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Review article

AQP4 as a vintage autoantigen: what do we know till now?

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1. Introduction

Autoimmune diseases are characterized by the presence of autoantibodies against autoantigens that induce inflammatory responses that damage tissues and organs, leading to leading to irreversible disturbances [1]. Autoimmune responses attack a specific organ, or tissue in an early phase and after becoming multisystemic [1]. Some autoimmune diseases are related to previous exposure to pathogens [2, 3]. Molecular mimicry between antigens from pathogens and humans is considered a key factor involved in triggering the autoimmune response [4, 5]. This could lead to the development of systemic autoinflammatory disorders that enhance damage, releasing new antigens that continue to exacerbate and activate the disease [6]. In this immune response, autoantibodies and T-cell receptors play pivotal roles that increase the loss of tolerance to self-antigens and promote tissue injury and damage to organs [6]. In neuromyelitis optica, the human antigen AQP4 is attacked by autoantibodies that alter water channels in astrocytes and other cells, resulting in neuropathological diseases [1]. This phenomenon has been characterized in autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus. However, what do we know about its genesis or pathophysiology? This review updates these issues and explores the phenomenon's origin.

2. A structural reappraisal of AQP4

Aquaporin 4 (or AQP4) belongs to an extensive family that includes at least 13 members (Aqp0-12) and is regulated by the AQP4 gene in chromosomal location 18q11.2. AQP4 is expressed in the blood–brain and brain–cerebrospinal fluid interfaces of glial cells, where it acts as a water channel or glycerol. Alterations in their activity are associated with neuropathological diseases, such as brain edema, stroke, and head injuries [7]. Its folding is characterized by six and two half-length alpha-helices forming a tetramer [7] (Figure 1A and B). It has an amino acid sequence constituted by 323 residues with a molecular weight of 34.8 kDa. This protein has posttranslational modifications where carbohydrate motifs are added to asparagine residues 153 and 206 [8]. Oligomerization is influenced by loop D hydrogen bonding interactions provided by water molecules passing through the channel [9, 10]. Additionally, lipids can help stabilize oligomeric structures [10]. These facts about AQP4 as an osmoreceptor are important to understand how autoreactive responses impact water flux within the central nervous system and astrocytes.

3. Clinical perspectives about anti-AQP4 seropositive neuromyelitis optical spectrum disorders (NMOSD)

NMOSD is an autoimmune disease classically characterized by destruction of the optic nerves (optic neuritis), however more severe presentations involving spinal cord, area postrema, brainstem, diencephalic, cerebral and transverse myelitis may occur [11], raising the term of anti-AQP4 seropositive NMOSD to emphasize the clinical manifestations around the anti-AQP4 autoimmune response [11, 12], not bypassing that seronegative presentations also occur in the clinic and may be explained by autoantibody response to myelin oligodendrocyte glycoprotein (MOG) and/or yet unidentified autoantigens. Anti-AQP4 seropositive NMOSD prevalence ranges from 0.56 to 10.4 per 100.000 in countries such as Denmark, Japan, and Sweden [13, 14] to 0.37 to 4.2 in Latin American countries [15]. In contrast to multiple sclerosis, in anti-AQP4 seropositive NMOSD the destruction is directed against the oligodendrocytes expressing the AQP4 autoantigen and not the axons myelin. Clinical manifestations depend on the effected central nervous system structures and span from red–green color misperceptions and persistent vomiting to blindness and transverse myelitis. MRI neuroimaging shows optic nerve edema injury and round lesions affecting subcortical, juxtacortical, brainstem, and

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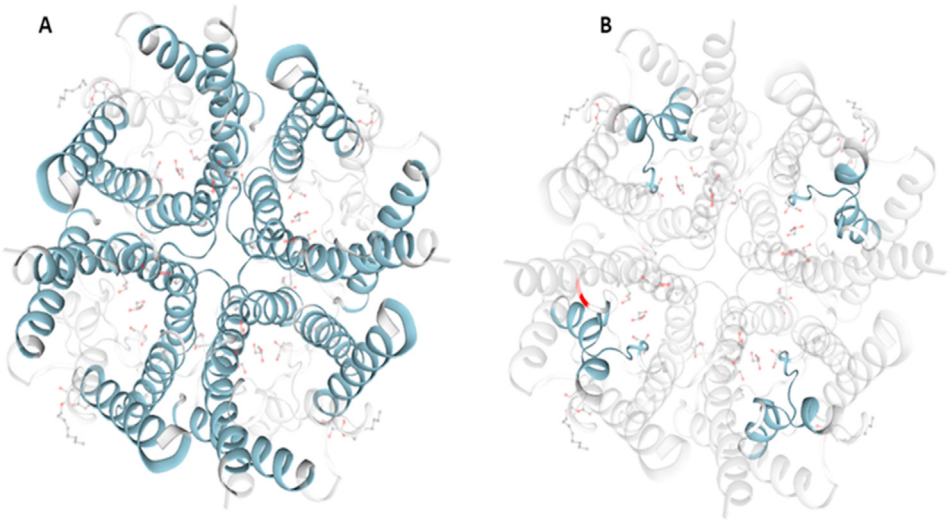

Figure 1. Tridimensional structure of human AQP4. A. In blue are shown transmembrane regions. B. In blue are shown intramembrane regions. All 3D models were generated by modeling based on homology, and visualization was performed with PyMOL Software.

myelitis spanning 3 or more vertebral spaces in T2-weighted sequences. This disease has a highly disabling and painful presentation, and treatment is based on a palliative approach [16, 17]. Classically, NMO management has been based on a stepwise approach, beginning with methylprednisolone pulses plus steroids and azathioprine as maintenance immunosuppression in the less severe clinical scenario [17]. Plasmapheresis as a second-line therapy option plus steroids and azathioprine as maintenance therapy or the anti-CD20 monoclonal antibody rituximab as a relapsing preventing medication. Recently, three new monoclonal antibodies have proven efficacious and safe in NMO treatment: eculizumab (anti-C3a mAb), inebilizumab (anti-IL6 mAb) and satralizumab (anti-CD19 mAb); however, randomized clinical trials (RCTs) comparing these mAbs with rituximab are lacking. As in multiple sclerosis [18], B-cell-depleting therapies seem to be efficacious in achieving disease remission [19, 20, 21]. The anti-CD20 strategy depletes from mature naïve B cells to memory B4 cells but not plasmablasts, and the anti-CD19 from naïve B cells to peripheral plasmablasts, leaving untouched a subset of plasmablasts in bone marrow that do not express CD19 but produce antibodies [22, 23]. All of them have inconvenient nonspecific immunomodulation, increasing infection susceptibility. In addition to MOG seropositive cases, NMO seems to be caused by the autoimmune response against AQP4 autoantigen, opening the possibility for the study of the genetic control of immune response by studying seropositive and negative individuals. In accordance, the only GWAS comparing seropositive and seronegative cases found two independent signals in the major histocompatibility complex (MHC) region associated with NMO-IgG+ individuals [24]. In multiple sclerosis, a similar autoimmune disease, various autoantigens have been reported: myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG), and myelin-associated glycoprotein [25, 26, 27, 28, 29, 30, 31]. Additionally, it has been shown that administration of peptides containing various T-cell epitopes to a mouse model of experimental induced encephalomyelitis (EAE) in the postpriming period induced a tolerogenic response [32]. Even ATX-MS-1467, a cocktail of four myelin antigen peptides given intradermally, has been shown to induce tolerance in human preclinical studies [33]. In this scenario, immunotherapy and tolerance induction appear to be alternative approaches to nonspecific immunomodulation management without collateral infection increasing the risk.

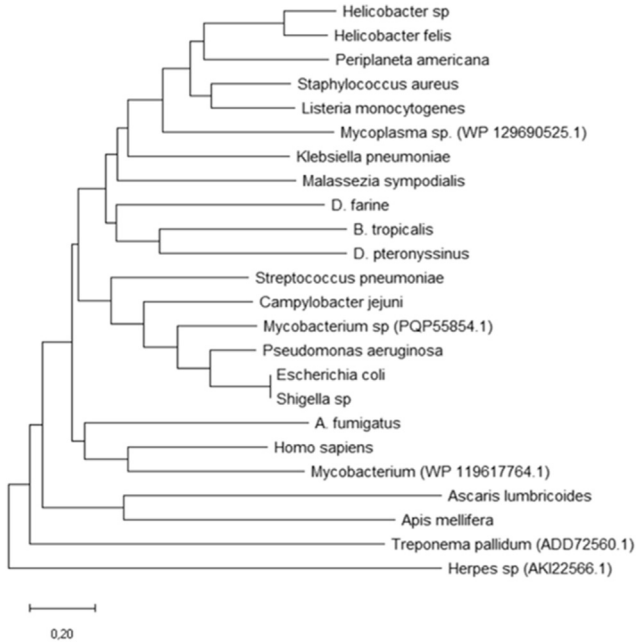

Figure 2. Phylogenetic analysis of aquaporins from several sources, such as: bacteria, fungi, insects, human, virus, and mites. Analysis revealed a closest relationship between aquaporin from human and bacteria. Analysis was performed with MEGA 11 software.

4. Beyond autoantibodies IgG

Classical literature about AQP4 involve just autoreactivity to AQP4; however, autoimmune, or autoreactive response mediated by cellular component is poorly understood. Currently, we know that AQP4 can elicit polarization of T cells to a Th17 response. Initial studies revealed that monocytes stimulated with AQP4 produced IL-6, a Th17-polarizing cytokine. IL-6 activates astrocytes and promotes the survival of plasmablasts, which helps to maintain the production of autoreactive IgG1 anti-AQP4 by B lymphocytes [33]. Even the blockade of the IL-6 receptor has great effects for refractory patients with NMO, so IL-6 appears to be an important key. Additionally, an experimental approach identified an overexpression of CD40 and CD80 costimulatory molecules, suggesting an innate immunologic dysfunction. All these immunological events were induced by a T-cell epitope derived from AQP4 that spans residues 5 p61–80; this T-cell epitope was associated with HLA genotypes DRB1*0301 and DRB3 [34].

By 2016, a new study confirmed that Th17 cells are critical in maintaining the autoreactive response to AQP4. However, the Th1 profile seems

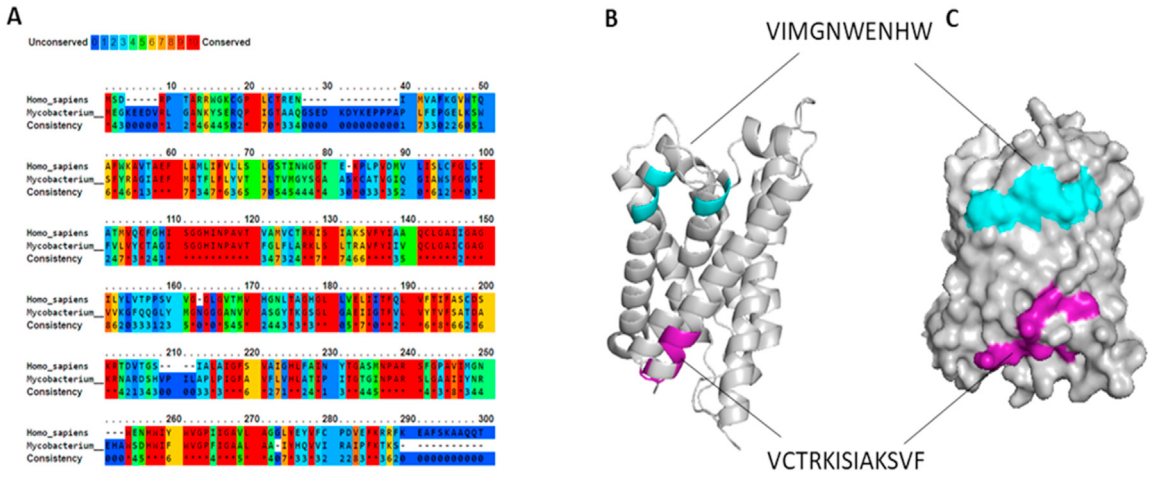

Figure 3. Identity analysis and epitope prediction on aquaporin. A. Aquaporins from human and mycobacterium share a 40% in identity in their amino acid sequences. B–C. In magenta and violet are highlighted cross reactive antigenic regions predicted between AQP4 and MycAqp. Identity analysis was made with IBIVU PRALINE tool (https://www.ibi.vu.nl/programs/pralinewww/index.php).

to play a pivotal role in this phenome. New evidence indicates that four T-cell epitopes spanning the extracellular domains of AQP4 induce INF-y secretion by cells from patients with NMO. This response is like that characterized in multiple sclerosis. During the evolution of the autoreactive response, IFN-y promotes the production of the autoantibody subclass IgG1. Additionally, this cytokine modulates the chemokines CCL10/IP-10 and CCL17/TARC. CCL17 modulates the chemotaxis of T cells through CCR4 [35]. This increases the infiltration of T cells in NMO lesions. Recently, a new player has been added to the cellular mechanism involved in NMO pathogenesis. Mast cells appear to play a role in promoting inflammation in the central nervous system (CNS), liberating proinflammatory cytokines such as TNF and IL-1 [36]. These cytokines can promote the activation of astrocytes, causing tissue inflammation. Mastocytes modulate inflammation in the CNS due partly to their anatomic location; they are in vascularized regions near vessels, nerves, smooth muscles, and meninges [36]. All proinflammatory mediators released by mast cells can be triggered by IgG antibodies using FcR receptors on the mast cell surface, so IgG1 autoantibodies to aquaporins can be the main player in promoting this cellular response [37, 38].

5. Finding the genesis: cross reactivity and molecular mimicry, maybe?

Molecular mimicry was defined as homology and identity in amino acid sequences found between antigens present in pathogens and human hosts [5]. However, today this concept involves even allergenic molecules not found in pathogens but are like some human protein. Molecular mimicry has been postulated to explain the capacity of some infectious agents to induce autoimmune responses, such as Sjogren's syndrome, systemic sclerosis, and systemic lupus erythematosus [5, 39]. In his seminal review entitled "Neuromyelitis optica pathogenesis and aquaporin 4", Graber et al. highlighted the fact that the development of neuromyelitis optica (NMO) in some patients was preceded by different infections, including bacterial and viral infections [40, 41]. For example, several reports indicate that infection by mycobacterium occurs before the development of NMO disease. Just in South Africa, a higher proportion 6 of active pulmonary tuberculosis in NMO patients compared with healthy controls has been described (79% vs. 14%, $P = 0.0013 < 0.05$) [42]. This has been reported in different populations across the world [42, 43, 44, 45, 46, 47]. Our phylogenetic analysis showed that aquaporin from *Mycobacterium* sp. (AqpMyc) is related to AQP4 (Figure 2), and both have a 40% identity between amino acid sequences (Figure 3a). Using epitope prediction, we found two antigenic regions shared between AqpMyc and AQP4 (Figure 3A), which could explain the potential cross reactivity and genesis of NMO after exposure to Mycobacterium sp. Infection caused by Mycobacterium sp in tuberculosis disease can be latent, which means that the immune response is sustained through the time of the infection course without evidence of clinical symptoms of active tuberculosis disease [48, 49]. Levels of antibodies to AqpMyc can be raised during this time and be in a state of preparedness to react against human aquaporin. Since mycobacterium infection is prevalent around the world and highly prevalent in Latin America, but in contrast, NMO and NMOSD prevalence is scarce, it seems counterintuitive to propose Mycobacterium AQP4 as an environmental trigger of autoreactive response and autoimmunity in NMO and NMOSD. However, their effects could be directed in both directions: as a protector and initiator of the autoreactive response.

Additionally, autoantibodies are detected in the circulation before the initiation of the first symptoms of NMO [35]. Considering that AQP4 is not fully accessible to antibodies, human aquaporins may be the initial trigger of the autoimmune response. Therefore, which is the origin of the initial autoantibodies IgG to AQP4? Cross reactivity with aquaporins homologous to several environmental sources is a potential explanation for this. Phylogenetic analysis revealed that AQP4 shares a relationship with aquaporins from other biological sources, and regions involved in loops that are more exposed to antibodies are variables among the aquaporin family (Figure 4A–D), limiting cross reactivity. However, a murine model indicated that antibodies raised against aquaporin Z (AqpZ) from *Escherichia coli* reacted with AQP4. IgG antibodies obtained from patients suffering ONM recognized both aquaporins. Ren et al [50], showed that cross-reactive autoantibodies induced system complement activation against astrocytes in the murine model, generating inflammation and its destruction, this promotes the development of NMO disease. This indicates that the antibodies generated could activate the complement system, being important in the development of this disease. Longitudinal studies show that patients suffering from NMO have higher levels of C3a, in addition, they have autoantibodies against C1q than healthy individuals. In NMO patients, C3a levels were linked with disease activity, neurological impairment, and aquaporin-4 IgG, indicating a role for the alternative complement pathway in the pathophysiology of NMO and supporting the therapeutic complement inhibition strategy [51]. Also, axonal damage and loss, neuroinflammation, demyelination, and astrocytopathy are AQP4-IgG-induced cord diseases that are associated with mild motor deficits. These complement-independent pathophysiologies probably aid in the early development of NMOSD lesions [52].

Epitope mapping revealed that the immune response is directed against the antigenic region located on the loop exposed on the surface (Figure 3B and C). This is because the region formed by the alpha helix is inserted into the membrane of the cells, limiting recognition by autoantibodies.

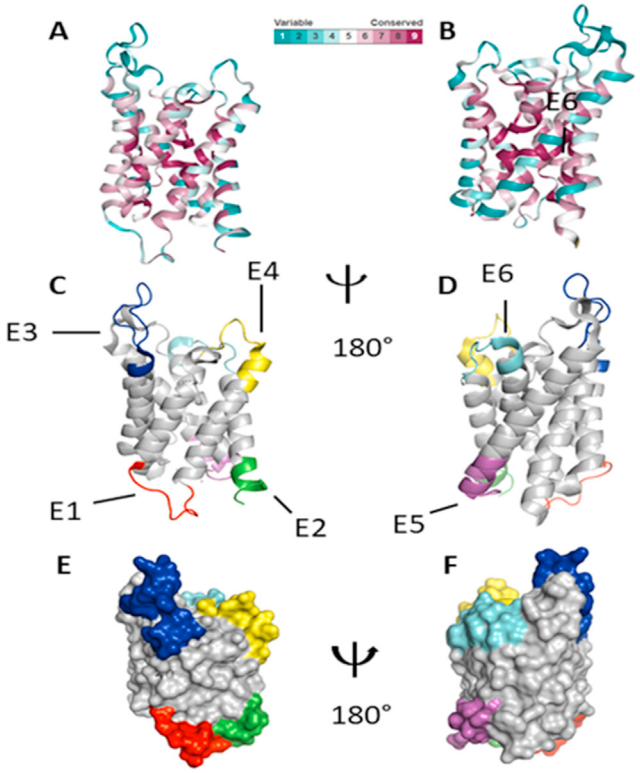

Figure 4. Structural analysis of Aquaporins. A–B: structural homology analysis. Loops are less conserved among aquaporins family. C–D: cartoon models showing epitope predicted on aquaporin. In total, six epitopes were predicted by our group. E–D: surface models showing area surface occupied by epitopes predicted. Structural homology analysis was generated with Consurf tool (https://consurf.tau.ac.il/consurf_index.php).

A cytotoxicity assay found that antibodies raised against aquaporin mediated the destruction of astrocytes by fixing complement. This assay mimicry pathomechanism was observed in a clinical context, where damage was found in the optical nerve and central nervous system, helping with the development of NMO [50, 53]. These findings suggest that there is cross reactivity between human and bacterial aquaporins [50]. Additionally, they have serious implications because they indicate that a common microorganism such as *E. coli* could be the trigger of autoreactive antibody production.

However, *E. coli* is not the only microorganism implicated in this process. According to Varrin-Doyer et al., AQP4 is homologous to the adenosine triphosphate-binding cassette (ABC) transporter permease of *Clostridium perfringens* [34, 54]. Bioinformatic analysis revealed that both proteins share identity in their amino acid sequences and have the capacity to induce the proliferation of Th17 cells derived from patients suffering NMO [34]. This microorganism is commensal to humans. This is an important issue because the gut microbiome could be relevant for the development of autoimmune responses in systemic NMO and lupus erythematosus, where AQP4 is a relevant autoantigen. Therefore, it is understood that the balance of the gut microbiome is critical to avoid autoimmune diseases, not only due to its anti- or proinflammatory properties but also because the gut microbiome is a source of antigens capable of inducing autoreactive responses by molecular mimicry [55].

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Additional information

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