The role of aquaporin 1 in knee osteoarthritis: a contemporary review

G Musumeci*

Abstract
Introduction
The aim of this article is to critically review literature about aquaporin 1 and its involvement in joint diseases. In particular, we focused our research on osteoarthritis of the knee. We reviewed the literature regarding aquaporin 1 role in joint cavity disease. We examined the current literature through searching PubMed and Scopus using appropriate keywords in relation to aquaporin 1 and osteoarthritis. Main research articles were selected for review.

Discussion
Aquaporin 1 is an integral membrane protein expressed in different normal and pathological tissues, for example, erythrocytes, renal tubule cells and in knee tissues (synoviocytes, articular chondrocytes and fibrochondrocytes). In knee tissues, aquaporin 1 is also expressed in human synovitis and in chondrocytes of patients with rheumatoid arthritis and osteoarthritis. The process of development and ageing of articular cartilage is related to its nutrition and function, which depend mainly on the water molecular transmembrane transport. Water transport is taken by aquaporins. The regulation of the water and solute content of chondrocytes will profoundly affect their anabolic and catabolic functions. The chondrocytes are supplied by diffusion, helped by the pumping action generated by compression of the articular cartilage or flexion of the elastic cartilage. Chondrocytes exist in an unusual and highly variable ionic and osmotic environment in the ECM of articular cartilage. Alterations to this environment influence the volume and ionic content of the cells, which, in turn, modifies the rate at which ECM macromolecules are synthesized and degraded. Thus, regulation of the water and solute content of chondrocytes will profoundly affect their anabolic and catabolic functions.

Conclusion
This review reports recent findings about the involvement of aquaporin 1 in the function of the articular cartilage and its possible role in knee osteoarthritis.

Introduction
Cartilage is a flexible connective tissue found in many areas in human and animal bodies, including joints between bones. It is composed of specialized cells called chondroblasts that produce a large amount of extracellular matrix (ECM) composed of collagen fibres, abundant ground substances that are rich in proteoglycan and elastin fibres. According to the amount of these last three components, the cartilage is classified into three types: elastic cartilage, hyaline cartilage and fibrocartilage. Unlike other connective tissues, cartilage does not contain blood vessels. Chondroblasts that reside in the matrix are called chondrocytes; they are located in lacunae (chondron) within the matrix and represent only 5–10% of the total cartilage volume but are crucial to the maintenance of a stable ECM. The chondrocytes are supplied by diffusion, helped by the pumping action generated by compression of the articular cartilage or flexion of the elastic cartilage. Chondrocytes exist in an unusual and highly variable ionic and osmotic environment in the ECM of articular cartilage. Alterations to this environment influence the volume and ionic content of the cells, which, in turn, modifies the rate at which ECM macromolecules are synthesized and degraded. Thus, regulation of the water and solute content of chondrocytes will profoundly affect their anabolic and catabolic functions. Water represents one of the most important substances in the human body (Figure 1). Water content of cartilage or flexion of the elastic cartilage. The water content of cells is effectively influenced by the abundance of aquaporin water channels.

Figure 1: Water content of different adult organs.

* Corresponding author
Email: g.musumeci@unict.it

Department of Bio-Medical Sciences, Human Anatomy and Histology section, University of Catania, Italy

cells is effectively influenced by the abundance of aquaporin (AQP) water channels. AQPs are a family of hydrophobic membrane channel proteins for water transport that are expressed in a variety of cell types in different organ systems (Table 1), usually in epithelial and endothelial cells. AQPs are homotetramers with six bi-layer spanning domains and N-glycosylation sites that facilitate the transport of water through the cell membrane in response to osmotic gradients. The channel consists of three topological elements, an extracellular and a cytoplasmic vestibule connected by an extended narrow pore or selectivity filter. Within the selectivity filter, four bound water molecules are localized along three hydrophilic nodes, which punctuate an otherwise extremely hydrophobic pore segment. This unusual combination of a long hydrophobic pore and a minimal number of solute binding sites facilitates rapid water transport. This function is conserved in animals, plants and bacteria. They operate as selective pores through which water crosses biological membranes bi-directionally, regulating osmotic homeostasis in relation to solute movement and the extracellular environment. Several studies have described their involvement in various physiological functions and pathological conditions. The family of AQPs may be subdivided into two groups based on structural differences.

Table 1. Tissue and cellular distribution of mammalian aquaporins.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Previous nomenclature</th>
<th>HgCl2 sensitivity</th>
<th>Aquaporin or aquaglycerop/nin</th>
<th>Tissue cellular localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQP0</td>
<td>MIP26</td>
<td>No</td>
<td>AQP</td>
<td>Lens fibre of the eye</td>
</tr>
<tr>
<td>AQP1</td>
<td>CHIP28</td>
<td>Yes</td>
<td>AQP</td>
<td>Kidney (proximal tubule and thin descending limb of the loop of Henle), RBC, capillary endothelium, choroid plexus, eye, ear, lung, GI tract, skeletal muscle, heart muscle, smooth muscle, Meckel’s cartilage synoviocytes, chondrocytes and fibrochondrocytes.</td>
</tr>
<tr>
<td>AQP2</td>
<td>WCH-CD</td>
<td>Yes</td>
<td>AQP</td>
<td>Kidney (principal cells of the collecting duct and connecting tubules; apical surface and subapical vesicles), ear</td>
</tr>
<tr>
<td>AQP3</td>
<td>GLIP</td>
<td>Yes</td>
<td>GLP</td>
<td>Kidney (principal cells of the collecting duct and connecting tubules; basolateral surface), airways, lung, GI tract, brain, ear, fibrochondrocytes</td>
</tr>
<tr>
<td>AQP4</td>
<td>MIWC</td>
<td>No</td>
<td>AQP</td>
<td>Brain, kidney (collecting duct principal cells; basolateral), retina, ear, airways, lung, GI tract, fast-twitch skeletal, muscle</td>
</tr>
<tr>
<td>AQP5</td>
<td></td>
<td>Yes</td>
<td>AQP</td>
<td>Salivary gland, lacrimal gland, airways, lung, ear, eye</td>
</tr>
<tr>
<td>AQP6</td>
<td>hKID, AQP2L</td>
<td>Yes</td>
<td>AQP</td>
<td>Kidney (intercalated cells of the collecting duct; intracellular vesicles)</td>
</tr>
<tr>
<td>AQP7</td>
<td></td>
<td>Yes</td>
<td>GLP</td>
<td>Testis, sperm, kidney (proximal tubule)</td>
</tr>
<tr>
<td>AQP7L</td>
<td></td>
<td></td>
<td>GLP</td>
<td>Adipose tissue. The locus named AQP7L has recently been assigned for an AQP7-like cDNA identified from adipose tissue. It is currently unclear as to whether this is a novel gene or an alternative form of the AQP7 gene</td>
</tr>
<tr>
<td>AQP8</td>
<td></td>
<td>Yes</td>
<td>AQP</td>
<td>Testis, sperm, GI tract, placenta, kidney (proximal tubule and collecting duct), airways, liver, salivary glands</td>
</tr>
<tr>
<td>AQP9</td>
<td></td>
<td>Yes</td>
<td>GLP</td>
<td>Liver, testis, sperm, spleen, brain, leucocytes</td>
</tr>
<tr>
<td>AQP10</td>
<td></td>
<td>Yes</td>
<td>AQP</td>
<td>Duodenum, jejunum</td>
</tr>
</tbody>
</table>

AQP, aquaporin; cDNA, complementary DNA; GI, gastrointestinal; GLP, aquaglyceroporin; RBC, red blood cell.
and functional differences. Group 1 members (AQP0, 2, 4, 6 and 8) are primarily water selective channels, whereas group 2 members (AQP3, 7, 9 and 10) or ‘aquaglyceroporins’, transport glycerol and other small molecules, including urea. They exert a crucial role in water movement across the membrane, active near-isomolar fluid absorption/secre-
tion, neuronal signal transduction, cell metabolism and proliferation. AQP channels may also be involved in joint swelling of the knee OA. OA is the most common joint disorder; it is caused due to ageing and wear and tear on a joint. It is a common cause of pain and disability in the general population and its socioeconomic significance is well known. OA is progressive and involves all joint components, including bone, cartilage, meniscus and synovium. OA results from an imbalance between chondrocyte-controlled anabolic and catabolic processes that is characterized by a progressive degradation of ECM components within articular cartilage. Although OA is more evident in the knees, other joints can also be affected by it. At this level, one of the protection mechanisms against cartilage wear comes from the presence of the two menisci. They play a vital role in load transmission, shock absorption, stability and jointly and lubricate the articular cartilage of the knee. Compared with other connective tissues, cartilage grows and repairs more slowly. Unfortunately, no specific therapy has been identified to reverse OA, even if several medical approaches may at least retard its consequences (e.g. by correcting alignment using chondro-protection, hyaluronic acid injection, etc.). Therefore, joint replacement surgery is often ultimately the only therapeutic option. Over the last few years, surgeons and scientists have elaborated a series of cartilage repair procedures that help to post-pone the need for joint replacement. Bioengineering techniques are being developed to generate new cartilage using a cellular ‘scaffolding’ material and cultured cells to grow artificial cartilage. In this critical review, we describe benefits and disadvantages of the AQP1 in knee OA.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

AQP1 expression in OA synoviocytes and OA chondrocytes

Articular chondrocytes are responsible for synthesizing and maintaining the ECM of articular cartilage. The cartilage matrix consists primarily of water (~70% of total tissue weight), type II collagen, large aggregating proteoglycans and smaller non-collagenous matrix proteins. The cross-linked collagen network traps aggregating proteoglycans and attracts cations (mainly Na+, K+ and Ca2+) into the matrix. This is followed by movement of water, which results in swelling of the proteoglycans, increasing the tension within the collagen network. This swelling mechanism provides ECM the ability to resist tension and shear forces, so cartilage can oppose the compression under static and dynamic mechanical load. Mobilization of osmotically active solutes (osmoles) and osmotically obligated water and their transport across the chondrocyte membrane regulate the cell volume. It is also known that the fenestrated synovial endothelium lining the joint capsule is responsible for production of a nutrient and proteoglycan-rich synovial fluid. AQP channels may also be involved in the transport of water and small osmoles across the synoviocytes. Synoviocytes and chondrocytes are mesenchymederived cells and are responsible for the production of the synovial fluid which contains water, nutrients, growth factors, dissolved.
A protein-rich effusion in the joint barrier leads to the development of inflammatory disorder of the synovium, barrier. In synovitis, an inflammatory process is involved in this process. It is tumour necrosis factor-α (TNF-α) such as interleukin-1 β (IL-1β) and that pro-inflammatory cytokines, caspase-3 in OA models. The Caspase-3 up-regulation of AQP1 and the expression of the AQP1 and Caspase-3 in OA models. The gas movement in OA cartilage may be related to the chondrocyte apoptosis, and the changes of AQP1 expression may involve in the pathogenesis of OA.

AQP1 in OA fibrochondrocytes The meniscus is typically an avascular structure with the primary blood supply limited to the periphery. The meniscus is composed of three parts: the inner rim, the central core and the outer rim. Studies have demonstrated that the meniscus is vascularized only in the outer rim, actually 10–30% of it, while the inner free margin of the meniscus is avascular and nourished by the diffusion of synovial fluid. Meniscal cells are generally considered to be a cross between chondrocytes and fibroblasts, known as fibrochondrocytes, due to the fact that they exhibit characteristics of both fibroblasts and chondrocytes. These cells are very important for tissue homeostasis as they synthesize, maintain and/or degrade the ECM. Meniscus’ main functions are to buffer axial, rotational and shearing forces and to protect cartilage. Meniscal tears, with the consequence of meniscectomy, lead to early OA as already reported in another study. My research group recently has demonstrated an increased AQP1 expression in fibrochondrocytes from rat OA meniscal tissue, both in vivo and in vitro. Three months after anterior cruciate ligament transection, performed to induce OA, histomorphometrical parameter modifications due to articular degenerative process occur. The results showed a very strong AQP1 expression in explanted OA meniscal tissue and in monolayer fibrochondrocytes compared to the weak expression of their respective controls. The role of AQP1 on ECM maintenance might be an important regulatory cellular mechanism, through which the cells could regulate their own volume and maintain ECM homeostasis. It is known that the effects of loads determine a constant fluid flow within the tissue, which allows metabolic and nutrient changes in an avascular tissue. Articular chondrocytes are particularly sensitive to changes in ionic and osmotic extracellular environment, in response to mechanical compression. The latter results in a modification of cell shape and cellular organization that is due to cytoskeletal reorganization and activation of cytoplasm membrane transport mechanisms. This biological regulation is essential for ECM homeostasis maintenance and metabolic activity. Water movement results in tissue swelling due to the presence of proteoglycans that subsequently aid in increasing the tension within the collagen network. This swelling mechanism enables the ECM to resist tensile and shear forces, thus allowing the tissue to resist compression under static or a dynamic mechanical load. It is well known that the knee joint is subjected to continuous loading during ambulatory function. However, during the progression of OA, cartilage releases proteoglycans and its water retention capability decreases. As the AQP1 induction by OA is demonstrated, it may be an endogenous mechanism induced by the cells to enable remodelling in OA articular joints.

Conclusion AQP1 is an integral membrane protein expressed in many normal and pathological tissues. In this review, we deepen the role of this protein in OA disease. The water transport in joint cavity cells (synoviocytes, articular chondrocytes and fibrochondrocytes) influences the ionic and osmotic variations, and it is involved in cell morphology changes and affects the viscoelastic mechanical properties, growth and metabolism. The high expression of AQP1 in synovium, articular OA cartilage and OA meniscus suggests that it...
may play a role in the pathogenesis of OA joint swelling and oedema by interfering in water reserve mechanisms and water balance disorders. The study of the AQP1 role in the occurrence and progression of OA may represent the biological basis for a preventative treatment that could preserve tissue function and prevent cartilage damage. It appears, moreover, clear that further and longer term animal and in vitro studies are needed to understand the exact mechanism of production and regulation of AQP1 in fibro-cartilaginous tissue and synovium.

**Abbreviations list**

AQP, aquaporin; IL-1β, interleukin-1 β; OA, osteoarthritis; RA, rheumatoid arthritis; TMJ, temporomandibular joint; TNF-α, tumour necrosis factor-α

**Acknowledgement**

I would like to thank Prof Carla Loreto from the Department of Bio-Medical Science, Section of Human Anatomy and Histology, University of Catania, Italy for her valuable help and advice and Dr Francesco Maria Trovato from the Department of Internal Medicine, University of Catania, Italy for commenting and making corrections to the article. I would also like to thank Claudio Cocuzza/ADD Design for providing illustrative materials.

**References**

