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·Review·

Experimental models of neuromyelitis optica: current status, challenges and future directions

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Neuromyelitis optica (NMO) is a recurrent inflammatory disease that predominantly attacks the optic nerves and spinal cord. NMO-IgG, the specific autoantibody present in the vast majority of NMO patients, targets the astrocytic water channel protein aquaporin 4 (AQP4), and differentiates NMO from multiple sclerosis. The growing clinical and research interest in NMO makes it urgent to produce an animal model of NMO. The pathogenic effect of anti-AQP4 antibodies derived from the serum of patients paves the way to generating an experimental model based on the anti-AQP4-mediated astrocyte damage. In this review, we discuss the contribution of experimental models to the understanding of the pathogenesis of the disease and drug development. Key questions raised by the existing models are also discussed.

Keywords: neuromyelitis optica; animal model; NMO-IgG; astrocyte

Introduction

Neuromyelitis optica (NMO) is a severe autoimmune demyelinating disease of the central nervous system (CNS). It predominantly targets the optic nerve and spinal cord, leading to blindness and paralysis[1]. Some patients show a limited form of NMO, which has been referred to as NMO spectrum disorder (NMOSD) that includes optical neuritis and longitudinally extensive transverse myelitis[1]. NMO was initially considered to be a special form of multiple sclerosis (MS), as optic neuritis is present in 20%–50% of MS patients[2-5]. The presence of NMO-IgG further distinguishes NMO from MS[6]. The prevalence of NMO is far lower than MS worldwide, but NMO is more common in Asian populations[7]. NMO has a more severe outcome than MS, with frequent and early relapses[8, 9]. Vision and ambulation are impaired within 5 years of the first attack in half of the patients, and one third of patients die of respiratory failure[9]. Currently, there are no FDA-approved drugs for NMO treatment. Besides the low incidence (6.4 per 100 000)[10], the biggest obstacle to drug development is the lack of an appropriate animal model.

Although circulating NMO-IgG and the astrocytic water channel protein aquaporin 4 (AQP4) are recognized as specific biomarkers and well-defined target antigens in most NMO cases, it remains challenging to induce experimental NMO. Passive transfer of NMO-IgG into naive animals or immunizing animals with recombinant AQP4 failed to induce NMO-like lesions. So far, little is known about why NMO-IgG specifically targets astrocytic AQP4 without affecting peripheral AQP4-bearing cells and what factors are required for NMO-IgG to induce clinically overt disease. Despite these limitations, attempts have been made to create NMO models mainly based on the pathogenicity of NMO-IgG, which can represent parts of the pathogenesis of human NMO disease, and some novel therapies targeting NMO-IgG-AQP4 binding and complement-dependent cytotoxicity (CDC) inactivation have been evaluated on available animal models.

Pathology of NMO

Uncovering the pathophysiological processes is the reason for establishing animal models. NMO, also known as Devic's disease, was first described as a result of inflammation of the optic nerves and spinal cord by Eugène Devic in 1894[11]. The immunopathology of NMO includes restricted demyelination and inflammation of the optic nerves and several spinal segments[12]. The unique pathological characteristics that distinguish NMO from MS are the deposition of immunoglobulin (mainly IgG1 and IgM) and activated complement (C3a and C5a) in perivascular regions[13] as well as extensive infiltration of macrophages, neutrophils, and eosinophils[13]. In 2004, Lennon's group found that NMO-IgG is present in most NMO patients and subsequently revealed that NMO-IgG selectively binds to AQP4[6, 14]. These findings provoked research on the pathogenesis of NMO-IgG. Investigators found a pattern-specific loss of AQP4 immunoactivity in the CNS of NMO patients[15, 16], and further pathologically distinguished NMO from MS. From then on, the pathogenicity of NMO-IgG (anti-AQP4 autoantibodies) has been investigated in primary astrocytes, brain and spinal cord slices, and intact animals. These attempts contributed to the initial NMO model. All the pathogenic data above suggested that NMO-IgG-mediated humoral immunity plays a central role in the pathogenesis of NMO.

Attempts to Establish Experimental Models of NMO

The known pathology of NMO was derived from research on the pathogenic significance of AQP4-specific autoantibodies on primary astrocytes and cultured brain and spinal cord slices. From then on, all attempts at the creation of experimental NMO have been based on anti-AQP4 autoantibody (AQP4-ab). The development of NMO models is summarized in Figure 1. Over a very short period, both *in vitro* and *in vivo* NMO models have been created. Despite many limitations, the models can be used to mimic, at least in part, the pathogenesis of anti-AQP4, and thus have contributed to several drug-screening experiments. Several drugs tested for therapeutic effectiveness based on these models have entered clinical trials.

In vitro Cellular Models

As a disease-specific circulating marker, NMO-IgG can target the AQP4 protein. Makoto Kinoshita's group demonstrated for the first time that sera from NMO patients with AQP4-ab can induce necrosis in rat astrocytes *in vitro*, mainly through a classical complement-dependent pathway[17]. This study not only dissected the complement-dependent cytotoxicity of AQP4-ab, but also supplied a cellular model to mimic the autoantibody-mediated astrocyte loss in the development of NMO. In addition, NMO-IgG itself can activate astrocytes and induce inflammatory phenotypic changes in primary cultured astrocytes[18]. Research has revealed that the pathogenic mechanisms of NMO-IgG include: (1) breaking down blood-brain barrier (BBB) permeability by inducing AQP4 internalization and disrupting the polarized expression of AQP4; (2) mediating perivascular inflammatory infiltration by-products of complement activation (C3a and C5a); and (3) inducing astrocyte injury and demyelination by antibody-dependent cellular cytotoxicity (ADCC) and the disruption of glutamate homeostasis[19-21]. Autoantibody-mediated astrocyte injury is the driving force for downstream progress of disease, thus NMO-IgG-treated primary astrocytes with or without complement can be used as an *in vitro* cellular model for screening drugs that keep astrocytes alive and block NMO-IgG-mediated astrocyte phenotypic changes and cell death.

Ex vivo Spinal Cord Slice-Based Models

As NMO is a typical inflammation-mediated demyelinating disease, the *in vitro* cellular model cannot mimic the demyelination process. As NMO-IgG purified from NMO patients can recognize and react with AQP4 on the surface of living astrocytes not only from humans[14], but also from rats[22] and mice[14], cultured rodent spinal cord slices can easily be used as an ex vivo tissue model to uncover the pathological mechanisms of NMO-IgG or screen drugs for treating the disease. The first *ex vivo* NMO organ model was constructed by Verkman's group[23]. In this model, vibratome-cut transverse spinal cord slices were used. The slices were cultured on porous transwell supports for several days and NMO-like lesions (GFAP, AQP4, and myelin loss) occur when slices are exposed to NMO-IgG with complement for 1–3 days. The lesion is AQP4- and

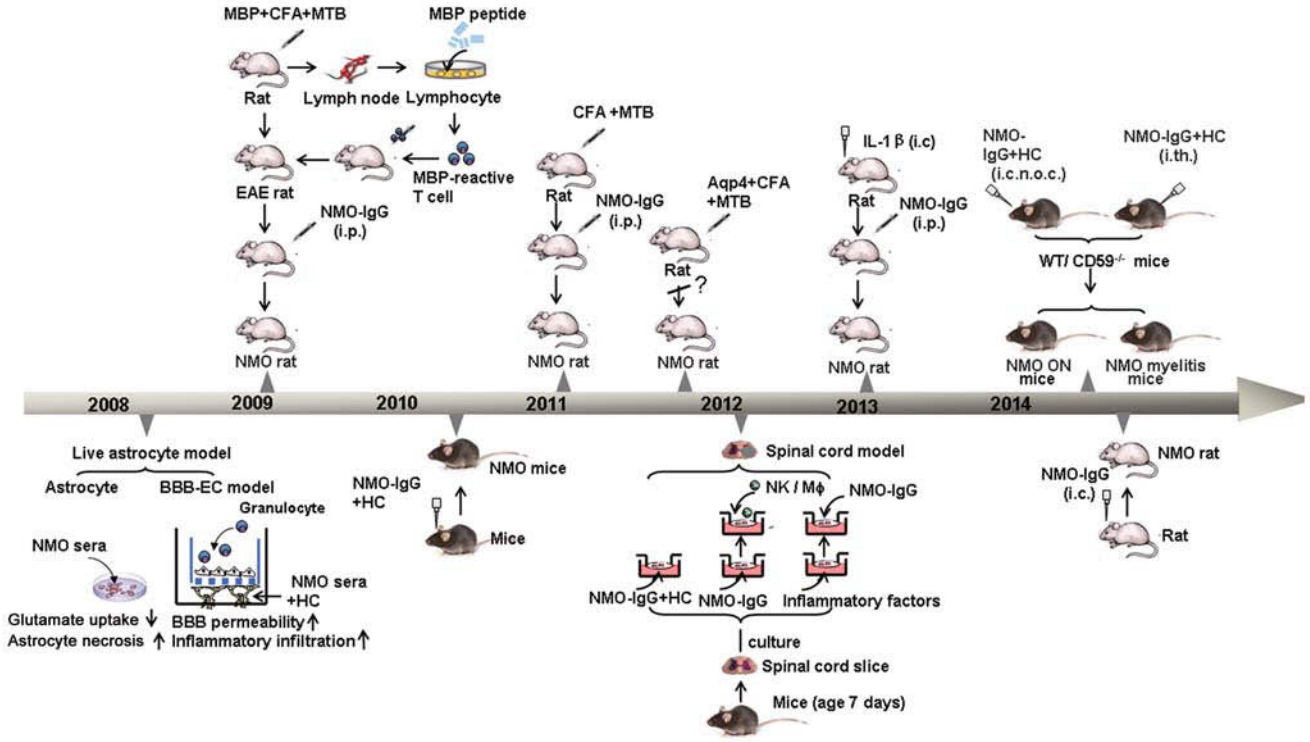

Fig. 1. The development of NMO model. In 2008, the *in vitro* cellular model was established, in which the patient AQP4-ab can induce astrocyte necrosis and impair glutamate uptake. In addition, NMO serum can breakdown BBB and recruit granulocytes to pass through the BBB. In 2009, the earliest *in vivo* NMO model was obtained through passive transfer of NMO-IgG to rats pre-immunized with bovine MBP emulsified with CFA or pre-adoptive transferred MBP-reactive T cells. NMO-IgG passive transfer can exacerbate EAE and induce NMO-like lesion. Subsequently, in 2010, researchers developed an NMO rat model using the similar method with CFA and MTB but without MBP immunization or MBP specific T cells adoptive transfer. In the same year, another NMO model was developed by intracerebral injection of NMO sera with human complement. In this model, NMO-like lesion including myelin loss was induced. In the year 2011, AQP4 immunization failed to induce experimental NMO although AQP4 antibody could be detected in serum. It is worth mentioning that another animal model, *ex vivo* spinal cord model, was induced in this year, in which the vibratome-cutted transverse spinal cord slice was used, and NMO-like lesion could be induced when slices were exposed to NMO-IgG and human complement. Inflammatory mediators (NK, macrophage and inflammatory cytokines) can expand NMO-lesions. Good news is that just in 2014, many types of NMO models were established. Other than the brain, co-injection of NMO-IgG and human complement near the optic chiasma or at the L5-L6 spinal cord of mice produced optic neuritis and longitudinally extensive NMO spinal cord pathology, respectively. Very recently, the complement-independent NMO rat model has been developed, in which brain and spinal cord pathology is produced. BBB-EC, blood-brain barrier-endothelial cell; CFA, complete freund's adjuvant; HC, human complement; i.c., Intracerebral injection; i.c.n.o.c., intracerebral injection near the optic chiasm; i.p., intraperitoneal injection; i.th, intrathecal injection; MBP, myelin basic protein; MTB, mycobacterium tuberculosis.

complement-dependent. Using this model, they also found that inflammatory mediators (neutrophils, natural killer cells, macrophages, or soluble factors including TNF-α, IL-6, or IFN-γ) expand the lesions. Other than spinal cord slices, the optic nerve and hippocampal slices have also been used as *ex vivo* organ models of NMO. These models can be used for the direct manipulation of putative effectors of NMO pathogenesis in a disease-relevant tissue[23].

In vivo Rodent Models

Passively transferred NMO-IgG- and pre-inflammation-mediated rat model Based on the data from *in vitro* experiments, researchers attempted to establish a rodent animal model of NMO. The earlier attempts involved passively transferring pathogenic NMO-IgG to animals. Several recent studies have demonstrated

that passive transfer of NMO-IgG from patient serum to a rat pre-immunized with bovine myelin basic protein (MBP) emulsified with complete Freund's adjuvant (CFA)[24], or pre-adoptive transferred MBP-reactive T-cells[22], can exacerbate the clinical course of experimental allergic encephalomyelitis (EAE), and induce NMO-like lesions, e.g., complement activation, immunoglobulin deposition, granulocyte influx in perivascular areas of the spinal cord, and AQP4 and astrocyte loss. Although these models have several pathological features, the lack of myelin damage is the key limitation. However, NMO-IgG is not pathogenic when transferred to a naïve rat, young rats with a leaky BBB, or after transfer of a non-encephalitogenic T-cell line[24]. It seems that only in the presence of CNS antigen-specific T-cells can NMO-IgG be pathogenic *in vivo*. This attitude was challenged by a subsequent study demonstrating that in addition to disruption of the BBB, myelin-specific T-cells may not be necessary in the NMO-IgG passive transfer model[25]. Pre-treatment with CFA alone, which disrupts the BBB but causes very little T-cell infiltration, is sufficient for AQP4-Ab to display its pathogenic action *in vivo*. However, the pathogenicity is limited, as AQP4-ab-mediated cytolysis only occurred in rat-CFA with one of three patient samples, which had the highest anti-AQP4 titer and the greatest pathogenic effect[25].

Unlike the above methods, it has been reported that a pre-inflammatory CNS condition can be induced by stereotaxic injection of different chemokines (e.g., CXCL2) and pro-inflammatory cytokines (such as TNF-α, IL-6, or IFN-γ) into the striatum[26]. This demonstrated that all the cytokines and chemokines promote NMO-IgG entry into the injected hemisphere, but only IL-1β induces the formation of NMO-like lesions along with the systemic transfer of NMO-IgG, such as loss of AQP4 and GFAP, and the formation of perivascular lesions[26]. In addition, it was revealed that IL-1β upregulates ICAM-1 expression in endothelial cells, enhances chemokine expression in astrocytes and microglia, and promotes the perivascular accumulation of C1q, resulting in increased BBB permeability and granulocyte accumulation[26].

Passively transferred NMO-IgG- and human complement-mediated mouse models Later on, another NMO-IgG passive transfer mouse model was developed. In this model, NMO-IgG from NMO seropositive patients was directly injected into the mouse brain. NMO-like lesions including AQP4 loss, astrocytic swelling, perivascular complement deposition, and granulocyte infiltration were seen after the NMO-IgG was intra-parenchymally injected into a mouse supplied with human (but not mouse) complement[27, 28]. Most importantly, this model can produce extensive myelin loss[27], and provides direct evidence of NMO-IgG pathogenicity by complement activation without a pre-inflammatory condition. Most importantly, based on this model, several preclinical therapeutic methods have been tested[29-32]. Other than the brain, co-injection of NMO-IgG and human complement near the optic chiasma or at the L5–L6 spinal cord of mice can produce NMO-like optic nerve pathology[33] or longitudinally extensive white-matter lesions in the lumbar spinal cord[33, 34]. Both of these are helpful in the study of NMO pathogenesis and therapeutics.

Intracerebral or intrathecal passively transferred NMO-IgG-only-mediated rat models Other than the mouse model, a passive transfer of NMO-IgG-mediated rat model was developed by intracerebral administration of NMO-IgG alone in naive rats, in which the endogenous rat complement was used and pre-existing neuroinflammatory or human complement was not needed[35]. In this model, a single intracerebral injection of NMO-IgG to adult Lewis rats produced robust NMO-like lesions around the needle track with marked AQP4, GFAP, and myelin loss, granulocyte and macrophage infiltration, vasculocentric complement deposition, BBB disruption, microglial activation, and neuronal death. Besides these central lesions, a distinct "penumbra" was found around the central lesions. The penumbra showed AQP4 loss but GFAP and myelin were preserved. It was reported that the formation of a penumbra was complement-independent as it was seen in the NMO-IgG passively transferred complement-deficient rat[35]. Interestingly, "penumbra-like" lesions with loss of AQP4 but preserved astrocytes adjacent to destructive lesions with complement activation have also been reported in spinal cord sections from NMO autopsy cases[36]. In addition, the penumbra-like lesions suggest a unique type of ADCC-dependent lesion because a penumbra was not seen if the NMO-IgG was passively transferred to rats lacking both CDC and ADCC effector functions[35].

Very recently, an NMO-IgG passive transfer-mediated rat spinal cord disease model has been developed. Repetitive intrathecal (i.t.) administration of patient NMO-IgG or recombinant human anti-AQP4 antibodies *via* implanted catheters leads to a complement-independent, progressive, and reversible spinal cord disease without inflammatory cell infiltration, complement activation, and changes in the integrity of axons, myelin, and oligodendrocytes in the areas of immunoglobulin deposition[37]. Penumbra-like lesions have also been found in this model[37].

Immunization-mediated mouse models Differing from the passive transfer rodent model, the immunization model has also been tried by researchers. Indeed, AQP4-specific T-cells are found in the peripheral blood of NMO patients and in the natural T-cell repertoire of wild-type C57BL/6 mice[38]. AQP4 stimulation promotes T-cell proliferation[39]. However, even when the AQP4-ab is detected in mouse serum after immunizing mice with intact AQP4 or its peptide in CFA, no clinical and pathohistological features are seen[38]. So far, no AQP4 immunization-mediated NMO model has been reported. It is still a challenging hurdle to generate cytopathic AQP4 antibodies in animal models and to understand the source of NMO-IgG in humans.

Other NMO-related animal models Unlike the above NMO animal models based on NMO-IgG pathogenicity, other NMO-like animal models that do not involve NMO-IgG or AQP4 have been published. They mimic NMO in either the localization of the disease to the optical nerves and spinal cord or in their tissue pathology. The "2D2" EAE model was developed in which mice harboring T-cells directly against myelin oligodendrocyte glycoprotein$_{35-55}$ (MOG$_{35-55}$) were crossed with mice with the transgenic B-cell receptor to MOG[40, 41]. Our previous study using high field-strength MRI revealed that early BBB breakdown occurred in most of the 2D2 mice, while the majority of the mice showed little to no brain lesions. The inflammatory infiltrates and demyelination in the brain and spinal cord, as assayed by immunohistology, mirrored the sites of MRI lesions with a decrease in AQP4 protein at the lesion site[42]. The mice spontaneously developed optic neuritis and severe inflammatory spinal cord lesions similar to those seen in NMO patients. This suggested that the 2D2 mouse might serve as a model for NMO research, but this model has the shortcoming that there was no evidence of the complement deposition or granulocyte recruitment found in NMO pathology.

Challenges of NMO Models

Although different limitations exist in each of the above experimental NMO models and no one model mimics all the immune changes and pathophysiology of NMO, there has been sustained progress in identifying the pathogenesis of NMO and developing novel therapeutics based on these models. Confronting challenges in the existing NMO models will help us make better models to reveal disease pathophysiology and develop novel and effective treatments.

Contribution of Immune Phenotypes to NMO

As noted above, the current NMO animal models are mainly based on transferred human NMO-IgG, and methods for activating a peripheral immune response to mimic NMO pathogenesis have not been reported. It is known that, AQP4-ab is of the IgG1 isotype, suggesting that the development of NMO requires $CD4^+$ T-cells to complete class-IgG isotype switches[43, 44]. Evidence shows that AQP4-specific T-cell responses occur in mice, further demonstrating that Th1 and Th2 respond to the AQP4 antigen *in vivo*[38, 39]. Moreover, T-cell activation is found in the peripheral blood of NMO patients during relapses, and AQP4[39] and proteolipid protein (PLP) activate the proliferation of T-cells derived from NMO patients[39, 45]. These findings imply that $CD4^+$ T-cells play important roles in the initiation of NMO. Furthermore, it has been found that AQP4-specific T-cells in NMO patients exhibit Th17 bias and these T-cells recognize the *Clostridium* ABC transporter[39]. NMO patients have a larger proportion of Th17 cells than MS patients. Serum from NMO patients has high levels of Th17-related cytokines (IL-21, IL-23, and IL-17)[46]. In addition, the cerebrospinal fluid levels of IL-17[47] and the neutrophil-recruiting cytokine IL-8[48] are higher in NMO than in MS patients and healthy individuals. Our recent project suggested that the circulating follicular helper T (Tfh) cells are associated with the course of NMOSD, and the serum IL-21 and IL-6 levels are higher in NMOSD than in MS patients and healthy people[49]. Taken together, these data suggest that T-cells, especially Th17 and Tfh

cells are involved in the peripheral immune response in NMO pathogenesis. A novel animal model that can mimic immune responses is urgently needed for basic and clinical NMO research.

Quantitative and Stable NMO-IgG or Anti-AQP4 Antibodies for Passive Transfer

It is notable that the NMO-IgG used to induce NMO models is polyclonal and was initially purified from a seropositive NMO patient during plasmapheresis. Because of individual differences and the stage of disease, it is difficult to guarantee consistency from batch to batch. In addition, the titers and cytopathic effects of AQP4-ab vary between patients. The NMO-IgG from some patients is not effective *in vivo* due to a low titer or a weak cytopathic effect[25]. In 2009, Bennett's group developed a series of recombinant antibodies to AQP4, which were cloned using single-cell PCR from intrathecal plasma cells from patients with an early diagnosis of NMO. Both of the original methods for NMO-IgG purification and strategies for this recombinant production of anti-AQP4 antibodies are summarized in Figure 2. Several recombinant anti-AQP4 antibodies have strong CDC and ADCC activity both *in vitro* and *in vivo*. These findings not only provide a method for obtaining enough and sufficiently specific anti-AQP4-ab to induce an NMO animal model[50], but the antibodies can also be used to generate non-pathogenic, high-affinity, competitive antibodies without CDC or ADCC activity for developing targeted therapies for NMO[29]. But because of the heterogeneity of the disease, more recombinant anti-AQP4-abs need to be investigated following Bennett's protocols, especially from patients in Asian countries, as it is recognized that NMO in Asian populations may differ from that in Caucasians.

Seronegative NMO

Although 75%–90% of NMO patients are NMO-IgG-positive, 20%–40% of NMOSD patients lack detectable AQP4-ab. It has been shown that the clinical and epidemiological characteristics of these patients differ from those with NMO-IgG[51,52]. However, the mechanism of autoimmune responses in these patients remains unclear. Evidence shows that plasma exchange or B-cell depletion is beneficial for NMO-IgG-negative patients[53,54], indicating that other autoantibodies may be involved in AQP4-ab-seronegative patients. A growing number of reports, including our unpublished data, show that MOG-Ab is present in some NMOSD patients[55-57], and MOG T-cell receptor transgenic mice spontaneously develop NMO-like disease, implying that MOG may be another autoantigen in NMO patients[40,42]. A recent study demonstrated that MOG-IgG from NMO patients is primarily the IgG1 subtype and can activate complement *in vitro*[58]. It has also been found that MOG-IgG from NMO patients who lack AQP4-abs causes reversible complement-independent lesions in mouse brain, including myelin changes and alterations in the expression of axonal proteins, but without producing inflammation, axon loss, and neuronal and astrocytic death when directly delivered to the mouse brain[59]. The differences in MOG-IgG-mediated lesions mirror the better outcomes for patients with MOG-IgG than those with AQP4-IgG, and raise the possibility that MOG-IgG contributes to the pathology in some NMO patients. Besides MOG-IgG, Aquaporin-1 antibody has also been found in NMO patients[60]. Our unpublished data suggest that there is a high proportion of other myelin antigen-specific autoantibodies (including antibodies against MBP, PLP, and myelin-associated oligodendrocyte basic protein) in NMOSD patients. These data suggest that AQP4-IgG-seronegative NMO patients might have antibodies against other myelin, astrocytic, or neuronal autoantigens, and the pathogenicity of these autoantibodies needs to be further investigated. Adding to the complexity, very recent reports have shown that some NMO patients harbor more than one type of autoantibody, e.g., both AQP4-ab and anti-Ro/SSA[61], AQP4-ab and anti-N-methyl-*D*-aspartate receptor[62], or AQP4-ab and MOG-IgG[63]. The pathophysiology of these coexisting autoantibodies in NMO development needs to be addressed.

Evaluation Method Other Than Pathology

Currently, evaluation of the severity of NMO in animal models is mainly dependent on pathogenic analysis. This method has some limitations, for example, it cannot be used to assess disease severity in live animals, nor can it be used to analyze other dynamic pathophysiologic changes, e.g., demyelination, edema, visual-evoked potentials (VEPs), and visual function. In addition, the method of pathogenic analysis is not sufficiently objective. Therefore, in order to evaluate animal models objectively and comprehensively, it is better to combine MRI, optical

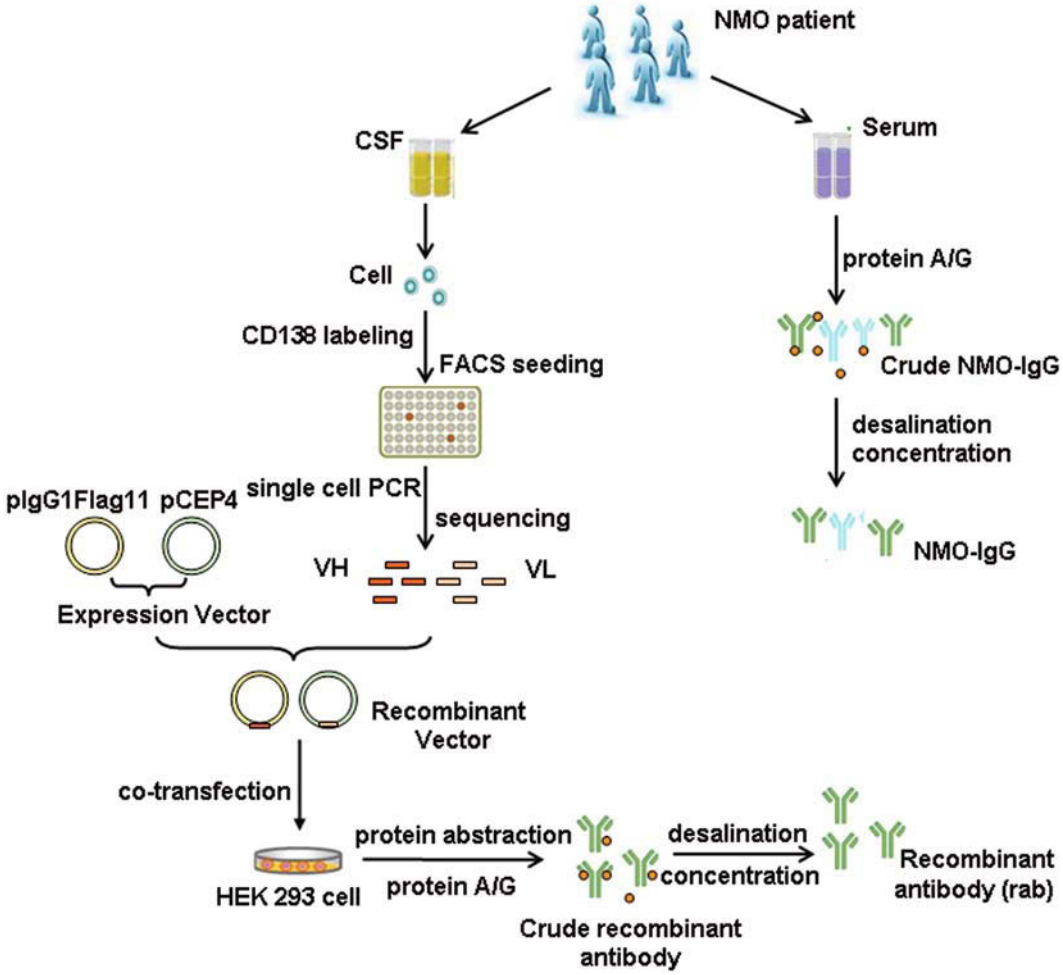

Fig. 2. Summary of original methods for NMO-IgG purification and recombinant AQP4 antibody (rab) production. For NMO-IgG purification, serum is obtained from NMO-IgG seropositive individuals, and the total IgG was purified by protein A/G beads. Then the crude IgG was desalted with dialysis and concentrated by Ultra Centrifugal Filter Units. For recombinant AQP4-antibody production, the sorted CD138+ plasma cells from CSF of NMO-IgG seropositive patients were seeded into a 96-well plate, and VH and VL chains of IgG were amplified by performing single cell RT-PCR. Then different pairs of VH and VL fragments were inserted into expression vectors pIgG1Flag11 and pCEP4, respectively. Then the recombinant vectors were co-transfected into 293T cells. One week later, the culture supernatant was collected and the recombinant IgG was purified by protein A/G beads. Further, the purified IgG was desalted and concentrated for future identification. CSF, Cerebrospinal fluid; VH, heavy chain variable region; VL, light chain variable region.

coherence tomography (OCT), VEPs, and behavioral analysis . Most recently, a good start has been made in that spinal imaging has been used to evaluate the lesions in an NMO rat model[36].

Future Directions

In the past 10 years, the awareness of NMO has developed very quickly. The diagnostic value and pathogenicity of anti-AQP4-abs have raised the hope of uncovering the pathophysiology of NMO. The experimental models of NMO play pivotal roles in understanding the pathogenic mechanisms and developing effective targeted therapeutics. The animal model of NMO widely used at present is based on pre-existing NMO-IgG pathogenic action, which partially mimicks NMO lesions. No one model is expected to present all of the pathophysiology of the disease, but

the peripheral pro-inflammatory cascade deserves to be given much attention in establishing new animal models of NMO. Combining passive transfer and active immunization models may be a better way to understand the individual pathological events in NMO lesions. Environmental factors have been reported to be closely associated with NMO disease. Anti-*Helicobacter pylori* neutrophil-activating protein (HP-NAP) antibody is significantly higher in anti-AQP4-ab-positive MS/NMO patients[64,65] and AQP4-specific T-cells in NMO patients recognize the *Clostridium* ABC transporter[39], suggesting pathogens may be involved in the pathogenesis of NMO. It has also been reported that low levels of vitamin D in NOSD are associated with disability[66]. These environmental factors should be considered in the future development of animal models. The rodent species needs to be carefully chosen, as different species may have different complement or complement-inhibitor systems that affect disease development. Objective and live-animal monitoring methods (MRI, OCT, VEP, and behavior) should be used to evaluate the models. The ongoing research focused on developing NMO animal models is expected to provide new insights into the critical events of the disease and identify novel therapeutic targets with improved efficacy and limited side-effects. A multidisciplinary effort between clinicians, pathologists, and basic scientists based on the models may have a bright future in developing new experimental models of NMO and therapeutic strategies to minimize or repair the tissue damage in NMO patients.

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