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Review

Aquaporins: Unexpected actors in autoimmune diseases

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ABSTRACT

Aquaporins (AQPs), transmembrane proteins allowing the passage of water and sometimes other small solutes and molecules, are involved in autoimmune diseases including neuromyelitis optica, Sjögren's syndrome and rheumatoid arthritis. Both autoantibodies against AQPs and altered expression and/or trafficking of AQPs in various tissue cell types as well as inflammatory cells are playing key roles in pathogenesis of autoimmune diseases. Detection of autoantibodies against AQP4 in the central nervous system has paved the way for a deeper understanding in disease pathophysiology as well as enabling diagnosis. This review provides a comprehensive summary of the roles of AQPs in autoimmune diseases.

1. Introduction

Autoimmune diseases are characterized by tissue-specific or systemic immune responses directed against self-antigens [1,2]. The resulting immune responses trigger downstream inflammation leading to tissue damage. As such, the spectrum of clinical manifestations stretches from general and non-specific symptoms such as fatigue, low grade fever to more severe and life-threatening events such as kidney failure.

The pathophysiology underscoring autoimmune diseases are complex and not yet fully understood but several lines of evidence harbor the cardinal roles of both innate and adaptative immune systems in disease initiation as well as perpetuation. As part of the adaptative immune system, T-cell and B-cell activation and proliferation are primary in relation to cytokine production as well as autoantibody production. Myeloid leucocytes (monocytes, macrophages, dendritic cells and neutrophils) [3] and innate lymphoid cells [4] represent first-line effectors of the innate immune system. They can act as antigen-presenting cells or as accessory cells secreting cytokines and chemokines.

Aquaporins (AQPs) are a family of transmembrane proteins containing six transmembrane helical domains forming a pore permeable to water [5]. They organize in functional tetramers [6]. Since the discovery and purification of the first AQP (named AQP1) from red blood cells [7], other AQPs have been discovered in all other living organisms and the family comprise 13 mammalian AQPs (named AQP0 to AQP12) [5].

AQPs have been implicated in cell migration [8–11]. In the current model of cell migration, AQPs facilitate water influx at the cell's leading edge, causing plasma membrane expansion, formation of a concentration gradient of actin polymers, and actin repolarization to stabilize the formation of filopodia and lamellipodia [10].

This review provides a comprehensive summary on the roles of AQPs in the activation, migration, proliferation of immune cells, and in the pathogenesis of some autoimmune diseases such as neuromyelitis optica, Sjögren's syndrome and rheumatoid arthritis.

2. Role of AQPs in immune cells

Dendritic cells (DCs), macrophages and B cells are professional antigen-presenting cells (APCs) sensing and integrating various foreign antigens, and transferring information from innate to adaptative immunity to induce immunity to foreign antigens [12–14]. At the site of infection, APCs subsequently internalize foreign antigens through receptor-mediated endocytosis and phagocytosis, process antigens, and present resulting antigen peptides on major histocompatibility complex class II (MHC II) to CD4+ T-helper cells (TH cells) along with costimulatory molecules (such as CD83 and CD86) [13–15]. In addition, neutrophils, eosinophils and basophils have been suggested to also act as APCs [16,17]. T cells represent the main actors in adaptative immunity and can influence the function of other immune cells involved in both innate and adaptative immunity [18].

2.1. Dendritic cells

DCs have been shown to express AQP3 [19–22], AQP5 [20], AQP7 [21,23] and AQP9 [24,25]. Both AQP3 and AQP7 are expressed in

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immature DCs, down-regulated in mature DCs, involved in phogocytosis but not receptor-mediated endocytosis, macrosolutes concentration and water movement [19,21]. In addition AQP3 was suggested to modulate migration of DCs and DCs subsets populations as *Aqp3* knockout mice displayed lower splenic CD4+ DCs but higher CD103 expression in CD8+ DCs [19]. Using *Aqp5* knockout mice, AQP5 expression in immature DCs has been involved in the regulation of CD80 and CD86 expression playing a role T-cell activation, endocytosis and cell migration [25]. Using *Aqp7* knockout mice, AQP7 has been involved in antigen uptake and migration in DCs [23]. In *Aqp9* knockout mice, AQP9 has been shown to contribute to DCs migration and secretion of inflammatory cytokines [24]. Overall, AQPs involved in cell volume regulation are playing important roles in DCs functions.

2.2. Macrophages

Macrophages exert different function according to their activation state including resting (M0) and polarized (M1 and M2) states. M1 macrophages, the classically activated macrophages, arise in the presence of interferon gamma (IFN-γ) released by T helper type 1 T cells (TH1), natural killer and APCs, while M2 macrophages, the alternatively activated macrophages, arise in the presence of interleukin 4 (IL4) and/or interleukin 13 (IL13) released by T helper type 1 T cells (TH2), basophils, eosinophils, and mast cells. In addition, M1 macrophages can repolarize to M2 macrophages in the presence of IL4 and M2 macrophages can repolarize in M1 macrophages in the presence of IFN-γ [26–28]. M1 macrophages possess pro-inflammatory, anti-tumor and anti-microbial properties. Instead, M2 macrophages exhibit anti-inflammatory properties and play a role in tissue remodeling, healing and repair [27,28].

Macrophages undergo rapid changes in cell volume during their activation. Several AQPs, including AQP1 [29], AQP3 [30], AQP4 [31], AQP7 [32] and AQP9 [32–34] have been shown to be expressed in macrophages. AQP1 played opposite roles in M0 and M1 macrophages; suppressing or stimulating respectively their migration [29]. AQP3 was also involved in macrophage migration as well as phagocytosis through cellular mechanism involving facilitated water and glycerol movement [32]. While AQP1 supressed M0-M2 phenotype switch [29], AQP4 had the opposite effect [31]. AQP1 repressed M1 polarization by inhibiting p38 mitogen activated protein kinase (MAPK) activation [35] and promoted M2 polarization through a phosphoinositide 3-kinase (PI3K)-dependent mechanism [36]. AQP3 was involved in H_2O_2 transport and subsequent nuclear factor-kappa B (NFkB) activation and M1 activation [37]. Besides, neutralizing anti-AQP3 antibodies were capable to inhibit these AQP3-induced effects [37]. A quorum sensing signal molecule of *Pseudomonas aeruginosa* has been shown to increase AQP9 expression, redistribute AQP9 to the leading and trailing edges and increase water flux through AQP9. These events affected macrophage volume and promoted phagocytosis [33,34]. As such, modulation of AQPs expression resulting from bacteria-macrophage interaction may influence macrophage function and subsequent immune response.

Macrophage inflammasome activation and concomittant release of interleukin 1 beta (IL1ß) can be triggered by cell swelling [38]. Besides, AQPs have been involved in the regulation of inflammasome-mediated pro-inflammatory cytokines production. Indeed, water influx mediated by AQP1 [39] and AQP3 [30] have been shown to induce NOD-like receptor protein 3 (NLRP3) inflammasome activation and subsequent release of IL1ß by M1 macrophages. Further studies are necessary to assess if AQP4 is also involved in inflammasome activation and if AQP3 proxiporin activity contributes to an increase in reactive oxygen species followed by subsequent inflammasome activation.

2.3. B cells

The expression of AQP1, AQP3, AQP5 has been detected in activated B cell, but not in inactivated B cells [20]. However, the role of these AQPs in B cell function has not been elucidated. AQP8, though the passage of H_2O_2, was incriminated in B cell activation and differentiation into plasma cells [40]. Indeed, AQP8, allowing the entrance of H_2O_2 (produced extracellularly by NADPH-oxidase 2 (NOX2) during B cell receptor (BCR) activation, potentiated tyrosine kinase signaling and induced IgM production and secretion [40].

2.4. T cells

While the expression of AQP1 and AQP5 was detected in activated but not in inactivated T cells, the functional role of these AQPs in T cell function remains to be determined [20]. The expression of two others AQPs have been detected in T cells: AQP3 [20,41] and AQP4 [42]. Using *Aqp3* knockout mice, it was shown that AQP3, through the passage of H_2O_2 rather than of water or glycerol, promoted chemokine-dependent T cell migration by activating Rho GTPase cell division cycle 42 (Cdc42) and subsequently actin polymerization [41]. AQP4 promoted T cell proliferation as well as the expression of Sphingosine-1-Phosphate Receptor 1 (S1PR1) and C—C Motif Chemokine Receptor 7 (CCR7), binding respectively *Sphingosine 1-phosphate and* C—C Motif Chemokine Ligand 21 (CCL21), that mediate cell migration [42].

2.5. Neutrophils

AQP9 was mainly located at the neutrophil edges when phosphorylated possibly through a Rac Family Small GTPase 1 (Rac1)-dependent pathway [11]. AQP9 ensured water fluxes playing important role in cell-volume increase accompanying membrane extension during neutrophil migration [43]. In addition, using *Aqp9* knockout mice, AQP9 was shown to participate to increased water entry, actin remodeling and cell migration in neutrophils activated with CCR7 ligands such as C—C Motif Chemokine Ligand 19 (CCL19) and CCL21 [44]. It needs to be considered that the entry of H_2O_2 through AQP9 may regulate downstream signaling pathways during cell migration [45].

Overall, additional studies are necessary to further decipher the molecular mechanims underlying the role of AQPs in immune cell functions and to determine if AQPs inhibition may be considered as a potential therapeutic approach in autoimmune diseases.

3. AQPs autoantibodies and autoimmune diseases

Autoantibodies against AQPs have been found mainly in two autoimmune diseases: neuromyelitis optica (NMO) and primary Sjögren's syndrome (pSS).

3.1. Autoimmune AQP4 channelopathies

NMO, first described by Eugene Devic in 1984 and thereby often named Devic's disease, is an autoimmune inflammatory disease of the central nervous system [46]. NMO predominantly affects primarily the spinal cord and the optical nerves leading to blindness and paralysis [46]. The discovery of antibodies targeting aquaporin-4(AQP4) in NMO has markedly changed the clinical practice in enabling its distinction from multiple sclerosis. Diagnostic criteria for any neuromyelitis optica spectrum disorders (NMOSD) requires the presence of anti-AQP4 antibodies, found in about 70–80% of the patients in the context of an inflammatory attack on the central nervous system [47–49]. However, the diagnosis of anti-AQP4-seronegative NMOSD remains a challenge and requires various additional criteria to be fulfilled. A study revealed that about 17% of suspected NMOSD patients had anti-AQP1 antibodies of the complement-activating IgG1 subclass, with the majority binding to the extracellular domain of AQP1 [50]. Further studies are required to assess the possible pathogenic role of anti-AQP1 antibodies in patients with NMOSD.

3.2. Primary Sjögren's syndrome (pSS)

pSS is an autoimmune epithelitis characterized by inflammatory infiltrates within exocrine glands, and predominantly salivary and lacrimal glands [51]. Autoantibodies against AQP5, playing a key role in saliva secretion, were detected in Korean [52] and non-Korean [53] pSS patients. Furthermore, in non-Korean pSS patients, the anti-AQP5 autoantibodies were associated with serological and histopathological features of the disease [53]. The anti-AQP5 autoantibodies recognized functional epitopes located within the three extracellular loops of AQP5 and inhibited AQP5-mediated water flow [54]. Other autoantibodies directed against AQPs, including AQP1 [55], AQP3, AQP8 and AQP9 [56] have also been described in some pSS patients. As opposed to anti-AQP5 autoantibodies, anti-AQP1 autoantibodies have not been associated with reduced salivary flow rate [55]. The presence of anti-AQP autoantibodies (against AQP1, AQP3, AQP8 or AQP9) was associated with more severe xeropthalmia [56]. However, due to the low frequency of these autoantibodies, their individual clinical usefulness remains to be evaluated in a larger cohort of pSS patients.

4. Involvement of AQPs in the pathogenesis of autoimmune diseases

Several AQPs have been involved in the pathogenesis of autoimmune diseases, such as NMO, pSS, and rheumatoid arthritis.

4.1. Neuromyelitis optica spectrum disorders

There are corroborating lines of evidence suggesting defective B cell tolerance checkpoints in NMSOD leading to increasing numbers of autoreactive immature B cells that are not cleared and can therefore be activated. In patients suffering from NMSOD, memory B cells as well as plasma cells depict significant somatic hypermutation, underscoring evidence that germinal centers per se are the main site of autoreactive B cell activation [47]. Anti-AQP4 autoantibodies were shown to penetrate the central nervous system though endothelial transcytosis or at areas of disrupted blood-brain-barrier and then to bind with AQP4 isoforms M1 and M23 with variable avidity (M1 and M23 isoforms differ at the cytoplasmic N-terminal end; M21 possesses 22 additional amino acids) [57]. Patients with NMO have antibodies targeting specifically GRP78 (glucose-regulated protein 78), that are present on the surface on the brain microvascular endothelial cells, and display reduced claudin-5 expression thereby facilitating AQP4-specific IgG passage into the brain parenchyma. Binding of anti-AQP4 antibodies to AQP4 occured on the surface of astrocytes that predominantly express AQP4 at their end-feet and induce preferential M1 isoform internalization and aggregation of M23 isoform [58]. The expression of glutamate transporter 1 (GLT1), capable to form protein-protein interaction with AQP4 [59], was also decreased in response to AQP4-IgG binding to AQP4 and led to a concomitant decrease in glutamate uptake by the astrocytes [60]. The consequent reduced uptake of glutamate, accumulated within the synaptic cleft after synaptic transmission, is thought to contribute to exocytic death of oligodendrocytes and subsequent neuronal demyelinization [47]. Moreover, AQP4-IgG binding to AQP4 resulted in transcriptional and translational events within the astrocytes that promoted granulocytes recruitment and preceded classical complement and antibody-dependent cytotoxicity [61]. Among a wide range of possible therapeutic options to treat NMOSD, AQP4-IgG blocking and inactivation strategies have also been considered but have not led to any clinical trial [62,63]. For example, aquaporumab, an engineered high-affinity AQP4 antibody lacking complement-dependent cytotoxicity/antibody-dependent cytotoxicity can preferentially thrwart pathogenic AQP4 antibodies.

4.2. Primary Sjögren syndrome

AQPs have been involved in the pathogenesis of pSS. While AQP5 is predominantly expressed at the acinar apical membrane in healthy human salivary glands and lacrimal glands, its localization is altered in pSS patients (basolateral and cytoplasmic) [64–66]. Modified AQP5 distribution within acinar cells has also been shown in salivary glands from mouse models of the disease [67,68]. Based on experimental data, several hypotheses may account for the altered AQP5 trafficking and/or localization: a) autoantibodies against muscarinic receptor subtype M3 [69]; b) disturbed interaction between AQP5 and some of its protein-interacting partners such as prolactin-inducible protein [70–72] and ezrin [73–75]; c) inflammatory environment [76,77] and cytokines such as tumor necrosis factor alpha (TNFα) [78,79] and interferon gamma (IFNγ) [80,81]; d) perturbation of the acinar tight junctions [51,82]; e) autoantibodies against AQP5 [52,53] (Fig. 1).

Interestingly, AQP1 gene therapy (providing a facilitated water permeability pathway) restored saliva secretion and decreased both local and systemic inflammation in pSS mouse model [83]. However, further studies are necessary to decipher the underpinning mechanisms and to determine the effect of such therapy on AQP5 localization. Besides,the pathophysiological relevance of reduced AQP1 [84] and AQP4 [85] expression in salivary glands from pSS patients remains to be proven as *Aqp1* and *Aqp4* knockout mice do not shown any saliva flow modification [86].

4.3. Rheumatoid arthritis (RA)

AQP1 was involved in fibroblast-like synoviocytes (FLS) proliferation, migration and invasion of the cultured rat collagen-induced arthritis through β-catenin signaling pathway [87]. Using RA FLS, it has also been shown that AQP1 overexpression increased cell migration and invasion through the activation of Wnt/ß-catenin pathway [88]. In other cell types, protein-protein interactions between AQP1 and ß-catenin, protein LIN-7 homolog (Lin7), and focal adhesion kinase (FAK) also participated in cytoskeleton rearrangement, cell adhesion and cell migration [89,90].

Interleukin-6, found in synovial fluid from RA patients, induced convergent increased expression of both sodium-potassiul-chloride cotransporter 1 (NKCC1) and AQP1, leading to RA FLS swelling ultimately resulting in cytotoxic edema [91]. These data suggested AQP1 inhibitors [92] may be useful for the treatment of RA. In FLS, both AQP3 and AQP9 were also detected and AQP9 expression was increased by TNFα [93]. Further studies are required to further precise the role of these AQPs in RA FLS.

In a rat collagen-induced arthritis, articular chondrocytes exhibited higher AQP4 expression than normal rats [94]. In addition, AQP4 was involved in interleukin 1 beta (IL1ß)-induced chondrocyte apoptosis though the activation of p38 MAPK [94]. These data suggested AQP4 inhibition preventing chondrocyte apoptosis may be used as a therapeutic option for the treatment of RA.

The role of AQP9 expression in osteoclasts differentiation, previously suggested by a study using aspecific inhibitor [95], has been ruled out using *Aqp9* knockout mice [96]. Further investigations will be required to assess the role of AQP9 in osteoclast function under normal and pathophysiological conditions such as RA.

As such, AQPs expressed in FLS, chondrocytes and osteoclasts are likely participating to RA pathogenesis.

5. Conclusions

The concept of AQP defined as simple water channels has been broadened to several pathophysiologic processes. AQPs have been implicated in several autoimmune diseases where they participate actively in tissue related damage. The underlying autoantibodies against AQP can confer pathogenicity by several mechanisms including

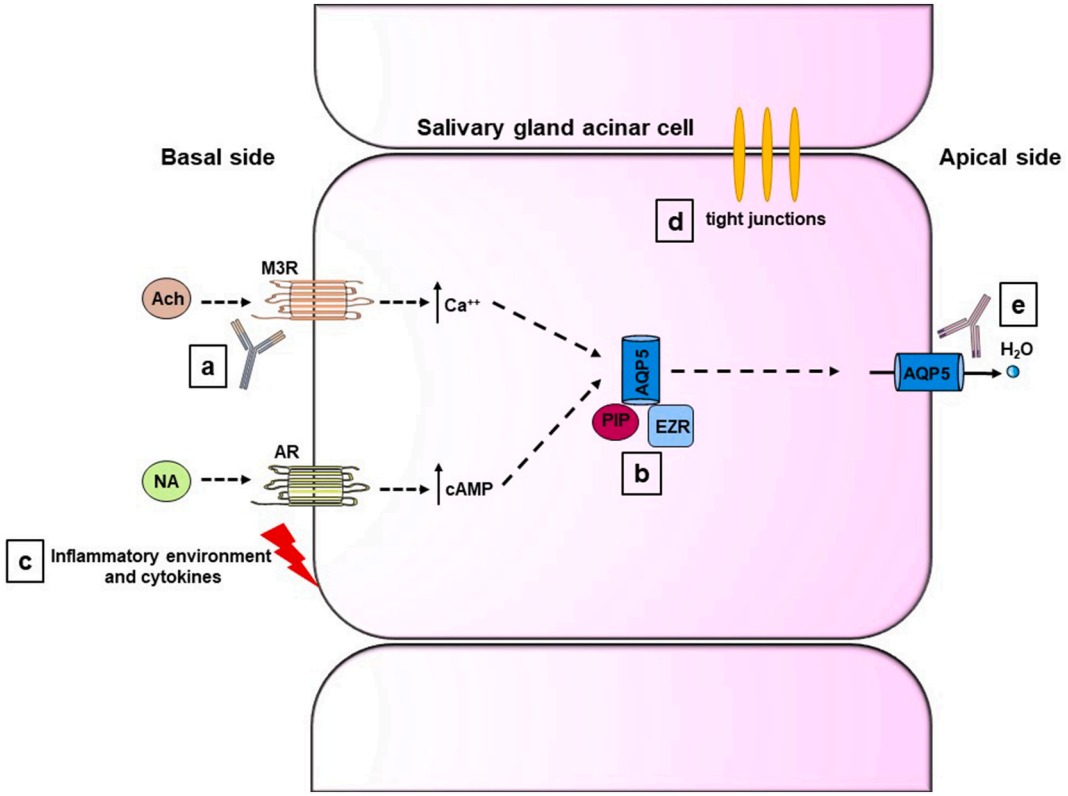

Fig. 1. Hypotheses that may account for the altered AQP5 trafficking and/or localization in salivary gland acinar cells in pSS.
Hypotheses are a) autoantibodies against muscarinic receptor subtype M3; b) disturbed interaction between AQP5 and some of its protein-interacting partners such as prolactin-inducible protein (PIP) and ezrin (EZR); c) inflammatory environment and cytokines; d) perturbation of the acinar tight junctions; e) autoantibodies against AQP5. Ach: acetylcholine; AQP5: aquaporin-5; AR: adrenergic receptor; Ca^{++}: intracellular calcium; cAMP: cyclic adenosine monophosphate; EZR: ezrin; NA: noradrenalin; M3R: muscarinic receptor subtype M3; PIP: prolactin-inducible protein.

antibody-mediated complement activation. Future research should strive to decipher the molecular mechanisms underpinning the role of AQP in the context of autoimmunity. This could pave the way for the discovery of innovative therapies targeting antigen specific molecules with lessened side effects as opposed to classical immunosuppressants.

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Christine Delporte: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Muhammad Soyfoo:** Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors 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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