chondrocytes. In connection with this we summarized that GPCRs, VEGF receptors, integrins, TLRs, LRP receptors, chemokine receptors and growth factor receptors are the main receptors on chondrocytes. We have discussed different receptors involved in chondrocyte differentiation and those activating proliferation in chondrocytes. We conclude that among the myriad of protein receptors expressed by chondrocytes, some (TLRs, LRPs and chemokine receptors) have the important role in osteoarthritis (OA). These receptors could be targeted by pharmaceutical agents to treat intra-articular injuries including osteoarthritis.

Keywords

Chondrocytes; Protein receptors; Osteoarthritis; ECM; Differentiation; Inflammation; Slater

Introduction

Chondrocytes are critical cells in the extracellular matrix (ECM) of articular cartilage. The plasma membrane of articular chondrocytes is comprised of varied membrane proteins such as channels, transporters, enzymes, receptors, and anchors for intracellular, cytoskeletal and ECM proteins and other macromolecular complexes which determine the cell surface phenotype of the cells (Figure 1).

Interestingly membrane proteins are valuable pharmaceutical targets and are crucial for chondrocyte function [1,2]. This review details the myriad of studies of protein receptors on chondrocyte and high-light the need for further, more-comprehensive research to validate clinical receptors-based approaches towards diseases.

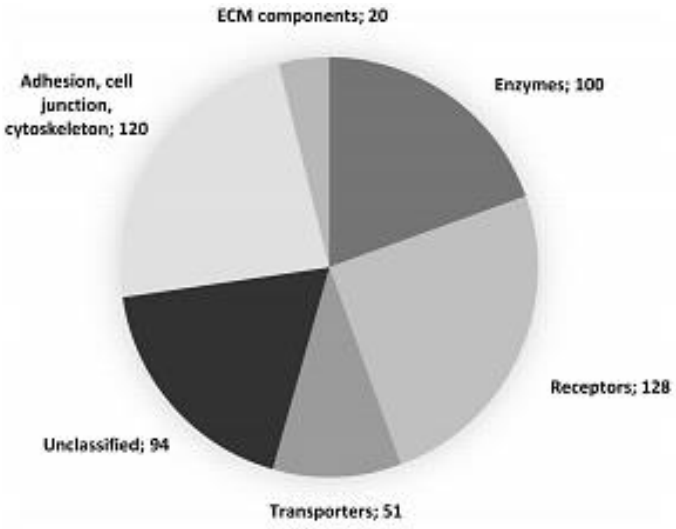

Figure 1: Distribution of the surface proteins on chondrocytes is identified in this study. One hundred proteins were classified as enzymes (23%), 128 proteins had receptor roles (30%), 51 proteins were involved in transport processes across the PM (12%), 120 proteins were involved in adhesion, cell-cell or cell-matrix junctions and cytoskeletal organisation (28%), and 20 proteins were structural ECM components (5%). Ninety-four proteins (22%) could not be assigned to one of the subgroups or their function was unknow.

G-protein coupled receptors (GPCR)

G-protein coupled receptors (GPCR), a large family of seven-transmembrane domain receptors, which consists of alpha, beta and gamma subunits [3], appear to contribute to exhibit bone expression, [4]] and control the proliferation, differentiation, and apoptosis of osteoblasts, osteoclasts, and chondrocytes by GPCR signalling [5].It seems that not only is Gαs a major participant in chondrocyte differentiation, but also it inhibits the differentiation process. The observations reported herein that the absence of Gαs in fetal [6] or postnatal [7] chondrocytes conduces to considerable stimulation of chondrocyte differentiation and termination of longitudinal bone growth. Alternatively, an isoform of Gαs (XLαs), with an alternative exon 1, is capable of initiating the downstream cyclic AMP (cAMP) signalling pathway [8], which suppresses markers of hypertrophic chondrocytes such as ALPase activity and collagen type X expression in differentiated cultured rabbit chondrocytes [9]. There are several GPCRs expressed by chondrocytes activating Gαs which controls chondrocyte hypertrophy. These include PTHR1 [10], receptors for prostaglandins [11,12], membrane estrogen receptor GPER [9], RDC1 receptor [13], adenosine (nucleotide P2Y) receptors [14,15], β-adrenergic receptors [16], histamine H2 receptors [17]. Although the absence of PTHR1 leads to a marked decrease in chondrocyte proliferation, and ectopic apoptosis of stemlike chondrocytes, effect of Gαs ablation was not observed upon [9]. On the other hand, pharmacological in vitro activation of PKC, the main downstream signalling pathway of

Gq/11, promotes chondrocyte differentiation [17,18].Gq/11 can prevent apoptosis in the absence of Gαs, whereas it contends with its action to suppress differentiation in the presence of Gαs [19].There is evidence that the ablation of Rac1 (as a member of the Rho family of small G proteins) in chondrocytes, has been found to cause hypocellularity, decreased proliferation and growth retardation [20]. Particularly, Gi that is activated by chemokine receptors of chondrocytes [21], inhibits the cAMP pathway, and opposes Gαs action [22], which would increase chondrocyte differentiation. Given that Gαs can be activated by PTHR1, it has the crucial role to prevent premature chondrocyte differentiation and absence of either one causes instantaneous chondrocyte differentiation [19]. PTH/PTHrP receptor mRNA is highly expressed in maturing chondrocytes, while its expression is not observed in premature or fully hypertrophic chondrocytes. There is striking observation that GPR30 (a G protein-coupled estrogen receptor) has been detected in the resting and hypertrophic zones, and is not exhibited in the proliferative zone, which demonstrates that GPR30 is possibly responsible for chondrogenesis[19].We found clear evidence of the impact of RDC1 (a class A orphan G-protein coupled receptor) not only on the expression of the genes correlated with chondrocyte hypertrophy, but also on increased matrix degradation and the factors of OA development [23]. Additionally, RDC1 activation leads to an induction of MMP13 [24], which is highly upregulated in disease and leads to cartilage degradation[25]. Intriguingly, PGE2 (Prostaglandin E_2) binds to one of four receptor isoforms, EP1,EP2, EP3, and EP4 which are coupled to G-proteins. The presence of EP-1 and 2 receptors was confirmed in rat growth plate chondrocytes [26,27] and EP4 receptors have been found in bovine articular chondrocytes [12]. EP1 is in consistent with Gq and promotes IP3 signalling and calcium transients [28]. Obviously, EP2 and EP4 associate with Gas and stimulate cAMP/PKA/CREB signalling which interfere in progression of chondrocyte differentiation [28,29], WhereasEP3 with EP2 and/or EP4 can downregulate activation of the cAMP/PKA/CREB cascade[28,29]. It has been found that an increase in EP4 and a decrease in EP3 receptor expressions occur through later stages of chondrocyte maturation [30,31].The experiment consistently showed the existence of P2 receptors (a family of G protein-coupled receptors) namely P2Y2 as an agent of interleukin (IL)-1 secretion [41], P2X2 and P2X5 [14]on chondrocytes [32]. Histamine receptors as another class of G protein–coupled receptors in chondrocytes, which noticeably increase cAMP while decreasing KS (keratin sulfate) [33], could be expressed during the development of arthritis [34]. In particular, a variety of glutamate receptors have central role in bone remodelling [35-37]. One of these receptors is named calcium-sensing receptor (CASR) that its gene (*Casr*) knockout in chondrocytes interestingly suppresses embryonic development and cartilage maturation [38].

VEGF-receptors

Chondrocytes are exposed to an inflammatory micro-environment in the extracellular matrix (ECM) of articular cartilage in joint diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA).The findings revealed that hypertrophic chondrocytes release angiogenic factors including VEGF, which is assumed to increase inflammation as well as its obligatory role for endochondral ossification [13]. Accumulating evidence suggests that VEGF-R1, VEGF-R2, VEGF-R3 and neuropilin-1 are expressed in osteoarthritic cartilage where chondrocytes demonstrate developmental differentiation [39,40]. Clearly, primary chondrocytes express three receptors for VEGF (neuropilin-1, VEGF-R2 and VEGF-R3), signifying that some VEGF might have a role in chondrocyte metabolism. Given VEGF-R2 (which bind VEGF-A and VEGF-C [41]) is expressed and stimulated by chondrogenic treatment, it implies that VEGF-A and VEGF-C may

directly affect mature chondrocytes.

Integrins

Extracellular matrix (ECM) proteins affect cell proliferation, differentiation, and morphogenesis [42]. Integrins are heterodimeric transmembrane molecules composed of an α- and a β-subunit. Several observations suggest that the interaction between chondrocytes and matrix proteins is mediated by the β1 subfamily of integrins [43]. Integrins interact with growth factors which might be important for cell adhesion, differentiation, growth, and survival in different cell types [44]. Additionally, Insulin-like growth factor I (IGF-I) which is identified to stimulate differentiation in chondrocytes [45,46], associates with β1 integrin in the chondrocyte adhesion to collagen type II[47]. Moreover,it has revealed that chondrocytes express the α1β1, α2β1, α3β1, α5β1, α6β1, α10β1, αvβ3, and αvβ5 integrins [48-53]. Indeed, α5β1 integrin, as the primary chondrocyte fibronectin (FN) receptor [45],is thought to be an important chondrocyte integrin accompanied with less expression of α1β1 and α3β1. Whilst, adult human chondrocytes have demonstrated the expression of α1β1, α5β1, and αvβ5 integrins compared to the less expression of α3β1 and αvβ3. Importantly, fetal chondrocytes and chondrosarcoma cells have higher expression levels of α2β1 and α6β1 integrins when Compared to adult chondrocytes [54,55]. Not only does the α1β1 integrin lead to adhesion of chondrocytes to type VI collagen [56], but also it mediates adhesion to cartilage matrix protein (matrilin-1) [57].

TLRs

According to the previous research, chondrocytes express TLR1, TLR2, and less TLR9. TLR is highly dependent on the activation and differentiation state of the chondroid cells, for instance the involvement of TLR9 is deciphered in inflamed (OA) chondrocytes, but far less in mature, resting chondrocytes [58]. In contrast, the expression of TLR-4 is shown in human articular chondrocytes on both the messenger RNA (mRNA) and protein level [44]. Fascinatingly, TLR-7 was only apparent in chondrocytes among patients younger than age 35 years, implying that a patient's age may influence TLR expression [59].

LRP receptors

Despite a large body of evidence demonstrating the role of LRP receptors (lipoprotein receptor-related proteins) in musculoskeletal homeostasis, LRP5 and LRP6 are critical for transmitting of canonical Wnt-signaling [60] which is linked with Cartilage and bone through processes such as endochondral ossification. Prior research highlights that in active Wnt-signaling, Wnts bind to the lipoprotein receptor-related protein (LRP) co-receptors [61]. Not only are LRP4, LRP5, and LRP6 within canonical Wnt-signaling regulated in simulated microgravity and cyclic hydrostatic pressure, but also these ones appear to contribute to cartilage degeneration[62].In addition, LRP5 has been found to be upregulated in osteoarthritis[63],whereas LRP6 loss-of-function mutation has been along with an enhanced progression of osteoarthritis [64].

Growth factors receptors

As has been previously reported in the literature, chondrogenic growth factors such as insulin-like growth factor (IGF)-1 and transforming growth factor (TGF)-β1 have influence on chondrogenic

redifferentiation as well as the expression of Col2 and GAGs in the cartilage tissue [65]. Nevertheless, IGF-1 which Its activity is mediated via IGF-1 receptors (IGFR1) [66], is a major factor for chondrocyte proliferation and matrix synthesis [23]. Not only is the TGF-β1 a primary stimulator of proteoglycans and Col2 synthesis in chondrocytes [67],but also it is able to induce the chondrogenic differentiation of mesenchymal stem cells *in vitro* [68].Signals are transferred by forming complex dimers of TGF-β receptor 1 (*TGFBR1*) and 2 (*TGFBR2*) [69]. Provided a deficiency of *TGFBR1* occurs, stimulation of TGF-β1 in chondrocytes is improved by upregulation of *TGFBR1*. Furthermore, the higher expression of *TGFBR2* under IGF-1 stimulation could also be Possible, due to a lack of the TGF-β1 in chondrocytes [70].

Chemokine receptors

As has been previously reported in the literature, chondrocytes also express chemokine receptors including CXCR3, CXCR4, CXCR5, CCR1, CCR3, CCR5 and CCR6 and several chemokines, namely IL-8, MIP-1α, GROαβγ, MCP-1, eotaxin-1 and RANTES, which might play significant roles in chondrocyte hypertrophy [71-72]. Undoubtedly, inappropriate activation of the chemokine network leads to inflammatory arthritis. For example, numerous chemokines are generated in joint tissues of patients with OA and after joint injury [73-74]. Research has provided evidence for the expression of CCL19 and its receptor CCR7 which is consistent with enhanced symptoms in the synovia of patients at an early stage OA [74]. Moreover, improved levels of CCL5 and CCL19 have been observed in synovial fluids derived from patients with both RA and OA [75-79].

Discussion

In summary, chondrocyte degradation as a process of ageing, disease and injury has a significant impact on everyones life. Chondrocyte biology is a controversial and emerging science. This article aimed to collect the recent research about chondrocyte proliferation, differentiation, and death and the pathogenesis of OA. Among all the protein receptors expressed by chondrocytes, RDC1, Histamine receptors, TLR9, LRP5, LRP6, CCR7, CCR7 have the most important role in OA development, whereas VEGF-R, β1 integrin, EP and Gi are the major activators of chondrocyte differentiation. It is believed that CASR and PTHrP have an important role in chondrocyte maturation, whilst IGFR1 and Rac1 seem to play a major part in chondrocyte proliferation. In light of all of the aforementioned studies, chondrocyte protein receptors present as a possible trigger for pharmacological targets.

Disclosure

Dr. Gordon Slater is medical director of Integrant Pty Ltd an orthobiologics company. He is a former director of Albury Day Surgery.

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