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Review

Pathogenic mechanisms of autoantibodies in neurological autoimmune diseases

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Over recent decades, the significance of autoantibodies has been increasingly recognized in neurological diseases. Breakthroughs, such as the identification of pathogenic autoantibodies targeting aquaporin-4 in central nervous system demyelinating disorders and N-methyl-D-aspartate receptors in autoimmune encephalitis, have revolutionized both the discovery and mechanistic investigation of autoantibodies in neurological diseases. Methodological advances, particularly the utilization of patient-derived monoclonal autoantibodies and cryogenic electron microscopy, have enabled the precise characterization of pathogenic human autoantibodies. In this review, we recapitulate the pathogenic mechanisms of autoantibodies in neurological autoimmune diseases. Furthermore, we propose a classification framework for autoantibodies based on their pathogenic hierarchies. This review aims to advance conceptual paradigms and inspire future mechanistic studies of autoantibodies in neurological diseases.

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Introduction

Autoantibodies, which are antibodies directed against self-antigens [1], have garnered growing recognition in neurological diseases. The foundational discovery in this field dates to 1973, when Patrick and Lindstrom demonstrated that rabbits immunized with the acetylcholine receptor (AChR) produced anti-AChR antibodies and developed myasthenia gravis (MG)-like symptoms [2]. By 1978, research had revealed that antibodies from MG patients accelerated AChR degradation through receptor cross-linking [3]. Subsequent milestones included the identification of neuronal antinuclear antibodies in 1985 (later termed anti-Hu antibodies) in patients with sensory neuronopathy and underlying lung cancer [4]. While numerous onconeural antibodies targeting intracellular antigens have since been identified, their direct pathogenicity remains unconfirmed [5].

A paradigm shift emerged with the discovery of pathogenic autoantibodies against aquaporin-4 (AQP4) in 2004 [6] and N-methyl-D-aspartate receptor (NMDAR) in 2007 [7] in central nervous system (CNS) autoimmune diseases. It triggered the discovery of additional antibodies targeting neuronal and glial extracellular antigens [8] and spurred detailed mechanistic investigations. Key pathogenic mechanisms uncovered involve cross-linking and internalization of surface NMDARs mediated by anti-NMDAR antibodies [9], as well as disruption of the leucine-rich glioma-inactivated 1 (LGI1) interaction with a disintegrin and metalloproteinase 22/23 (ADAM22/23) by anti-LGI1 antibodies [10]. Furthermore, disease-specific human monoclonal antibodies (mAbs) enabled the precise characterization of autoantibodies. Notably, anti-NMDAR mAbs alone recapitulate disease pathogenicity [11], and anti-γ-aminobutyric acid type A receptor ($GABA_AR$) mAbs exhibit both competitive and allosteric antagonistic effects on inhibitory neurotransmission [12]. Recent studies reveal binding epitopes of anti-NMDAR mAbs at atomic resolution [13,14].

Given accelerating progress in autoantibody mechanistic research in neurological diseases, this review summarizes current knowledge on their pathogenic roles, with emphasis on their cellular and molecular pathogenic mechanisms, and the classification framework based on their pathogenic contributions.

Pathogenic mechanisms of autoantibodies in neurological diseases

Pathogenic mechanisms can be categorized into two major groups. The first involves fragment crystallizable (Fc)-dependent antibody effector functions, which include complement activation, antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). The second encompasses antigen functional dysregulation mediated by the fragment antigen-binding (Fab) region, including receptor cross-linking and internalization, disruption of protein–protein interactions, receptor agonism or antagonism, and inhibition of enzyme activity.

Pathogenic autoantibodies in neurological diseases are predominantly of IgG1 or IgG4 subclasses. Antibodies against NMDAR, $GABA_AR$, $GABA_BR$, AQP4, myelin oligodendrocyte glycoprotein (MOG), and AChR (with IgG3 co-occurrence) are primarily IgG1, while those targeting LGI1, contactin-associated protein-like 2 (CASPR2), IgLON5, muscle-specific kinase (MuSK), CASPR1, contactin 1, and neurofascin are predominantly IgG4 [15]. IgG4 exhibits two unique properties compared with other IgG subclasses: (1) functional monovalency via Fab-arm exchange — a process involving the swapping of heavy-light chain pairs that generates monovalent bispecific antibodies, diminishing antigen cross-linking and immune complex formation; (2) attenuated Fc-mediated effector functions (including impaired complement activation and ADCC) due to critical amino acid substitutions that impair Fcγ receptor (FcγR) binding [16]. Consequently, IgG4 primarily relies on Fc-independent mechanisms, such as disrupting protein–protein interactions.

Activation of the complement system

IgM and most IgG autoantibodies (IgG1/2/3) can activate complement, inducing complement-dependent cytotoxicity (CDC), resulting in tissue damage. In patients with MG, complement is widely present at the neuromuscular junction [17]. Anti-AChR antibodies induce membrane attack complex formation, leading to shedding of AChR-enriched membrane and simplification of synaptic folds [18]. Therapeutic targeting of complement component C5 has demonstrated clinical efficacy [19].

AQP4, a transmembrane water channel protein in astrocyte end-foot processes at the blood–brain barrier (BBB), forms tetrameric assemblies that aggregate into orthogonal arrays of particles (OAPs). Complement activation is greatly enhanced by OAPs through the efficient, multivalent binding of C1q to clustered anti-AQP4 antibodies on these OAPs (Figure 1a) [20]. Experimental models and human histopathological studies in neuromyelitis optica spectrum disorder (NMOSD) demonstrate complement-mediated tissue injury. This mechanism is further supported by the therapeutic efficacy of complement inhibitors in NMOSD [21].

Notably, while anti-LGI1 encephalitis is primarily mediated by IgG4 antibodies, C9neo deposition in human neuropathology suggests complement system involvement [22]. Furthermore, complement activation also contributes to the pathogenesis of MOG antibody-associated disease (MOGAD), Lambert-Eaton myasthenic syndrome, and chronic inflammatory demyelinating polyneuropathy [23].

Antibody-dependent cellular cytotoxicity

ADCC involves the killing of antibody-coated target cells by effector cells expressing Fc receptors, particularly natural killer (NK) cells (Figure 1b). In NMOSD, patient-derived antibodies binding to human fetal astrocytes can trigger NK cell degranulation and subsequent astrocyte death [24]. Furthermore, NK cells significantly exacerbate demyelinating lesions produced by anti-AQP4 antibodies and complement in an *ex vivo* spinal cord slice model [25]. Unmutated anti-AQP4 antibodies generate extensive NMOSD lesions, while mutated variants with enhanced CDC but impaired ADCC capacity result in reduced pathology [26]. Additionally, significant reductions in lesion formation are observed in mice deficient in FcγRIII [26]. Collectively, ADCC is a central driver of NMOSD pathogenesis.

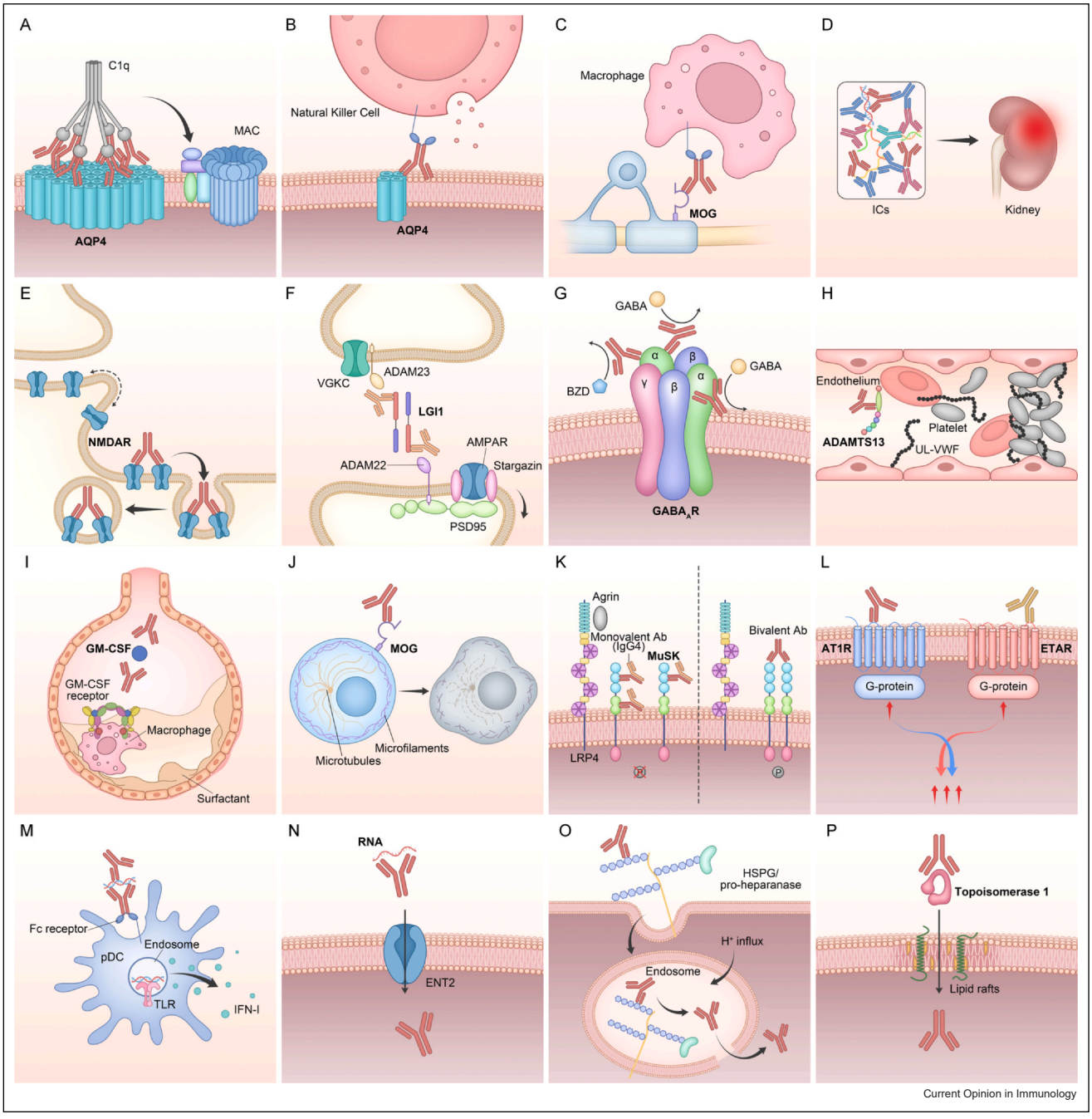
Antibody-dependent cellular phagocytosis

ADCP is a process in which antibody-opsonized target cells activate Fc receptors on phagocytes, inducing phagocytosis. In MG, patient-derived anti-AChR antibodies can induce ADCP, ADCC, and complement activation. However, antilipoprotein receptor–related protein 4 antibodies are effective in inducing ADCP and ADCC but have limited capacity to activate complement [27]. In MOGAD, sera can effectively mediate ADCP (Figure 1c), ADCC, and CDC [28].

Immune complex deposition

Neurological autoimmune diseases are characterized by autoantibodies directly targeting neural tissues. In contrast, systemic autoimmune diseases such as systemic lupus erythematosus (SLE) involve autoantibodies targeting free molecules (e.g. nuclear antigens), leading to the formation of pathogenic immune complexes (ICs) that preferentially deposit in certain tissues [1]. These deposited ICs activate the complement system, triggering pro-inflammatory mediator release and immune cell recruitment, thereby driving chronic inflammation in SLE (Figure 1d) [29]. Additionally, self-nucleic acids containing ICs are proposed to drive type I interferon (IFN-I) production in Fcγ receptor–expressing cells, particularly plasmacytoid dendritic cells (pDCs) [29]. In neuropsychiatric SLE, IC deposition is observed in the choroid plexus [30].

Figure 1


A
C1q
MAC
AQP4
B
Natural Killer Cell
AQP4
C
Macrophage
MOG
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ICs
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E
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VGKC
ADAM23
LGI1
AMPAR
ADAM22
Stargazin
PSD95
G
GABA
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Endothelium
Platelet
ADAMTS13
UL-VWF
I
GM-CSF
GM-CSF receptor
Macrophage
Surfactant
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MOG
Microfilaments
Microtubules
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Agrin
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MuSK
Bivalent Ab
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AT1R
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IFN-I
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ENT2
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HSPG/ pro-heparanase
H$^+$ influx
Endosome
P
Topoisomerase 1
Lipid rafts
Current Opinion in Immunology

Potential pathogenic mechanisms of autoantibodies in neurological diseases. **(a)** Complement system activation. Anti-AQP4 IgG1 antibodies bind to AQP4, recruit C1q, and activate the classical complement cascade. This leads to the assembly of the membrane attack complex, forming pores on the target cell membranes, resulting in cell lysis and death. **(b)** Antibody-dependent cellular cytotoxicity. Anti-AQP4 antibodies bind to AQP4 and activate NK cells via Fc receptors, triggering cytotoxic granule release (e.g. perforin, granzymes), leading to the death of the target cells. **(c)** Antibody-dependent cellular phagocytosis. Anti-MOG antibodies bind to MOG, facilitating Fc receptor–mediated phagocyte activation and subsequent engulfment of antibody-opsonized cells. **(d)** Immune complex deposition. In SLE, tissue-deposited ICs activate the complement system and trigger the release of pro-inflammatory mediators and recruitment of immune cells, promoting tissue damage. **(e)** Receptor cross-linking and internalization. Anti-NMDAR IgG1 antibodies cause cross-linking and internalization of NMDARs, reducing synaptic NMDAR levels. **(f)** Disruption of protein–protein interactions. Anti-LGI1 antibodies block the interaction of LGI1 with ADAM22/23, causing reduced synaptic clustering of AMPAR. **(g)** Antagonistic effects on receptors. Anti-$GABA_AR$ antibodies targeting β-α subunit interfaces act as competitive antagonists, while those targeting α-γ subunit interfaces near the benzodiazepine site act as allosteric antagonists, affecting modulator activity. **(h)** Inhibition of enzyme activity. In thrombotic thrombocytopenic purpura, anti-ADAMTS13 antibodies inhibit the protease activity and/or promote its clearance, causing accumulation of uncleaved ultralarge von Willebrand factor multimers, and subsequent platelet aggregation and microthrombi formation. **(i)** Blockade of circulating ligands. In autoimmune PAP, anti-GM-CSF antibodies irreversibly sequester GM-CSF within ICs or drive Fc-dependent degradation, impairing alveolar macrophage maturation and surfactant clearance, leading to alveolar surfactant accumulation. **(j)** Disruption of cytoskeleton. Anti-MOG antibodies disorganize cytoskeletal networks (e.g. microtubules, microfilaments). **(k)** Valency-dependent functional modulation. In MG, monovalent MuSK-Fab fragments inhibit agrin-induced MuSK phosphorylation and AChR clustering, whereas bivalent anti-MuSK antibodies activate MuSK phosphorylation and partially induce AChR clustering independently of agrin. **(l)** Synergistic effect of autoantibodies. In systemic sclerosis, agonistic autoantibodies targeting AT1R and ETAR synergistically enhance the vasoconstrictive and vascular remodeling effects of angiotensin II and endothelin-1. **(m)** Interferon system activation. In SLE, pDCs engulf nucleic acid–containing ICs, activating nucleic acid–sensing pattern recognition receptors (notably Toll-like receptor 7/9) and triggering IFN-I production. **(n)** Nucleoside transporter-mediated cellular penetrating. Nucleic acid–targeting autoantibodies (4H2) utilize ENT2 to translocate into the cytoplasm of living cells. **(o)** Endosomal escape mechanism. Autoantibody binds cell surface heparan sulfate proteoglycan (HSPG) and pro-heparanase complex, internalized into early endosomes. Acidic pH (via H+ influx) activates heparanase, releasing the antibody from HSPG, while simultaneously inducing antibody conformational changes that enhance membrane affinity. Antibody–membrane interactions destabilize the lipid bilayer, forming toroidal pores to enable cytosolic antibody release. **(p)** Lipid raft-mediated cellular penetrating. In systemic sclerosis, anti-topoisomerase 1 antibodies penetrate into cells through lipid rafts. Ab: antibody; ADAM: a disintegrin and metalloproteinase; ADAMTS13: ADAM with a thrombospondin type 1 motif, member 13; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AT1R: angiotensin II type 1 receptor; BZD: benzodiazepine; ENT2: equilibrative nucleoside transporter-2; ETAR: endothelin-1 type A receptor; $GABA_AR$: γ-aminobutyric acid type A receptor; GM-CSF: granulocyte-macrophage colony-stimulating factor; LGI1: leucine-rich glioma-inactivated 1; LRP4: low-density lipoprotein receptor–related protein 4; MAC: membrane attack complex; MuSK: muscle-specific kinase; NMDAR: N-methyl-D-aspartate receptor; P: phosphorylation; PSD95: postsynaptic density protein 95; TLR: Toll-like receptor; VGKC: voltage-gated potassium channel.

Cross-linking and internalization of receptors

Multivalent ligand-mediated cross-linking of surface receptors serves as a signal for receptor internalization, followed by degradation [31]. Anti-AChR antibodies cross-link AChRs to accelerate their degradation [3]. Similarly, anti-NMDAR antibodies mediate cross-linking and internalization of surface NMDARs (Figure 1e) [9]. Recent studies indicate that anti-NMDAR mAbs preferentially impair extrasynaptic NMDARs before affecting synaptic pools [32]. Structural analyses demonstrate that these mAbs bind at different stoichiometric ratios to distinct epitopes in the N-terminal domain of the GluN1 subunit, which are structurally suited for antibody-mediated NMDAR clustering and internalization [13,14]. Cross-linking and internalization are also involved in IgG1 subclass autoantibodies directed against α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor or glycine receptor [21].

Notably, mAbs targeting the leucine-rich repeat domain of LGI1 induce internalization of the LGI1-ADAM22/23 complex in both HEK293T cells and live hippocampal neurons. Importantly, this is independent of IgG bivalency, as Fab fragments alone retain the activity [33]. The same mechanism is also present in other IgG4 subclass autoantibodies, including those targeting CASPR2 [34] and IgLON5 [35].

Disruption of protein–protein interactions

Autoantibodies targeting LGI1 and CASPR2 (predominantly IgG4) exemplify the mechanism of protein–protein interaction disruption. In anti-LGI1 encephalitis, patient-derived IgG prevents the binding of LGI1 to ADAM22/23 (Figure 1f) [36], and mAbs directed against the epitempin repeat (EPTP) domain of LGI1 also block the interaction of LGI1 with ADAM22/23 [33]. Similarly, anti-CASPR2 antibodies inhibit the interaction between CASPR2 and contactin 2 [37], with mAbs targeting the discoidin domain of CASPR2 mediating this disruption [34].

This mechanism is also well-illustrated in pemphigus, a blistering skin disorder. Anti-desmoglein autoantibodies, also predominantly IgG4, cause acantholysis through steric hindrance of desmoglein-mediated adhesion, thereby inhibiting desmosome assembly [38].

Antagonistic and agonistic effects on receptors

Antibodies that bind to and activate specific receptors, thereby producing a biological response, are agonists, while those that inhibit this activity are antagonists. A well-characterized example involves autoantibodies targeting the thyrotropin receptor (TSHR), a G protein–coupled receptor (GPCR), in Graves' disease. Thyroid-stimulating antibodies cause Graves' hyperthyroidism, whereas

thyroid-blocking antibodies occasionally result in hypothyroidism [39]. Structural analyses reveal distinct conformational changes underlying the functional effects [40].

Neurological autoimmune diseases also demonstrate analogous mechanisms. In MG, rare anti-AChR autoantibodies targeting the ACh-binding site directly block neuromuscular transmission [41]. In anti-$GABA_AR$ encephalitis, autoantibodies function as competitive or allosteric antagonists of $GABA_ARs$ (Figure 1g) [12]. Similarly, patient-derived antibodies against glycine receptors exert direct antagonistic effects [42].

Inhibition of enzyme activity

The binding of autoantibodies to enzymes can induce conformational changes that either inhibit or enhance catalytic activity. Additionally, antibody binding may cause steric hindrance, thereby blocking substrate access to the active site [43]. For example, in immune-mediated thrombotic thrombocytopenic purpura, autoantibodies target ADAMTS13 — a circulating metalloprotease responsible for cleaving ultralarge von Willebrand factor (VWF) multimers. These autoantibodies inhibit the protease activity and/or promote its clearance from circulation [44]. Consequently, uncleaved ultralarge VWF multimers accumulate, triggering spontaneous platelet aggregation and formation of microthrombi (Figure 1h) [44].

In neurological autoimmune diseases, the intracellular enzyme glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamate in neurons to produce GABA. *In vitro* studies demonstrate that anti-GAD antibodies from patients with stiff-person syndrome inhibit GAD enzymatic activity and reduce GABA synthesis [45].

Blockade of circulating ligands or secretory proteins

A subset of autoantibodies targets circulating ligands or secretory proteins, such as cytokines, hormones, and growth factors. For example, anticytokine autoantibodies can exert dual roles in disease pathogenesis — either pathogenic or protective — by modulating cytokine signaling pathways or altering their circulation half-life [46].

A classic example is autoimmune pulmonary alveolar proteinosis (PAP), a lung disorder characterized by alveolar surfactant accumulation, impaired gas exchange, and respiratory failure. Surfactant clearance requires low levels of granulocyte-macrophage colony-stimulating factor (GM-CSF). In autoimmune PAP, neutralizing autoantibodies against GM-CSF are universally present [46]. These autoantibodies either sequester GM-CSF within high-molecular-weight ICs or induce Fc-dependent degradation of GM-CSF-autoantibody complexes *in vivo* (Figure 1i) [47].

Intrinsic factor (IF), a glycoprotein secreted by gastric parietal cells, mediates vitamin B_{12} absorption through the formation of an IF-vitamin B_{12} complex. Anti-IF antibodies disrupt this process by either blocking the vitamin B12 binding site on IF or preventing IF binding to its receptor [48], leading to vitamin B_{12} deficiency, resulting in pernicious anemia and neurological disorders, such as subacute combined degeneration and neuropathy.

Autoantibodies against IFN-α and interleukin-12 are commonly detected in patients with thymoma and/or MG, with significantly elevated titers during thymoma recurrence [49]. However, their pathogenic roles in these clinical contexts remain unclear.

Disruption of cytoskeleton

The cytoskeleton maintains structural integrity, facilitates intracellular transport, and enables motility. Autoantibody-mediated cytoskeletal disruption has emerged as a pathogenic mechanism in autoimmune diseases. For instance, autoantibodies targeting the neuronal cell adhesion molecule IgLON5 induce cytoskeletal disorganization in hippocampal neurons [50]. Another example involves MOG, whose physiological roles include stabilizing cytoskeletal microtubules [51]. Anti-MOG antibodies are associated with demyelination and disrupt oligodendrocyte cytoskeleton (Figure 1j) [52].

Valency-dependent functional modulation by autoantibodies

The structural plasticity of IgG4 antibodies, mediated through Fab-arm exchange to form functionally monovalent molecules, underlies their capacity for valency-dependent dual functionality in neurological autoimmunity. In mice, monovalent MuSK-Fab fragments suppress agrin-induced MuSK phosphorylation and AChR clustering, resulting in rapid and severe myasthenic muscle weakness. In contrast, bivalent MuSK antibodies activate MuSK phosphorylation and partially induce AChR clustering independent of agrin, thereby failing to induce muscle weakness (Figure 1k) [53]. Notably, monospecific bivalent antineurofascin-155 IgG4 antibodies have been detected in patients with autoimmune nodopathy, indicating that not all IgG4 antibodies have undergone Fab-arm exchange *in situ*. In rats, these bivalent antibodies strongly impair paranode formation, while monovalent Fab fragments do not [54].

Synergistic effects of autoantibodies

The synergistic effect refers to amplified outcomes from coordinated interactions of two or more processes, surpassing the simple additive effects of individual components, as exemplified in tumor immunotherapy and host antimicrobial defense mechanisms [55]. Emerging evidence indicates that autoantibody synergy also holds clinical relevance, observable in two scenarios: (1) two

different antibodies against two different antigens respectively or (2) two antibodies against the same antigen but with different epitopes. In the first scenario, in systemic sclerosis, agonistic autoantibodies targeting GPCRs — specifically angiotensin II type 1 receptor and endothelin-1 type A receptor — synergistically enhance the vasoconstrictive and vascular remodeling effects of angiotensin II and endothelin-1 (Figure 1l) [56]. In the second scenario, in MG, anti-AChR antibodies targeting different subunits of AChR exhibit synergistic effects in receptor clustering and complement activation [57].

Interferon system activation

Aberrant activation of the IFN system is a hallmark of immunological disturbances in SLE [58]. This process is initiated when pDCs engulf ICs containing nucleic acids, which in turn activate nucleic acid–sensing pattern recognition receptors (PRRs) and trigger IFN-I production [59]. The persistent IFN-I production creates a self-amplifying loop: it activates both the innate and adaptive immune systems, inducing the production of additional autoantibodies and IFN-I, which collectively contribute to the development of SLE (Figure 1m) [60].

IFN-I serves as a key component of the brain's innate immune system, providing protection against viral infection while also contributing to neuroinflammatory disorders [61]. However, the role of the IFN system in the pathogenesis of antibody-mediated neurological diseases remains to be fully elucidated.

Cellular penetrating effect of autoantibodies

The current dogma indicates that autoantibodies targeting intracellular antigens cannot access intracellular antigens through intact cell membranes. However, certain antinuclear antibodies can penetrate cells [62]. Notably, the 4H2 autoantibody — a nucleic acid–-targeting SLE antibody — specifically exploits the equilibrative nucleoside transporter-2 for endosome-independent membrane translocation (Figure 1n) [63]. This autoantibody binds and transports RNA into the cytoplasm of live cells, activating cytosolic PRRs and triggering cytotoxicity [63].

Furthermore, another SLE autoantibody, 3D8, employs an endosomal escape mechanism (Figure 1o) [62,64]. It binds to heparan sulfate proteoglycan (HSPG) and pro-heparanase complex on the cell surface, followed by internalization into the early endosome. Endosomal acidification activates heparanase, which mediates the dissociation of 3D8 from HSPG. Concurrently, acidic pH induces conformational changes in 3D8, enhancing its affinity for endosomal membranes. Antibody–membrane interactions destabilize the lipid bilayer, forming toroidal pores that enable cytosolic antibody release [64].

Alternatively, a pathway for autoantibody cell membrane penetration may involve lipid rafts. Antibodies against topoisomerase 1 in systemic sclerosis patients demonstrate lipid raft–dependent cellular penetration (Figure 1p) [65].

In addition, *in vitro* experiments demonstrated that anti-pyruvate dehydrogenase complex (PDC-E2) IgA, the major antibody isotype in patients with primary biliary cirrhosis, penetrates the cell membrane via the polymeric immunoglobulin receptor (pIgR) in pIgR-expressing Madin-Darby canine kidney cells [66,67]. Once internalized, anti-PDC-E2 IgA binds to PDC-E2 during mitochondrial transport and induces caspase activation, thereby increasing the susceptibility of exposed cells to apoptosis [68].

Collectively, these findings provide novel mechanisms by which intracellular-targeting autoantibodies cross the cellular membrane and exert pathogenic effects. It seems therefore valuable to re-assess known autoantibodies targeting intracellular epitopes and to identify further ones seen in patients with SLE, dementia, or psychosis.

Novel classification of autoantibodies based on their evidence of pathogenicity

Autoantibodies are frequently detected in patients with neurological autoimmune diseases, with substantial heterogeneity in their pathogenic potential. Based on the level of experimental proof for their contributions to disease pathogenesis, we suggest the following classification groups (Figure 2a):

- Pathogenic autoantibodies,
- Accessory autoantibodies,
- Potentially pathogenic autoantibodies,
- Autoantibodies of unknown significance, and
- Nonpathogenic autoantibodies.

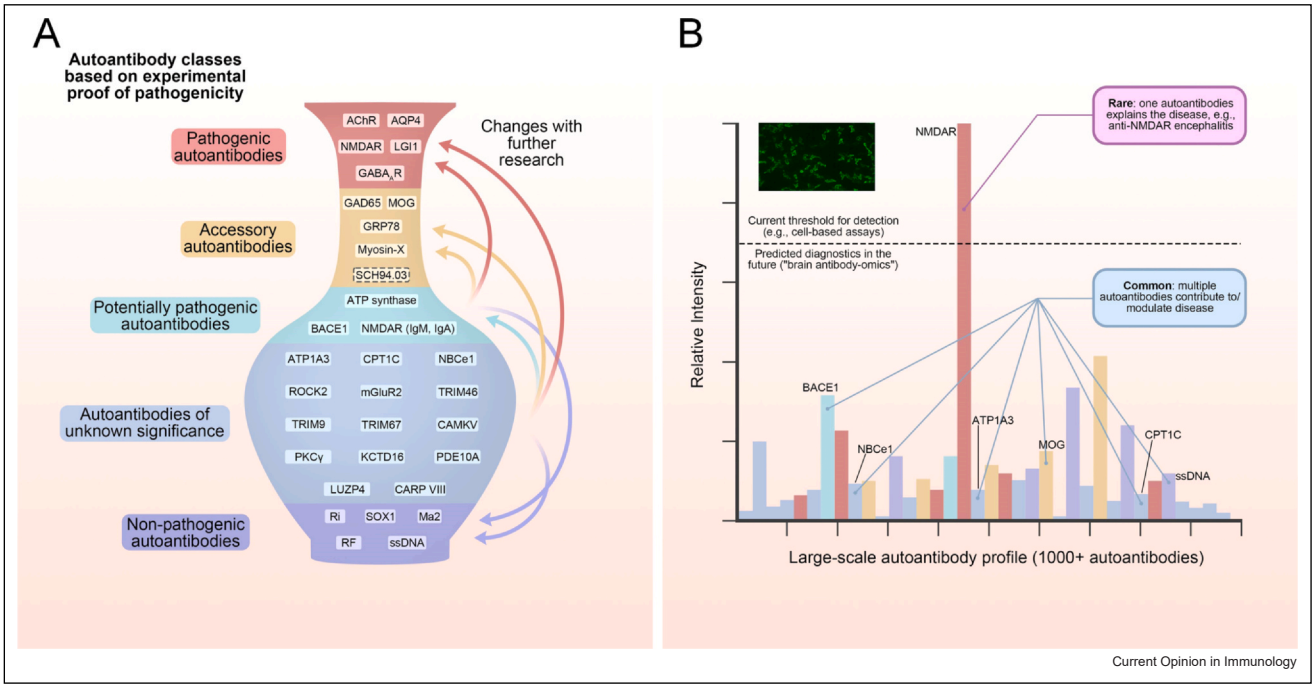
Pathogenic autoantibodies

Pathogenic autoantibodies are defined as autoantibodies for which profound scientific evidence can demonstrate direct pathogenicity for disease. They play central and causative roles in disease processes through their specific mechanisms and can largely explain the clinical phenotype. Representative examples include anti-AChR antibodies in MG, anti-AQP4 antibodies in NMOSD, and anti-NMDAR, anti-LGI1, and anti-$GABA_AR$ antibodies in autoimmune encephalitis. In these conditions, disease-specific mAbs alone are sufficient to induce pathogenicity [11,12,57].

Accessory autoantibodies

Accessory autoantibodies refer to autoantibodies that modulate disease progression. Although not serving as primary disease drivers, these antibodies regulate disease by enhancing pathological processes or modifying clinical

Figure 2



Novel classification of autoantibodies based on their evidence of pathogenicity in neurological autoimmune diseases. **(a)** Proposed classification of autoantibodies according to evidence of pathogenicity includes pathogenic autoantibodies, accessory autoantibodies (including beneficial antibodies [dashed line]), potentially pathogenic autoantibodies, autoantibodies of unknown significance, and nonpathogenic autoantibodies. The visualized relative numbers of antibodies per category remind the authors of a Chinese vase, with autoantibodies of unknown significance representing the largest antibody class (belly of the vase). With the advancement of antigen identification technologies in the future, many novel autoantibodies will be characterized experimentally, leading to transition from the autoantibodies of unknown significance or potentially pathogenic category to the group of accessory, pathogenic, or nonpathogenic autoantibodies. **(b)** Proposed 'brain antibody-omics' model for autoantibodies in neurological diseases. According to our hypothesis, collective contributions of thousands of autoantibodies regulate brain homeostasis and dysfunction in both health and disease. Today, clinical routine testing such as cell-based assays allows identification of the relatively rare high-titer pathogenic autoantibodies (e.g. anti-NMDAR antibodies) that directly drive disease pathogenesis (above dashed line). Future diagnostic approaches will rely on testing thousands of autoantibodies simultaneously, leading to a diagnostic spectrum (below dashed line). There, the individual composition of pathogenic and nonpathogenic autoantibodies will determine brain function and modulate disease progression.

manifestations. Some can even exhibit beneficial effects. For example, anti-MOG antibodies can induce complement activation, ADCC, and ADCP. However, MOG-specific T cells are essential for establishing experimental autoimmune encephalomyelitis (EAE) models. Although anti-MOG antibodies can exacerbate EAE and CNS demyelination, they are neither necessary nor sufficient to cause EAE [69]. Similarly, anti-GAD antibodies from patients with stiff-person syndrome can inhibit the enzymatic activity of GAD. Additionally, CSF from two patients with cerebellar ataxia and serum from a patient with epilepsy, both containing anti-GAD antibodies, can reduce inhibitory postsynaptic currents [45]. Nevertheless, cell-mediated immune responses play a central role in the pathogenesis of GAD-related neurological disorders. Pathology studies have revealed significant $CD8^+$ T cell infiltration in brain parenchyma in patients with anti-GAD limbic encephalitis [22], and monoclonal GAD65-specific $CD4^+$ T cells alone can induce lethal encephalomyelitis-like disease in animals [70].

Another example involves autoantibodies targeting glucose-regulated protein 78 (GRP78), which is expressed in brain microvascular endothelial cells. Anti-AQP4 antibodies (pathogenic group) are primarily produced peripherally but target astrocyte perivascular end-feet behind the BBB. Anti-GRP78 antibodies can modulate BBB permeability as accessory pathogenic antibodies. Depleting these antibodies reduces the biological effects of anti-AQP4 antibodies [71]. Similarly, autoantibodies against unconventional myosin-X in brain blood vessels occurred in patients with anti-NMDAR and anti-GABA$_A$R encephalitis. These autoantibodies cause decreased transendothelial electrical resistance, reduced occludin expression, and lower mRNA levels, implying endothelial disruption [72].

Beneficial or neuroprotective effects of autoantibodies may also occur. For example, small cell lung cancer patients with anti-Hu antibodies show improved outcomes [73]. Other autoantibodies, particularly IgM (e.g.

SCH94.03), enhanced CNS remyelination in experimental models of multiple sclerosis [74] and promoted rapid myelin clearance and effective axon regeneration in peripheral nerve injuries [75].

Potentially pathogenic autoantibodies

Potentially pathogenic autoantibodies refer to autoantibodies in which pathogenicity is possible but has not yet been fully established experimentally. Association with disease can be supported, for example, by strong clinical and epidemiological correlations, first experimental data, predicted phenotypes from *in silico* analyses, presence of a genetic counterpart with a related phenotype, or rarity of this autoantibody in control populations.

In ischemic stroke, nearly one-fourth of patients exhibit intrathecal Ig synthesis [76], and > 10% have serum anti-NMDAR antibodies (primarily IgA and IgM), associated with long-term outcomes, such as memory impairment [77]. However, the pathogenic role of anti-NMDAR antibodies in this condition requires further mechanistic evaluation. With experimental proof of pathogenicity in the future, for example, from ongoing experiments with patient-derived mAbs, these autoantibodies may switch from the group of potentially pathogenic autoantibodies to the group of accessory or pathogenic autoantibodies.

Likewise, immune mechanisms may contribute to the progression of Alzheimer's disease (AD). Some autoantibodies in AD were potentially protective (e.g. those directed against tau and amyloid-β [78]) and others potentially pathogenic (e.g. those directed against ATP synthase and β-site amyloid precursor protein-cleaving enzyme 1 [BACE1]). Autoantibodies targeting ATP synthase disrupt mitochondrial homeostasis and induce apoptosis in cell lines. Furthermore, intracerebroventricular administration of patient-derived autoantibodies against ATP synthase results in impaired cognitive performance *in vivo* and pronounced cell damage in the mouse hippocampus [79]. Elevated anti-BACE1 antibody levels in AD patients correlate with higher rates of brain amyloid positivity conversion [80]. Moreover, anti-BACE1 antibodies exacerbate brain amyloid deposition and subsequent AD-type pathologies in APP/PS1 mice [80]. Since the pathogenic role of these autoantibodies in AD is not fully elucidated, they are classified as potentially pathogenic autoantibodies.

Autoantibodies of unknown significance

Autoantibodies of unknown significance refer to autoantibodies detected in disease contexts but also healthy people, where conclusive evidence for pathogenicity is lacking, typically due to insufficient investigation. For example, numerous novel autoantibodies were identified in patients with COVID-19 [81]; however, their potential pathogenic mechanisms have not been characterized yet. In neurological disorders, advancements in antigen identification methodologies have led to the identification of many antineural autoantibodies targeting antigens such as ATP1A3, CPT1C, NBCe1, ROCK2, BRSK2, TRIM46, TRIM9/67, CAMKV, KCTD16, PDE10A, mGluR2, PKCγ, CARP VIII, and LUZP4 [5,82,83]. As long as the pathogenicity of these autoantibodies has not been investigated, they are classified as autoantibodies of unknown significance, by far the largest autoantibody category. With the emergence of high-throughput technologies (e.g. phage display, protein microarrays, immunoprecipitation/mass spectrometry), more and more antineural autoantibodies will be characterized, leading to reclassification as pathogenic or nonpathogenic in the future.

Nonpathogenic autoantibodies

Nonpathogenic autoantibodies are autoantibodies, for which comprehensive investigations have failed to demonstrate pathogenic effects. Therefore, they do not contribute to pathogenesis and may likewise occur in both patients and healthy individuals. Examples include certain classic onconeural antibodies, such as anti-Ri, anti-SOX1, and anti-Ma2 antibodies [5]. Additionally, numerous natural autoantibodies (e.g. antibodies against single-stranded DNA) are found in healthy individuals and considered nonpathogenic [1].

Neuronal autoantibody profiling — 'brain antibody-omics'

This novel classification of neuronal autoantibodies according to pathogenicity nicely substantiates the recently proposed concept of 'brain antibody-omics' [8], that is, the combination of many (potentially thousands of) autoantibodies that determines brain function and dysfunction in health and disease (Figure 2b). We predict that in the future, modern neurological autoantibody diagnostics will not rely on individual autoantibody tests, for example, by cell-based assays, but rather profile autoantibodies at large scale with highly improved sensitivity. In such an autoantibody profiling model, the number of pathogenic, accessory, and potentially pathogenic autoantibodies will certainly be weighted differently compared to nonpathogenic autoantibodies or autoantibodies of unknown significance. Only in distinct diseases, such as anti-NMDAR encephalitis, a single high-level pathogenic autoantibody will dominate the autoantibody profile leading to the clinical diagnosis (Figure 2b, top). In most cases, however, many autoantibodies may synergize, facilitate, or multiply pathogenicity; in other cases, they may compensate/neutralize pathogenic effects or even provide beneficial actions, such as remyelination or anti-inflammatory effects (Figure 2b, bottom).

Conclusion and future directions

Autoantibodies are not necessarily pathogenic, and their contributions to disease pathogenesis vary. For

pathogenic autoantibodies, various mechanisms can explain their involvement in disease. These include Fc-dependent antibody effector functions and Fab-mediated antigen regulation, such as receptor internalization, disruption of protein–protein interactions, receptor agonism or antagonism, and inhibition of enzyme activity. Advances in research techniques, including the use of disease-specific mAbs, will enhance our detailed understanding of the pathogenic mechanisms. They will also clarify the role of many of those autoantibodies, for which no experimental data are available until now, with particular relevance to emerging fields such as stroke, aging, and neurodegenerative diseases. Ultimately, large-scale autoantibody profiling will provide critical insights into the complex pathogenesis of a broad spectrum of neurological disorders.

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Data Availability

This study did not utilize any primary or secondary data, as it is based on theoretical analysis/literature review.

Declaration of Competing Interest

I declare that there are no conflicts of interest related to the submission of the manuscript "Pathogenic mechanisms of autoantibodies in neurological autoimmune diseases" by Siyuan Fan and Harald Prüss.

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