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Review Article

Aquaporins As Therapeutic Targets of Inflammation

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Abstract: Aquaporins (AQPs) are one of the important class of channel proteins that specifically transport water thereby maintaining the water homeostasis of the cells. Till date 13 mammalian AQP isoforms are known to be present. Certain AQPs have been known to carry out the movement of small molecules such as glycerol and urea. Owing to their function, AQPs are known to participate in a wide array of cellular processes. A number of different AQP isoforms have been found to be expressed in different cells and tissues throughout the body depending on their functions. Studies using murine models of AQP knockouts suggest the potential role of AQP in mammalian physiology such as urine concentration, glandular fluid movement, formation of edema, maintenance of intraocular pressure, migration of immune cells, phagocytosis etc. Recently, studies have been executed to evaluate the role of AQPs in the pathophysiology of various diseases with inflammatory conditions. Some common chronic inflammatory disorders such as arthritis, asthma, inflammatory bowel diseases, peritonitis, sepsis-induced cholestasis have been known to involve AQPs. Also, studies have shown that AQP expression is modulated in a number of cell types in response to Lipopolysaccharide-induced inflammation. Such studies propose that modulation of AQP can be promising therapy for conditions like neuroinflammation, obesity, as well as cancer. Nevertheless, effective AQP modulators for clinical applications are still to be discovered. This review is thereby intended to present information on the role of AQPs in pathophysiological processes of inflammation and therefore their potential as therapeutic target of inflammation.

Key words: Aquaporins, inflammation, lipopolysaccharide, therapeutic targets, cytokines

Introduction

The Aquaporins (AQPs) are a class of membrane channel proteins that aids in selective transport of water. However, apart from transporting water some members of AQPs are able to transport other molecules such as urea, glycerol and some small solutes (Agre *et al.*, 1998). AQPs have been reported to be diversely expressed in various cell types that are actively involved in fluid movements such as kidneys, eyes, lungs, and exocrine glands etc thus help maintaining the water homeostasis. The physiological importance of AQPs in a number of diseases has been widely studied using both *in vivo* as well as *in vitro* approaches. Moreover, AQPs have been in focus for their possible involvement in inflammation. Inflammation can cause massive tissue destruction which is unavoidable during which the immune system no longer recognize the target tissue as self. Inflammation is thereby a complex process that has drawn scientific interest. Evidence shows that AQPs plays a role in various cellular processes such as cell adhesion, cell signaling, cell migration, and regulation of cell volume and protein expression (Kitchen *et al.*, 2015). The cells of the immune system also express AQPs and thus help in certain immune cell functions like phagocytosis (Zhu *et al.*, 2011; Rabolli *et al.*, 2014). These important functions

of AQPs have provided new insights into their possible involvement in inflammation that may open up new avenues for therapeutic interventions in context of various inflammatory disorders. This review is mainly focused on the role of AQPs in the process of inflammation and their potential as therapeutic targets for developing new treatment for inflammation.

Structure and physiological importance of AQPs

Aquaporins (AQPs) are about 30kDa proteins that aids in the fast movement of water (Sales *et al*., 2013; Verkman *et al*., 2014). The AQPs are a family of membrane channel proteins responsible to selectively transport water (Wang *et al*., 2006). The AQP family consists of 13 AQPs in mammals. The members are represented as AQP0-APQ12, confined to different tissues. These 13 AQPs have been divided into two subgroups namely, *orthodox* AQPs (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6 and AQP8) which can conduct only water,

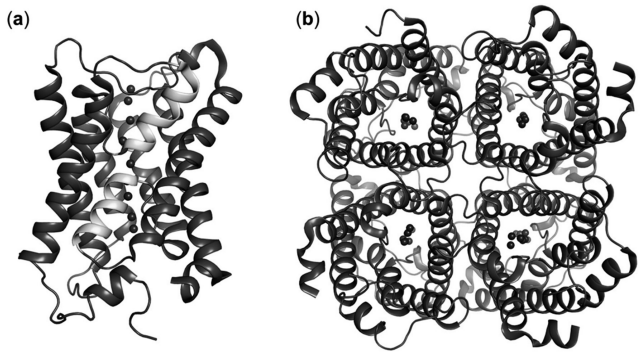

Fig. 1. The general structure of AQPs. (a) 3D view of the AQP monomer represented by the crystal structure of human AQP5 (PDB3D9S). The string of water molecules has been shown in the channel pore is marked as small solid spheres. (b) Homotetrameric structure with four monomer chains (Nesverova and Törnroth-Horsefield, 2019).

and the *aquaglyceroporins* (AQP3, AQP7, AQP9 and AQP10) which can conduct both water and neutral solutes mainly glycerol (Tesse *et al*., 2018). The AQP11 and AQP12 are also called as the *unorthodox* AQPs because of their different evolutionary pathway (Ishibashi *et al*., 2009). AQPs are present as homotetramers consisting of four identical subunits. Each subunit has six membrane-spanning á-helical domains forming a distinct water channel pore (Sui *et al*., 2001). Each subunit consists of two types of loops that contains the conserved amino acid sequence (Asn-Pro-Ala) also called the NPA motif that provides the barrel surrounding the pore (Fig1).

AQPs are important proteins that play a vital role in mammalian physiology. As mentioned earlier AQPs are present in a number of cell types that are engaged in rapid movement of water. However, AQPs are also found in most tissues that are not engaged in water movements such as the red blood cells (RBCs), fat cells, skeletal tissue. Mutation in these proteins has been reported that significantly affects the physiological function (Verkman *et al*., 2014). The Colton antigen is found on AQP1 and is reported in the kidney tubules as well as erythrocytes. AQP1 is responsible for maintaining the urine concentration. However, evidence suggests that mutation in this antigen led to urine concentrating defect (Agre *et al*., 1995). Similarly, AQP2 is an important protein expressed in the renal collecting duct in response to vasopressin signal. It plays a role in urine concentrating mechanism. Studies have shown that mutation of this protein leads to nephrogenic diabetes insipidus (Mulders *et al*., 1997). Different AQP isoforms thus play important physiological roles depending on the type of organs and therefore alterations in their expression patterns are of utmost significance that may indicate physiological dysfunctions.

Role of AQPs in the pathophysiology of inflammation

The members of AQP family have tissue-specific expression in our body that play important role in maintaining the cellular fluid homeostasis. However, their expression is altered in response to some inflammatory stimuli thus leading to functional changes.

Inflammation in some major organs involving AQPs

Liver is one of the main targets during sepsis which may suffer injury. AQP1, AQP8 and AQP9 have been reported to be abundantly present in the liver (Ferri *et al*., 2003; Nielsen et *al*., 1993; Garcia *et al*., 2001; Elkjær *et al*., 2001). Cholestasis is a condition known to occur during sepsis. This condition is characterized by the decrease or slowing down in the bile secretion. Evidence suggests that AQP8 present in the intracellular vesicles is transported to the canalicular plasma membrane and is known to be involved in the water movement

throughout bile secretion (Garcia *et al*., 2001; Huebert *et al*., 2002). *In vivo* studies in rats have demonstrated that AQP8 protein expression considerably decreased in response to the mechanical blockage in the common bile duct inducing extrahepatic cholestasis. However, the AQP8 mRNA expression was found to increase after the induction of bile duct ligation which could be attributed to its post transcriptional regulation (Carreras *et al*., 2003). The liver canalicular AQP8 protein expression was found to reduce drastically during lipopolysaccharide (LPS) induced cholestasis and thus leading to reduced water permeability of the bile canaliculi. The change in the canalicular AQP8 expression can be correlated with the bile secretory dysfunction. The canalicular water movements occur through lipid bilayer of the plasma membrane as well as the AQPs. A reduced AQP8 expression results in reduced water permeability of the canaliculi and decrease in bile formation (Lehamnn *et al*., 2008, Marinelli *et al*., 2011).

Many pathological conditions of the nervous system involve the alterations in the fluid homeostasis in the brain. Growing data have shown the involvement of AQP4 in brain inflammation (Nagelhus and Ottersen, 2013; Kakulavarapu *et al*., 2010; Papadopoulos *et al*., 2004). AQP4 plays a vital role in the fluid exchange between the glial cells and vascular endothelium and also glial cells and the CSF. AQP4 has been reported to be involved in cytotoxic brain edema formation (Manley *et al*., 2000). In the contrary to the cytotoxic brain edema, AQP4 plays a vital role in extracellular fluid clearance that is accumulated as a consequence of disruption of the BBB during vasogenic edema. It has been established that there is an increase in intracranial pressure in the aqp4 null mice during vasogenic brain edema (Papadopoulos *et al*., 2004; Papadopoulos and Verkman, 2005). Studies using aqp1 knockout mice reveal that the water transport is decreased in the choroid plexus and the intracranial pressure is decreased in comparison to the wild type mice (Oshio *et al*., 2005). Therefore, inhibition of AQP1 may provide a therapeutic approach for conditions like hydrocephalus.

An increased expression of AQP1 during acute kidney injury (AKI) in rats has been reported by (Sonoda *et al*., 2009). Studies in several models of sepsis reveal that the AQP2 expression in kidney is reduced. In LPS induced endotoxemic model the aqp2 expression in kidney was reported to fluctuate at different time points after LPS treatment (Olesen *et al*., 2009; Grinevich *et al*., 2004; Cui *et al*., 2011). In lungs, in order to avoid fluid accumulation in the alveoli, the channel protein and pumps are involved. Many pathogenic infections in the lungs cause trouble in the maintenance of this fluid homeostasis resulting in alveolar edema (Matthay and Zemans, 2011). It has been reported that the expression of aqp3 and aqp5 was upregulated in alveolar wall of sepsis induced blood-air barrier damage (Pires-Neto *et al*., 2016). Another study showed that in lung of septic rats, the expression of aqp1 and aqp5 was reduced (Ma and Liu, 2013; Chinnaiyan *et al*., 2001). On the contrary, increased expression of AQP5 was reported in the airway epithelium and bronchial sub mucosa of the asthma induced mice thus aiding in excessive mucus secretion. Also, reduced levels of bronchoalveolar lavage cytokines like IL-4 and IL-10 and increase in IL-2 and IFNα levels has been reported in the aqp5 KO in response to allergen (Shen *et al*., 2010). Towne *et al*., 2000 reported that the expression of aqp1 and aqp5 decreased in response to viral infection in mouse lung causing inflammation and subsequent edema formation. Their decreased expression has been linked to faulty fluid flux during the inflammatory process.

According to the study of Madonna *et al*. the cardiac dysfunction during the endotoxemia induced sepsis involves the altered expression of proteins like gelsolin, AQPl, iNOS, and STAT3 in young and old mice. They observed increased levels of AQPl, iNOS, and phosphorylated STAT3 in LPS exposed old mice (Madonna *et al*., 2012). Several studies suggest that the myocardial dysfunction during endotoxic shock is due to certain proinflammatory cytokines, enhanced permeability of the vessels, iNOS induced NO production (Tatsumi *et al*., 2004). It is thought that during sepsis the AQPs in the endothelial cells causes the movement of water from the interstitial space to the capillaries (Kellen and Bassingthwaighte, 2003).

Aquaporins involved in immune cell activity

Cell migration is one of the important functions of many immune cells that enable them to reach the site of infection for phagocytosis. These cells display a particular pattern during migration forming projections through actin reorganization resulting movement with a leading edge in the direction of movement. Several studies have revealed the involvement of AQPs in cell migration (Verkman *et al*., 2014; Papadopoulos *et al*., 2008). It is evident that during sepsis, there is a reduction of AQP3 and enhanced AQP1 expression in leucocytes (Vassiliou *et al*., 2013) and in SIRS the AQP9 expression is lowered in neutrophils (Matsushima *et al*., 2014). Gram negative bacteria stimulate macrophage to change shape and also influence their movement. In such macrophages there is an enhanced AQP9 expression (Holm *et al*., 2015). AQP1, AQP3 and AQP5 have been reported to be expressed in the activated B and T lymphocytes; AQP3, AQP5 and AQP7 have been reported expressed in naïve dendritic cells, and as mention earlier AQP9 is found to be expressed in the neutrophils (Huang *et al*., 2013; Moon *et al*., 2004; Hara-Chikuma *et al*., 2012). These AQPs plays important role in cell movements. Liu and coworkers established the protective role of AQP1 during inflammation through AQP1 silencing in RAW264.7 stimulated with LPS. AQP1 silencing led to upregulation of proinflammatory markers IL-6, TNF-á as well as iNOS. Thereby, it is speculated that AQP1 reduced the expression of the LPS induced proinflammatory cytokine level in RAW264.7 cells. Further, the role of AQP1 in macrophage polarization has also been studied. AQP1 silencing led to reduction in M2 phenotype (Liu *et al*., 2020). An enhanced cell migration is observed in Jurkat cells as a result of increased AQP5 expression (Rump *et al*., 2016). Studies have revealed that the resident peritoneal macrophages in sepsis induced mice were found to have increased expression of AQP3 resulting in increased migration (Zhu *et al*., 2011). The CD4+, CD25+ regulatory T-cell expansion in the thymus has been known to involve the expression of AQP4 (Chi *et al*., 2011). Dendritic cells are antigen presenting cells that express AQP7 which promotes antigen uptake (Hara-Chikuma *et al*., 2012; Moniaga *et al*., 2015). De Baey and Lanzavecchia (2000) investigated the role of aquaglyceroporins (AQP3 and AQP7) in maintaining the water and salt flux across the membranes of the immature dendritic cells (IDCs) since IDCs take up large fluid volumes and display efficient endocytosis (Steinman and Swanson, 1995). The role of AQP4 in astrocyte migration has partly been investigated whereby it was found that in the astroglia of AQP4 null mice the migration was affected considerably in comparison to wild type mice (Saadoun *et al*., 2005a).

Modulation of AQP expression by LPS

LPS is a bacterial endotoxin that can produce significant inflammatory response in the body and therefore has wide application in inflammation research. Low dose of LPS administration have been shown to cause marked increase in the inflammatory markers like increase in iNOS, COX-2, cortisol, TNF-α, IL-6 and IL-8, CRP (C Reactive Protein) etc. (Lee *et al*., 2003; Nordgreen *et al*., 2018). Similarly, reports suggest that the expression AQPs is also modulated on LPS exposure. Chiadak *et al*. (2016) observed LPS-induced increased expression of AQP3 and decreased expression of AQP7 and 11 in adipocytes. LPS decreases the expression of AQP3 in human colon epithelial cells via p38/JNK signaling pathway but increases the expression of AQP9 in rat brain by a signaling pathway that remains unclear (Li *et al*., 2015; Wang *et al*., 2009). Studies have shown that intracerebral administration of LPS in the wildtype mice led to considerable inflammatory response compared to the aqp4 KO mice (Li *et al*., 2011). Increased AQP1 expression has been reported in cardiac cells after LPS treatment leading to defective cardiac function (Montiel *et al*., 2014). In a study involving human monocytes (THP-1), it was reported that there was an enhanced expression of AQP1 and decreased AQP5 expression after LPS stimulation (Rump *et al*., 2013).

Correlation between AQPs and Cytokines

Recent studies have established the association between the inflammatory mediators like cytokines and AQPs. In a study using co-culture system of RAW264.7 cells and HT-29 cells the correlation between cytokines and AQP3 expression was evaluated. The cytokines IL1-â and TNF-α produced by

Table 1. Physiological role of AQPs in different tissues during inflammatory conditions.

Cells/Tissue	Physiological role of AQPs	AQPs involved	References
Immune cells	· Cell migration · Phagocytosis · Macrophage polarization · Expansion of regulatory T-cells · Antigen uptake	AQP1, AQP3, AQP9, AQP5, AQP4, AQP7	Verkman *et al.*, 2014; Vassiliou *et al.*, 2013; Holm *et al.*, 2015; Liu *et al.*, 2020; Zhu *et al.*, 2011; Chi *et al.*, 2011; Hara-Chikuma *et al.*, 2012
Liver	· Decrease bile formation · Decrease bile secretion	AQP8	Carreras *et al.*, 2003; Lehamnn *et al.*, 2008
Heart	· Movement of water from the interstitial space to the capillaries · Myocardial dysfunction	AQP1	Madonna *et al.*, 2012; Kellen and Bassingthwaighte, 2003
Brain	· Fluid exchange between the glial cells and vascular endothelium · Fluid exchange between the glial cells and CSF · Increased water transport in choroid plexus · Increase fluid buildup causing brain edema	AQP1, AQP4	Tourdias *et al.*, 2009; Papadopoulos *et al.*, 2008; Manley *et al.*, 2000; Oshio *et al.*, 2005
Lungs	· Blood-air barrier damage · Excess mucus secretion · Pulmonary edema · Increased levels of bronchoalveolar lavage IL-4, IL-10, IL-2 and IFNã	AQP1, AQP3, AQP5	Pires-Neto *et al.*, 2016; Shen *et al.*, 2010; Ma and Liu, 2013; Chinnaiyan *et al.*, 2001
Kidney	· Increased water excretion	AQP1, AQP2	Sonoda *et al.*, 2009; Höcherl *et al.*, 2010; Olesen *et al.*, 2009; Cui *et al.*, 2011
Intestinal system	· Gut inflammation · Intestinal fluid leakage · Electrolyte and water transport dysfunction	AQP1, AQP3, AQP8	Chao and Zhang (2017)

RAW264.7 cells in response to an inflammatory stimulus led to increased expression of AQP3 at both the mRNA and protein level in the HT-29 cells. This association was further established using an NF-κB inhibitor namely BAY11-7082 that led to the inhibition of both cytokine release as well as AQP3 expression thus suggesting that NF-κB signaling pathway regulated the expression of AQP3 (Yu *et al.*, 2018). Further, Horie *et al.* (2009) investigated the role of TNF-α in modulating the AQP3 expression in DJM-1 keratinocytes. AQP3 expressed in the skin keratinocytes mediates water and glycerol flux promoting hydration and healing. TNF-α is reported to be a key player in the inflammatory response and also induction of apoptosis. TNF has been reported to induce its effects through different signaling pathways. Studies have established the relation between AQP and the secretion of IL1-α by macrophages. It has been reported that inhibition of AQP *in vitro* prevent NLRP3 (NOD like receptor protein 3) inflammasome activation decreasing the IL1-α secretion by macrophages. In addition, *in vivo* studies have reported that AQP1 plays a role in IL-1α secretion during acute lung injury (Rabolli *et al.* (2014). The formation of NLRP3 inflammasome in macrophages is an important event for the secretion of mature IL-1α. This multiprotein complex can be stimulated by a variety of stimuli. This wide range of stimuli stimulates the inflammasome through ion transport. Cell distension is reported to be important for the release of IL-1α. Exposure to inflammasome activator results in the increased volume of macrophage (Talwar *et al.*, 2006). It is important to note that inflammasome activation is not involved in the secretion of other proinflammatory cytokines like IL-6. Reports suggest that not only AQP1, but the other AQPs like AQP9 and other AQPs have also been found to involve in the activation of inflammasome (Talwar *et al.*, 2006; Schorn *et al.*, 2011).

Table. 2. AQPs involved in some inflammatory-based diseases in experimental models and the techniques used for study

Inflammatory conditions	Experimental models	AQPs studied	Techniques used	References
Rheumatoid arthritis	Rats, articular chondrocytes and synoviocytes	AQP1 AQP4	Real-time PCR, IHC, Western blot,	Cai et al. 2017; Mobasheri *et al.* 2012
Osteoarthritis	Rats and articular chondrocytes and synoviocytes	AQP1 AQP3 AQP9	Real-time PCR, RNA interference, Western blot, ICC, IHC	Meng et al.2007; Musumeci et al. 2013; Gao et al.2016; Takeuchi et al. 2018; Tan et al.2019
Asthma	Mice, Rats	AQP1 AQP3 AQP4 AQP5	Real-time PCR, IHC, DNA Microarray, ELISA, Western blot	Krane e al. 2009; Ablimit et al. 2013; Ikezoe et al. 2016; Zhang et al. 2015
Inflammatory bowel disease	Mice, Rats	AQP1 AQP3 AQP4 AQP7 AQP8	Real-time PCR, ICC and immunoblot, IHC, Confocal microscopy, Western blot	Thiagarajah *et al.* 2007; Ricanek *et al.* 2015; Chao and Zhang 2017; Wang *et al.* 2019
Pancreatitis	Mice	AQP1	Real-time PCR, ICC, IHC	Venglovecz *et al.* 2018
Sepsis- induced Cholestasis	Rats	AQP1 AQP8 AQP9	RT-PCR, Immunoblot, IHC	Calamita *et al.* 2008; Carreras *et al.* 2007; Lehmann *et al.* 2008; Tamai *et al.* 2006
Meningitis	Mice, Rats	AQP1 AQP4	ELISA, Immunoblot, Western blot, ICC, IHC	Blocher *et al.* 2011; Papadopoulos and Verkman 2005; Huang et al. 2014; Du et al. 2015;
Hydrocephalus	Mice, Rats	AQP1 AQP4	Real-time PCR, Western blot, Immunoblot, IHC	Bloch et al. 2006; Mao et al. 2006; Paul et al. 2010
Neuromyelitis optica	Mice	AQP4	RT-PCR, RIPA, FIPA, IHC	Paul et al. 2007; Waters et al. 2008; Yick et al. 2018
Peritonitis	Mice	AQP3	RT-PCR, Immunofluorescence, Immunoblotting	Zhu et al. 2011
Parkinson disease	Mice, Rats	AQP4	Real-time PCR, MRI, Western blot, IHC	Dong et al. 2020; Sun et al.2016
Systemic Lupus Erythematosus	Mice	AQP4	Real-time PCR	Foxley et al.2013

AQPs as therapeutic targets for various inflammatory disorders

The expression of AQPs and their possible function in the pathogenesis of a number of inflammatory diseases have been evidenced by a number of researchers. A number of studies have provided data on several inflammatory diseases that involves AQPs. It has been established that the chief pathological fact linked with disease like rheumatoid arthritis (RA) and Osteoarthritis (OA) are described by extensively increased levels of inflammatory cytokines produced by activated immune cells that results in the damage to bones. Certain AQPs are expressed in cartilage cells where they control the passage of ions thus regulating the bone physiology (Mobasheri *et al.*, 2004). The participation of AQPs in the progression of this disease was studied in the cartilage of osteoarthritis model. Reports suggested that AQP1 mRNA expression was increased that was linked to the chondrocyte death (Gao *et al.*, 2016). In a study using adjuvant-induced arthritis rat model, it has been established that AQP4 might also play an important role in the pathophysiology of RA (Cai *et al.*, 2017). Apart from AQP1 and AQP4, AQP9 is reported to be involved since it has been found to be regulated by TNF-α in RA (Nagahara *et al.*, 2010). Severe neuro-inflammatory disorder is mainly characterized by brain edema. AQP4 is reported to be predominantly present in the brain and is known to be involved in conditions like hydrocephalus, during which there is an increased pressure in the brain due to buildup of CSF in the cavities. AQP4 expression increases in the brain astrocytes on induction of hydrocephalus (Bloch *et al.*, 2006; Tourdias *et al.*, 2009; Mao *et al.*, 2006). Meningitis

is also characterized by brain edema where AQP4 is known to play an important role (Huang *et al*., 2014; Du *et al*., 2015). Papadopoulos and Verkman (2005) reported that disruption of AQP4 gene in mice alleviates the swelling in brain as well as lethality in pneumococcal meningitis. Compounds that can inhibit the AQP4 expression may therefore serve as a critical treatment for inflammation induced brain edema (Papadopoulos *et al*., 2008). In neuromyelitis optica, antibodies are produced that targets AQP4 in astrocytes. It involves the stimulation of the complement system that causes cytotoxicity and inflammation (Jarius *et al*., 2008; Waters *et al*., 2008; Yick *et al*., 2018).

Similarly, the role of AQPs has been investigated in other diseases with inflammatory conditions involving the gastrointestinal tract (Laforenza, 2012; Pelagalli *et al*., 2016). AQPs play important role in the intestinal system by maintaining the permeability and secretion (Squillacioti *et al*., 2015). The dysfunction of the electrolyte and fluid homeostasis in the gut as a result of persistent inflammation are signs of inflammatory bowel disease (IBDs) (Zhou *et al*., 2009; Martínez *et al*., 2012). Therefore, AQPs have widely studied for their potential involvement in IBDs. Studies in IBD models suggests that expression AQP1, AQP3 and AQP8 is linked to NF-kB signaling that is responsible for regulating the cytokine production (Chao and Zhang, 2017). During acute pancreatitis the AQP1 downregulation leads to decrease pancreatic secretions (Venglovecz *et al*., 2018) AQPs also play important role in the disease involving the inflammation of the respiratory system such as asthma. It has been reported that the AQP3 deficient mice showed a decreased inflammation compared to the wild-type mice attributing to its role in production of CCL24 and CCL22 by modulating the quantity of H2O2 in alveolar macrophages (Ikezoe *et al*., 2016). Krane *et al*. (2009) studied the expression of AQP3, AQP4 and AQP5 in inducible asthma mice models. Increased expression of AQP1 and AQP5 in small airways in rat models of asthma shows that their role in the formation of submucosal edema and elevated mucus secretion (Ablimit *et al*., 2013). Some of the important diseases with inflammation involving AQPs have been listed in Table 2.

Conclusion

Several investigations on AQPs imply their role as possible targets in drug therapeutics. AQPs are expressed in different types of cells which maintain the fluid homeostasis and have been reported to be involved in the pathogenesis of inflammation. Alterations in expression of AQPs at transcriptional as well as translational levels have been evidenced in response to different kind of inflammatory stimuli making them potential targets in many inflammatory disorders. Therefore, the association between AQPs and inflammation would further increase the understanding of the underlying mechanisms involved in the inflammatory process. Owing to the role played by AQPs in inflammation, these proteins can be thereby targeted to minimize the progression of inflammation thus providing a therapeutic approach.

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