Ion Channels as Emerging Metabolic Regulators and Therapeutic Targets in Osteoarthritis: Nav1.7 as a Recent Exemplar

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Running Title: Osteoarthritis and Nav1.7

Abstract

A recent paper has revealed the potential of a subtype of voltage-gated sodium channel (VGSC) as a metabolic regulator and therapeutic target in osteoarthritis (OA). Functional $Na_v1.7$ expression was identified in human OA-associated chondrocytes and shown in several genetic mouse models to promote disease progression. Thus, targeting and modulating it, including pharmacologically, could represent a previously unexplored avenue for developing therapeutic interventions to manage the disease. This work further highlights the need to understand the chondrocyte “channelome” more completely to unravel the diverse roles of ion channels in cartilage homeostasis and their clinical potential.

Keywords: osteoarthritis; cartilage; chondrocyte; metabolic regulation; ion channel; $Na_v1.7$; therapeutic target

Introduction

Osteoarthritis (OA) is a highly prevalent condition worldwide. It is the most common form of arthritis and a leading cause of joint pain and physical impairment, leading to disability and mounting societal cost (1). The prevalence of OA and the disability associated with OA varies across different populations and is influenced by factors such as age, gender, genetics, obesity and lifestyle (2). OA is a mechano-inflammatory, immunometabolic, degenerative and highly progressive ‘whole joint disease’ that affects the knees, hips, hands and spine (3,4). It involves multiple components of load-bearing synovial joints, leading to structural and functional alterations in articular cartilage, synovium, subchondral bone, peri-articular connective tissues and skeletal muscle. These structural changes lead to pain, stiffness, and decreased joint flexibility. Despite its prevalence and global impact, there is no approved or proven disease-modifying osteoarthritis drug (DMOAD) (5,6). This represents a significant unmet for the management of the disease.

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 ‘non-excitatory’ cells (Figure 1). In the context of OA, these channels are involved in pain perception, inflammation, and cartilage homeostasis as well as playing crucial roles in maintaining the structure and function of this highly specialized connective tissue (7). Targeting specific ion channels in peripheral nerves is the ‘classic’ avenue for managing OA symptoms. Ion channels in chondrocyte are known to be involved in signal transduction, volume regulation and maintenance of electrochemical balance (8,9). Fu et al. have now identified the voltage-gated sodium channel (VGSC) subtype $Na_v1.7$ in chondrocytes and have shown it to be key player in the pathophysiology of OA (10).

Evidence for functional $Na_v1.7$ Channel expression in Chondrocytes

The study by Fu et al. is the first study to demonstrate expression of functional $Na_v1.7$ channels in human chondrocytes in OA (10). There were 350 to 525 channels per cell, giving a density of 0.1 to 0.15 channels per μm^2. However, the use of primary human chondrocytes passaged three times raises the possibility that the reported VGSC expression/activity may be associated with a partially dedifferentiated chondrocyte phenotype.

Voltage-gated ion channels are not abundant in so-called “non-excitable” tissues but that does not necessarily indicate lack of function. The relatively low density of $Na_v1.7$ channels in chondrocytes reported by Fu et al. is in line with earlier reports from fibroblasts, astrocytes and macrophages (11). Previous studies have used electrophysiological techniques to look for transient inward sodium currents in primary chondrocytes. Sugimoto et al. were the first to demonstrate the presence of voltage-gated ion channels in cultured rabbit articular chondrocytes, using primary chondrocytes in first expansion culture after the fourth and fifth days *in vitro* (12). Although they were unable to induce action potentials (APs) by applying a depolarizing current, they were able demonstrate the presence of tetrodotoxin (TTX)-sensitive Na^+ channels (12).

Fu et al. identified VGSC currents in chondrocytes that were large enough to support conventional excitability and sodium dependent APs in these also “non-excitable” cells (10). They concluded: i) that human chondrocytes and an associated human chondrocyte cell line (C28I2) can generate sodium currents by $Na_v1.7$ alpha subunits; and ii) that activity of this population of sodium channels (as judged by inhibitory effects of TTX and a second selective blocker ProTxII) can modulate the secretory activity – cytokine release - from this cell line. These important new insights raise questions that need to be addressed before they can be fully understood in terms of their physiological or pathophysiological relevance or used effectively in drug discovery initiatives. Additional research will need to consider: i) Why do only approximately 20% of these chondrocytes (primary cells or the chondrocyte-like cell line) exhibit this pattern of sodium channel expression? ii) Given that an increase in intracellular sodium can alter intracellular calcium and thus modulate secretion of pro-inflammatory cytokines, what properties of this sodium channel are responsible? Also, the relatively depolarized resting potential of the chondrocyte preparations have the consequence that $Na_v1.7$ sodium channels would be strongly inactivated and therefore not able to support sodium influx within the operating or physiological range of membrane potentials. Previous work from the Waxman laboratory offered an important insight: $Na_v1.7$ channels can, in fact, inactivate quite slowly in a small but physiologically-relevant range of chondrocyte membrane potentials (13). These maintained or ‘late’ sodium influxes (denoted ‘ramp currents’ by these authors) may be responsible for the observed increase in intracellular sodium in the diseased chondrocytes (10).

Serial genetic ablation of $Na_v1.7$ in multiple pre-clinical mouse models demonstrated that $Na_v1.7$ channels expressed in dorsal root ganglia neurons are involved in pain, which has highlighted them as potential targets for new pain therapeutics. $Na_v1.7$ is known to regulate cytokine secretion in dendritic cells (14) and this suggests that it can occur even in cells where expression levels are very low, e.g. astroglial and microglial cells (15). Thus, these channels play functionally important immunoregulatory roles induced by cytokines and chemokines. Interestingly, this sodium channel is already being investigated as a target for drug development in the contexts of OA and post-surgical pain (notably chronic pain following knee replacement surgery). One example is funapide, which has been used in clinical trials of neuralgia, and has been formulated for extended release in a thermosensitive hydrogel to support local administration as a $Na_v1.7$ inhibitor and peripheral nerve block for the non-opioid control of post-operative pain (https://clinicaltrials.gov/study/NCT04826328).

Used gene silencing and pharmacological blockade of $Na_v1.7$ with selective or clinically used pan-Na_v channel blockers in genetic mice models, Fu et al. provided multi-faceted evidence that $Na_v1.7$ channels are functionally important in chondrocytes and that their activity promotes OA progression (10). It was also shown that this strategy significantly ameliorated the progression of structural joint damage and reduced OA pain behavior. These observations are clinically relevant regarding the overlap between OA and cardiovascular disease and further justify drug repurposing efforts. Mechanistically, $Na_v1.7$ blockers also appear to regulate intracellular Ca^{2+} signaling and the chondrocyte secretome, which in turn affects chondrocyte biology and OA progression. Identification of $Na_v1.7$ as a chondrocyte-expressed, OA-associated channel has uncovered a dual target for the development of DMOADs and the simultaneous efforts to identify safe and efficacious non-opioid pain relief treatments for OA. These results demonstrate that in addition to its well-known and extensively studied function of controlling pain signaling in spinal sensory neurons, $Na_v1.7$ in chondrocytes can play a previously unrecognized and potentially important immunoregulatory role in OA.

It is important to emphasize that $Na_v1.7$ is not the only channel that has been implicated in OA. A host of other ion channels, as illustrated in Figure 1, have been identified with varying frequencies in a number of articular cell types. Whilst the exact

function(s) for many of these channels remain unknown, they may present promising pharmacological targets for existing and future treatments.

Author Contributions

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

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Figure legend

Figure 1. Schematic illustration of the major ion channels, transporters and pumps expressed in chondrocytes. ECM, extracellular matrix; RPM, resting membrane potential; K_{Ca}, Ca^{2+}-dependent K^+ channel; Ca_V, voltage-gated Ca^{2+} channel; K_V, voltage-gated K^+ channel; Na_V, voltage-gated Na^+ channel; NCX, Na^+/ Ca^{2+} exchanger; Na^+/K^+ pump, Na^+, K^+-ATPase; PMCA, plasma membrane Ca^{2+}-ATPase; TRPV, transient receptor potential cation channel subfamily V; NMDAR, N-methyl D-aspartate receptor; K_{ATP}, ATP-sensitive K^+ channel; ClC, Cl^- channel; AQP, aquaporin. Image created with BioRender.com (licensed).