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The interplay between inflammatory mediators and mechanotransduction is mediated by ion channels in articular chondrocytes: Functional consequences in osteoarthritis

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In their recent review article in this issue of Physics of Life, Segarra-Queralt and co-authors [1] discuss and explore how various biological mediators influence the behaviour of articular chondrocytes under mechanical load in healthy cartilage and in osteoarthritis (OA). The aim of their review is to provide a functional overview of the biochemical exposome of chondrocytes and how it may alter the process of mechanotransduction in these highly specialised cells.

Chondrocytes are terminally differentiated cells that are located within the extracellular matrix (ECM) of cartilage, which is avascular, aneural and alymphatic [2]. However, despite their low metabolic activity chondrocytes are highly sensitive and responsive to alterations in their micro-environment [3]. These cells are routinely subjected to a complex mechanical environment consisting of tension, compression, shear, and hydrostatic pressure [4]. The absence of vasculature in mature and healthy articular cartilage means that the delivery of nutrients [5], disposal of metabolic waste products [6] and maintenance of metabolic homeostasis [7] must occur through the process of diffusion, which is facilitated by dynamic loading and streaming potentials and fluid flow through the pericellular ECM [8,9]. Under normal and pathophysiological conditions, chondrocytes exist in a low glucose [10] and low oxygen tension environment [11,12]. Consequently, articular cartilage has a low reparative potential and in the case of chondrocytes, this challenging microenvironment predisposes them to a variety of cellular dysfunctions, and limits the potential of fully differentiated mature cells in regenerative medicine strategies [13,14].

Research conducted over the last two decades has demonstrated that articular chondrocytes express a wide variety of ion channels, which constitute the "channelome" in these cells. These ion channels play crucial roles in essential physiological processes, including signal transduction, setting the resting membrane potential, cell volume regulation, and the responses to mechanical loading and chemical stimuli [15–17]. The chondrocyte channelome includes calcium channels, potassium channels, sodium channels, aquaporin water channels [18] and numerous P-type ATPases in addition to the ubiquitously expressed Na, K-ATPase

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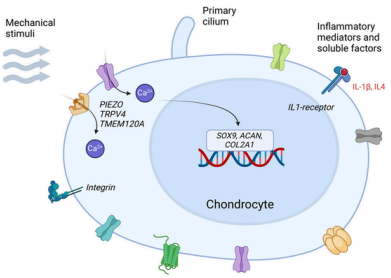

Fig. 1. A simplified illustration of a chondrocyte with its channelome, the components of which are involved in mechanosensation and mechanotransduction pathways, such as Transient Receptor Potential Vanilloid 4 (TRPV4), PIEZO and TMEM120A (TACAN) channels. These ion channels are permeable to Ca^{2+}, which under physiological circumstances promote pro-chondrogenic gene expression such as SOX9, ACAN, and COL2A1. Increased levels of extracellular interleukin 1 beta (IL-1β) or other soluble factors influence the activation of this channel. Mechanical signals mediated by integrins may cross-talk with the signals generated by soluble factors. Created with BioRender.com.

[19–21]. Changes in intracellular calcium levels $[Ca^{2+}]_i$ influence processes such as cell signalling and ECM synthesis. Chondrocyte calcium channels include voltage-gated calcium channels and transient receptor potential (TRP) channels. Mechanical stimulation can lead to changes in ion channel activity, affecting intracellular calcium levels and influencing cellular processes such as ECM synthesis and cell metabolism. Several non-selective cation channels including TRPs [22], PIEZO [23,24] and TMEM120A (TACAN) [25,26] may be responsible in sensing and transducing mechanical signals into biochemical responses. Collectively, ion channels and gap junction proteins such as connexins play key roles in joint cartilage homeostasis by regulating the cellular physiology of chondrocytes [27] (Fig. 1).

The review by Segarra-Queralt and co-authors [1] presents and integrates essential knowledge concerning the regulation of chondrocyte mechanotransduction by local and systemic soluble factors. They highlight the importance of calcium influx through mechanosensitive PIEZO channels in chondrocytes and enhanced calcium flux through inflammatory stimulation by interleukin (IL)−1β, which also increases pro-catabolic activity in chondrocytes. They also focus on the role of growth factors in regulating the activity of TRPV4 in the context of chondrogenesis. Accordingly, they highlight the role of primary cilium and the regulation of its length by IL-1β and TRPV4 activation following application of tensile strain.

However, in addition to these important roles, it is noteworthy that ion channels in chondrocytes are likely to have many more diverse functions [28]. Recent evidence suggests that sodium, potassium, and calcium channels perform important roles in mechanotransduction and activation of kinase cascades [29] and mediate the delicate interplay between inflammatory, catabolic and anabolic mediators in the articular cartilage ECM, influencing chondrocyte biology and the behaviour of chondroprogenitors [30,31]. Therefore, exposure to systemic cardiovascular drugs that influence the function of these channels in cardiovascular cells and tissues may also have long-term functional consequences on osteoarticular tissues in patients with OA [32–35]. The same applies to intra-articular local anaesthetics, which have chondrotoxic effects [36]. Cardiovascular drugs and intra-articular anaesthetics are also likely to impact chondrocytes and synoviocytes, influencing their long-term functional viability, and mechanotransduction, which provide strong arguments for and against the use of certain pharmaceuticals intraarticularly versus systemically.

Authors' contributions

All authors made substantial contributions to discussion of the content, writing of the original outline, and reviewing/editing of the article before submission. All authors approved the final version for publication and agree to be accountable for the accuracy and integrity of the study.

Author disclosure statement

S.I. is an employee of Grünenthal GmbH, which has an interest in pain-modulating ion channels associated with osteoarthritis. H.C. is an employee of Kolon Advanced Research Cluster, which is developing cell-based gene therapies for osteoarthritis.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ali Mobasheri reports financial support, administrative support, and travel were provided by University of Oulu. Ali Mobasheri reports a relationship with University of Oulu that includes: employment, funding grants, and travel reimbursement. Ali Mobasheri consults for Kolon Advanced Research Cluster and Grünenthal GmbH. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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