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Review

From immunobiology to intervention: Pathophysiology of autoimmune encephalitis

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ABSTRACT

Autoimmune encephalitides (AEs) are neurological disorders caused by autoantibodies against neuronal and glial surface proteins. Nearly 20 years after their discovery, AE have evolved from being frequently misdiagnosed and untreated to a growing group of increasingly well-characterized conditions where patients benefit from targeted therapeutic strategies. This narrative review provides an immunological perspective on AE, focusing on NMDAR, CASPR2 and LGI1 encephalitis as the three most common forms of AE associated with anti-neuronal surface autoantibodies. We examine the autoreactive B cell subsets, the tolerance checkpoints that may fail, and the known triggers and predispositions contributing to disease. In addition, we discuss the roles of other immune cells, including T cells and microglia, in the pathogenesis of AE. By analyzing therapeutic strategies and treatment responses we draw insights into AE pathophysiology. Written at a time of transformative therapeutic advancements through cell therapies this work underscores the synergy between detailed immunological research and the development of innovative therapies.

1. Introduction

The identification of pathogenic autoantibodies targeting neuronal and glial proteins has established autoimmune encephalitis (AE) as a distinct and treatable category of neurological disorders. The first descriptions of autoantibodies against voltage-gated potassium channels (VGKC) in limbic encephalitis in 2001 [1], Aquaporin-4 (AQP4) in 2004 [2] and N-methyl-D-aspartate receptors (NMDAR) in 2007 [3], all responding to immunotherapy, catalyzed the identification of numerous additional autoantibodies [4]. To establish a relationship between seropositivity and disease, studies (1) detected the autoantibody in patient serum and/or cerebrospinal fluid (CSF), (2) demonstrated clinical improvement upon autoantibody removal, (3) showed functional alteration of the target antigen *in vitro*, and (4) reproduced disease phenotypes in *in vivo* models. For example, in the most prevalent type, NMDAR encephalitis (NMDARE), cohort studies have evaluated the success of immunosuppressive treatments that remove patient autoantibodies [5,6], and it is now established that early immunosuppressive therapy [7] is critical for favorable outcomes. *In vitro* models have revealed that autoantibodies can crosslink and internalize receptors (NMDAR [8]) interfere with protein-protein interactions (LGI1 and CASPR2 [9,10]), block binding of receptor agonists ($GABA_AR$ [11]) or activate complement (AQP4 [12]). This pathogenicity has also been confirmed in *in vivo* models, primarily through passive transfer of patient-derived autoantibodies into the CSF using osmotic pumps or intraperitoneal injection alongside agents that disrupt the blood-brain barrier [13–16]. Increasingly, active immunization models are also being utilized [17,18].

Despite significant progress in understanding disease pathology, some patients remain refractory to treatment or experience relapses both of which can be correlated with persistent autoantibodies in the CSF [19,20]. Therefore, a more comprehensive understanding of the immunological basis of autoimmune encephalitis is needed to guide development of optimal therapeutic strategies for individual patients.

This review focuses on AE with autoantibodies against neuronal surface antigens, primarily NMDAR, LGI1, and CASPR2 autoantibodies, which represent the most common and well-characterized subtypes. Other AEs, such as those with autoantibodies targeting glial antigens (e.g., AQP4, GFAP and MOG) or less-characterized neuronal antigens (e.g., $GABA_AR$, $GABA_BR$, IgLON5), are addressed only briefly and are subject of other reviews [21–23]. Diseases with peripheral autoantibody action (e.g., myasthenia gravis) or those involving intracellular antigens (e.g.,

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paraneoplastic syndromes) are not discussed. Here, we review the current knowledge on autoreactive B cell development in AE, emphasizing breaches in central and peripheral tolerance checkpoints, key triggers, and patient predisposition. Furthermore, we examine the contribution of other immune cells and highlight unexplored pathways. Finally, we discuss established and emerging therapeutic strategies informed by immunobiology.

2. B cell development

The presence of high-titer IgG antibodies against self-antigens in the serum or CSF of patients with AE indicates failure in tolerance mechanisms. For a refined understanding of AE pathophysiology and optimizing therapeutic approaches it is crucial to determine the point in B cell development at which tolerance mechanisms fail and self-reactivity develops.

2.1. Central tolerance

B cell autoreactivity is counter selected by central and peripheral tolerance mechanisms to prevent autoimmune responses. In the bone marrow, *central tolerance* eliminates self-reactive B cells through three primary processes: clonal deletion, receptor editing, and induction of anergy. Clonal deletion removes highly autoreactive B cells via apoptosis. Receptor editing involves secondary V(D)J recombination to generate non-autoreactive B cell receptors (BCRs). Anergy induction renders autoreactive B cells biochemically and genetically less responsive to activation [24]. Despite central tolerance mechanisms, approximately 20 % of autoreactive B cells escape elimination [25].

A critical question is whether naïve B cells exhibit CNS autoreactivity or if this autoreactivity is acquired later in the development through somatic hypermutation (SHM) in germinal center (GC) reactions. One method to address this question is the sequencing of patient-derived BCR genes and the comparison of mutated autoantibodies with their unmutated germline counterparts. These germline configurations, referred to as "unmutated common ancestors" (UCA), can be tested for binding and pathogenic properties alongside their mutated versions. If UCA exhibit autoreactivity, *central tolerance* mechanisms have failed to eliminate these B cell clones. In NMDARE, there is evidence suggesting that *central tolerance* checkpoints are defective. Indeed, a study analyzing monoclonal antibodies (mAbs) from eight patients with NMDARE demonstrated that the UCA retained strong binding to the NMDAR in

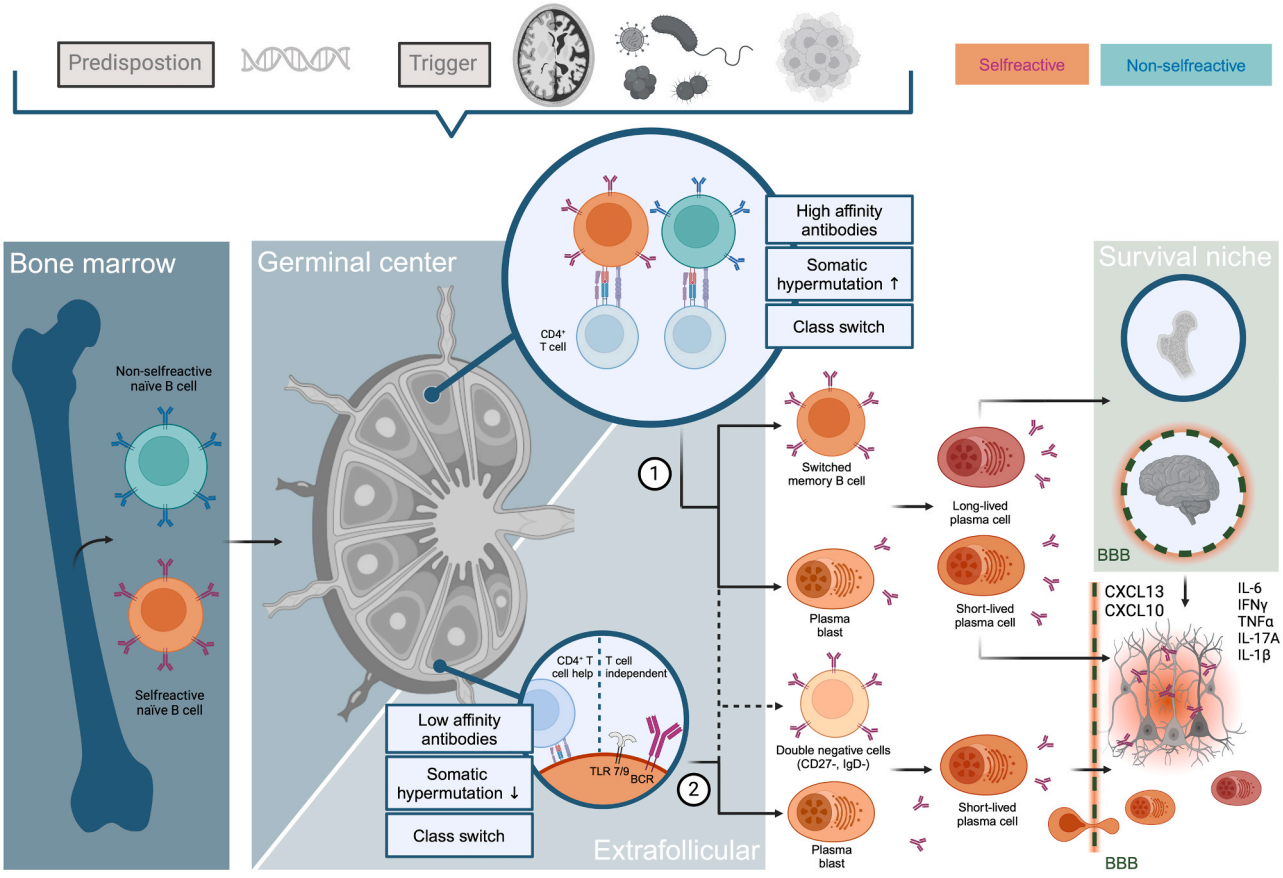

Fig. 1. Developmental pathways of autoreactive B cells in autoimmune encephalitis. Naïve B cells (on the left) can either be selfreactive (depicted in orange) by evading central tolerance mechanisms or non-selfreactive (depicted in blue). (1) In germinal center reactions selfreactive and non-selfreactive B cells interact with (selfreactive) CD4 + follicular helper T cells to undergo class switch recombination (CSR) and acquire somatic hypermutations (SHM). Here, previously non-selfreactive naïve B cells might acquire selfreactivity through SHM or selfreactive naïve B cells further affinity mature. Eventually, these cells leave the germinal center as either memory B cells or plasmablasts secreting autoantibodies. (2) In extrafollicular reactions autoreactive naïve B cells might gain limited SHM and might class switch with T cell help or T cell independent via strong crosslinked B cell receptor signaling [181] enhanced by toll like receptor signaling [182]. Extrafollicular reactions give rise to lower affinity antibodies and short-lived antibody responses while germinal center reactions can generate higher affinity antibodies and long-lived plasma cells that persist in "survival niches" such as the bone marrow or behind the blood brain barrier (BBB) in the CNS (on the right). Elevated cytokine levels in the CSF (on the right) could promote the entry and survival of these cells. Double negative B cells are thought to arise from early terminated germinal center reactions or extrafollicular reactions [183] and are increasingly studied in autoimmune diseases. Genetic predisposition can influence all stages of this development and triggers such as neurodegeneration, infections and tumors may act as initiators of this autoimmune process. BBB = blood brain barrier. Created in BioRender https://BioRender.com/t06k732.

hippocampal brain sections [26]. Additionally, one germline autoantibody, naturally lacking SHM, bound the NMDAR and exerted functional effects *in vitro*, albeit at lower affinity and higher concentrations than its mutated counterpart. In three patients with CASPR2 or LGI1 autoantibodies, over one-third (20/57) of the back mutated UCA bound the respective antigen in live-cell assays [27], indicating a role of preexisting autoreactive naïve B cells also in CASPR2 and LGI1 encephalitis. Another method to investigate B cell tolerance involves the ex vivo culture and stimulation of naïve B cells: Naïve B cells ($CD19^+/IgD^+/CD27^-$) from the peripheral blood of patients with acute NMDARE secreted IgG against NR1, the disease-defining antigenic subunit of the NMDAR, in three of 12 patients [28]. Together, these findings from UCA and ex vivo culture suggest that failures in early tolerance mechanisms contribute to disease pathogenesis in at least a subset of patients with NMDARE and potentially also other AE.

2.2. Germinal center reactions

Mature naïve B cells migrate to secondary lymphoid organs (Fig. 1) where several *peripheral tolerance* mechanisms exist to mitigate potential autoimmune reactions. These peripheral checkpoints include the absence of co-stimulatory, pro-inflammatory, or survival signals, as well as active suppression by regulatory T cells (Tregs) [24]. GCs within secondary lymphoid organs are the location where B cells undergo clonal expansion and SHM (Fig. 1). These B cells are thereby selected based on their affinity for antigens involving T follicular helper cells and follicular dendritic cells. Ultimately, affinity-matured and class-switched B cells leave the GC either as plasmablasts or memory B cells. To prevent autoreactivity, GCs employ at least two primary *peripheral tolerance* checkpoints [29]: Negative selection eliminates B cells that strongly recognize self-antigens. These cells undergo apoptosis via activation-induced cell death (AICD) if they receive strong BCR signals without additional survival signals. A process known as “clonal redemption” allows B cells with self-reactivity to acquire additional SHM, enabling them to "mutate away" from self-reactivity by reducing their binding to autoantigens while increasing their affinity for pathogenic antigens.

Several key observations have suggested that autoantibodies in AE originate from GC reactions. First, histopathological studies of associated tumors from patients with NMDARE frequently exhibit dense lymphocytic infiltrates, comprising T and B cells as well as mature dendritic cells surrounding neuronal tissue, resembling GCs [30,31]. $Bcl6^+$ B cells, a transcription factor critical for GC differentiation in B cells and $CD21^+$ follicular dendritic cells, the stromal cells that organize GCs, were found within these infiltrates [32]. These histologic findings suggest that NMDARE teratomas serve as ectopic sites with GC-like activity.

Second, class switch recombination (CSR) is a process traditionally associated with GCs [33]. CSR is initiated by the enzyme activation-induced cytidine deaminase (AID), which facilitates the replacement of the μ heavy chain gene in IgM-bearing B cells with an alternative isotype. In NMDARE, the predominant IgG subclasses are IgG1, IgG2, and IgG3, whereas IgG4 is absent [8,34]. In contrast, autoantibodies associated with CASPR2 and LGI1 encephalitis are typically of the IgG4 subclass [35–37] although IgG1, IgG2 and IgG3 also occur [38,39]. In $GABA_AR$ encephalitis, autoantibodies are primarily IgG1 [11,40], while in IgLON5 disease, both IgG4 and IgG1 autoantibodies are found [41,42]. IgM autoantibodies against the NMDAR, which are produced prior to class switching, have also been detected in longitudinally assessed serum samples from six of ten NMDARE patients [43]. In two of these patients, reductions in IgM levels paralleled declines in IgG levels, while low-level IgM fluctuations were observed in four patients. The authors linked this observation to B cells being repeatedly engaged in GC reactions rather than being activated by a single immunization event. Another study that investigated the BCR repertoire in paired CSF and serum samples of patients with LGI1 encephalitis found activated IgM-expressing B cells in peripheral blood that shared similar or identical BCR heavy chains with the intrathecal IgG-expressing cells [44].

Third, SHMs are considered a hallmark of GC activity and are also mediated by the AID enzyme, which is specifically expressed in GC B cells [29,45]. Evidence from mAb sequences shows that autoantibodies derived from the B cells or antibody secreting cells (ASC) in the CSF of NMDAR, LGI1 and CASPR2 encephalitis patients frequently carry SHM [8,27,38]. An intriguing exception is found in NMDARE: Kreye et al. (2016) reported that a subset of NR1-specific class-switched autoantibodies derived from CSF memory B cells ($CD20^+/IgD^-/CD27^+$) or ASC ($CD27^+/CD38^+$) exhibited minimal or no SHM and one of these unmutated autoantibodies was later found to have functional effects *in vitro* [26]. The overall SHM levels in the variable (V) regions of these NMDAR autoantibodies were significantly lower compared to non-NMDA receptor-targeting CSF antibodies from the same patients. These findings question the conventional assumption that GC reactions are the sole pathway for production of pathogenic autoantibodies, at least in NMDARE.

Lastly, evidence to support the involvement of GC reactions stems from genetic studies that indicate that some forms of AE, especially LGI1 encephalitis, are strongly associated with certain HLA class II genes [46–49] (see Section 4.3: Genetics). GC affinity maturation involves $CD4^+$ T follicular helper cells that recognize MHC II-presented peptides. Hence, the association of disease with MHC II encoding genes suggests T cell dependent B cell maturation and antibody production. Interestingly, HLA association studies in NMDARE have been inconsistent. Therefore, the pathophysiology of NMDARE may differ from that of other HLA class II associated forms of AE and may not rely on T cell dependent reactions in a similar manner.

Despite substantial evidence for the involvement of GC reactions, the mechanisms by which tolerance checkpoints are bypassed, allowing autoreactive B cells to evade clonal deletion or receptor editing, remain unclear. However, correlations with specific triggers and an increasing number of genetic predispositions have been identified (see Section 4.: Trigger).

2.3. Extrafollicular reactions

Traditionally, class switching and SHM were considered distinctive features exclusive to GCs. However, these processes can occur before GC differentiation [50] and at extrafollicular sites [51]. B cells can migrate to extrafollicular regions, where they differentiate into class-switched short-lived ASC. While the GC pathway presumably generates high-affinity antibodies through a slower, more complex process, the extrafollicular pathway provides a rapid, short lasting and less refined antibody response. This rapid response is crucial in early defense but is also implicated in the development of autoantibodies in autoimmune conditions [52–54]. The findings of class-switched IgG autoantibodies with surprisingly only low-level SHM in NMDARE [8], no clear HLA class II association, reduced NR1-specific T_H cell frequencies [55] and the evidence of autoreactive naïve precursors [8,55] may be explained by the involvement of extrafollicular responses in antibody production. These precursor cells might, by the combination of certain stimuli (infection, tumor) and genetic predisposition (see Section 4.: Trigger) become activated in extrafollicular pathways (Fig. 1). In systemic lupus erythematosus (SLE), extrafollicular pathways have been linked by multiple studies to the generation of pathogenic autoantibodies [56]; however, studies investigating this "alternative" pathway in AE are very limited with only anecdotal findings to date. For example, increased frequencies of double-negative (DN, $IgD^-/CD27^-$) B cells have been detected in peripheral blood of patients with acute NMDARE ($n = 20$) compared with those in remission ($n = 7$) or with disease controls [57]. DN B cells, which are also expanded in SLE, are thought to arise independently of GCs and potentially without T cell help owing to hyperresponsiveness to activating and pro-inflammatory stimuli, such as

dysregulated TLR7 signaling and IL-21 stimulation, and reduced levels of inhibitory regulators [58,59].

2.4. Central nervous system immunity and lymphocyte infiltration

For autoantibodies to exert their pathogenic effects on targets within the CNS, they must cross brain barriers. The CNS, long considered an 'immune-privileged' site, is now understood to actively regulate immune cell passage through barriers (blood-brain barrier (BBB), blood leptomeningeal barrier (BLMB), and blood cerebrospinal fluid barrier (BCSFB)) [60]. Autoantibodies may passively diffuse through regions of brain barrier disruption as some studies suggested that BBB breakdown in NMDARE is correlated with worse outcome [61]. However, in many cases of AE, the BBB remains intact, indicating that B cells and ASC actively infiltrate the CNS and produce autoantibodies locally (Fig. 1).

Indeed, numerous studies have provided evidence for B cell/ASC infiltration into the CNS in AE. In clinical practice, pleocytosis (increased white blood cell count in the CSF) and oligoclonal bands (OCB) are markers of immune cell infiltration and intrathecal antibody production. In addition, a positive autoantibody-specific index indicates intrathecal synthesis of antigen-specific antibodies by CNS-resident ASCs. In NMDARE many patients exhibit pleocytosis and OCB [62,63] and a recent monocenter retrospective cohort found elevated NMDAR-autoantibody indices in all patients (n = 42) [64], indicating that CNS infiltration and intrathecal autoantibody production is an inherent feature of NMDARE. In contrast, in LGI1 and CASPR2 encephalitis pleocytosis or OCB were rarely observed [62,63] but elevated CSF LGI1-specific autoantibody indices were associated with worse functional outcomes [65]. This suggests that while autoantibody production in these AE subtypes might be predominantly peripheral, in select cases secondary CNS infiltration could complicate disease. Further evidence for CNS infiltration comes from a histopathological study in two treatment-naïve patients with NMDARE, in whom infiltrates of plasmablasts/plasma cells ($CD79a^+$) and T cells ($CD3^+/CD8^-$) were found within the basal ganglia, amygdala, and hippocampus [66]. In contrast, B cells ($CD20^+$) were predominantly localized to perivascular spaces [66], indicating that only certain subsets of ASC can be reached by therapies that act mainly in the peripheral blood while subsets residing behind the BBB might be not depleted.

CNS-infiltrating B cells and plasma cells can be further investigated by flow cytometry. In these studies, CSF-derived cells and/or peripheral blood mononuclear cells (PBMC) from patients are stained for B cell or plasmablast/plasma cell markers and their respective antibodies are recombinantly expressed and tested for antigen reactivity. In NMDARE, 6 % of memory B cells ($CD20^+/IgD^-/CD27^+$) and plasma cells ($CD27^+/CD38^+$) isolated from the CSF of patients were NMDAR-reactive, providing evidence of antigen-specific cells in the CSF [8]. In contrast to the low numbers (6 %) in NMDARE, CNS infiltration and expanded clones in LGI1 or CASPR2 encephalitis were more frequently antigen specific: over 80 % of ASC ($CD138^+$) from the CSF of patients with LGI1 encephalitis were LGI1-reactive [38] and in CASPR2 encephalitis 45 % of antibodies generated from CSF ASC ($CD138^+$) were CASPR2-reactive [9]. CNS infiltrating cells have also been found in other AE subtypes. In IgLON5 disease intrathecal B cells ($CD19^+$) and plasma cells ($CD138^+$) have been identified [67]. In $GABA_AR$ encephalitis, ASC ($CD138^+$) sorted from the CSF of patients produced $GABA_AR$-specific autoantibodies [11] and in $GABA_BR$ encephalitis, B cells ($CD19^+$) and plasma cells ($CD138^+/CD19^+$) were elevated in the CSF compared to peripheral blood and localized in perivascular spaces [68]. Notably, in the two latter subtypes, in contrast to the previously mentioned AE, $CD8^+$ T cells appeared to play a prominent role, as they were observed within the brain parenchyma ($GABA_AR$ [69], $GABA_BR$ [68]).

A subsequent critical question is whether affinity maturation primarily occurs outside the CNS, followed by secondary CNS infiltration, or whether these processes take place within the CNS compartment itself. In NMDARE, NR1-reactive memory B cells and ASC circulating in peripheral blood and lymph nodes and BCR-sequencing studies suggest that initial immunization takes place in the periphery and CNS infiltration is secondary. A study that cultured PBMC of patients with NMDARE showed that nine of ten patient PBMCs could be stimulated to secrete NR1-IgG and -IgM across multiple timepoints in disease [43]. Qing et al. further refined this analysis by specifically stimulating different subsets of PBMCs [28] and found that indeed ASC, and, to a lesser extent, memory B cells and naïve B cells, in the peripheral blood produce NR1-IgG. Another compartment is the cervical lymph nodes which connects the periphery with the lymphatic system of the central nervous system [70]. Here, autoreactive cells were found: B cells cultured from lymph node biopsies of NMDARE patients produced NR1-specific IgG *in vitro* in three out of seven patients, with production correlating with higher serum autoantibody titers [32]. From sequencing of intrathecal memory B cells and ASC in NMDARE we learned that expanded clones have identical patterns of SHM, underlining that cells do not further affinity mature in the CNS [8]. High-throughput sequencing of BCRs has been performed in several studies, for example in MS patients, to identify the site of affinity maturation but many only compared CNS and peripheral blood compartments [71]. One study that also included cervical lymph nodes found that many B cells in MS mature in this compartment, providing a pathophysiological basis for MS therapies [72]. Such cross-compartmental analyses of B cell lineages are also needed in AE to understand where autoreactive B cells mature and thus where therapeutic agents must exert their effects.

Similarly, in LGI1 and CASPR2 AE only secondary brain infiltration is suspected. A recent study investigated the origin of intrathecal ASC by analyzing the BCR repertoire in the CSF of three patients (LGI1 (n = 2) or CASPR2 (n = 1)) [27]. By gene expression profiling, the authors demonstrated that this population of autoreactive ASC differentiated intrathecally from plasmablasts into plasma cells. Despite intrathecal differentiation and expansion of ASC, the analysis of SHM and autoantibody affinities showed that SHM and affinity maturation likely occurred before the migration of the cells into the CSF. The authors compared the amount of SHM and autoantibody affinities between "founders" (i.e. the least mutated clone of a clonally expanded group of ASC) and either the UCA (representing the peripherally derived germline version of the antibody) or the most distant member (i.e. the ASC within the clonal group that harbors the most SHM). They observed that the main change in SHM and autoantibody affinity was acquired between UCA and "founder" and not between "founder" and its most distant member. On the one hand, this indicates that in CASPR2- and LGI1-encephalitis affinity maturation occurs outside of the intrathecal compartment. This finding was corroborated by a recent multicenter study that found that only a low degree of intra-clonotype mutations in ASC in patients with CASPR2 and LGI1 encephalitis were acquired inside the CNS compartment [73]. On the other hand, another study that evaluated paired serum and CSF of six patients with LGI1 encephalitis found that besides clonally related peripheral and intrathecal BCR sequences, there were also intensive increases in SHMs within the CSF-derived cells, indicating that in some cases B cells might actively affinity-mature also behind the BBB [44]. However, in the latter study antigen-reactivity of the BCR sequences was not verified and should therefore be interpreted cautiously.

In summary, substantial evidence exists that B cells and plasmablasts/plasma cells cross the brain barriers. As a therapeutic implication, advanced treatment should account for the possibility that pathogenic cells reside behind the BBB, where conventional agents may have limited access. Higher doses or combination of immunosuppressive therapies may only increase systemic side effects without effectively targeting intrathecal immune activity. Deciphering the timepoint, route and mechanisms by which B cells and plasmablasts/plasma cells traverse the BBB could open a window for other approaches that inhibit CNS infiltration early.

3. The role of other immune system components

Other parts of the immune system have not been in the center of research in AE. A critical task for future research is to elucidate the mechanisms that facilitate CNS entry and persistence but also contribute to CNS inflammation in AE to find new therapeutic targets.

3.1. Cytokines

Cytokines play a central role in regulating immune cell maturation, proliferation, and the chemotaxis of immune cells to the brain. In NMDARE, CXCL13 has been consistently found to be elevated intrathecally [74–77] and was therefore suggested as a biomarker for disease activity and treatment response [77]. Produced primarily by stromal and follicular dendritic cells [78], CXCL13 recruits B lymphocytes to B-T cell interaction zones in lymphoid tissues, is a key chemoattractant for short-lived plasmablasts migrating to the CNS and is associated with tertiary lymphoid structures [79,80]. NMDARE patients with elevated CXCL13 levels exhibited higher intrathecal autoantibody production, poorer treatment responses, and increased relapse rates [77]. Elevated CXCL13 levels have also been observed in LGI1 and CASPR2 encephalitis, but unlike in NMDARE, CXCL13 levels did not correlate with treatment response in these subtypes [81,82]. Other cytokines involved in B cell survival, such as BAFF and APRIL, which are relevant in neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) [83], were rarely elevated in the acute phase of NMDARE [84] and other studies found no elevation beyond acute settings [74,76].

Moreover, cytokine profiles provide insights into T cell involvement in AE. Elevated TNF-α and interferon-γ levels in NMDARE indicate Th1 cell involvement [74,76]. Additionally, Th17 cells appear to contribute to the pathogenesis of NMDARE, consistent with the dysregulated Th17/Treg ratios observed in other autoimmune diseases [85,86]. IL-6, a cytokine with pleiotropic effects that increases BBB permeability and B cell differentiation to ASC but also drives Th17 development [87], was elevated in the CSF of NMDARE patients and correlated with poor clinical outcomes [74,75,88–90]. Cytokines produced by Th17 cells, IL-1β and IL-17A, were elevated in the CSF of NMDARE patients [90–92]. Of these two, IL-17A, a cytokine that, among other effects, increases BBB permeability to leukocytes [93], was associated with limited treatment response and higher relapse rates [90]. In LGI1 encephalitis, Th17-associated cytokines are less frequently elevated. When detected, they were associated with severe disease requiring intensive care unit admission [94], although another study reported no elevation [75].

In other AE (CASPR2, $GABA_AR$, $GABA_BR$, IgLON5) cytokines have been investigated, but small sample sizes and heterogeneous groups do not allow to draw clear conclusions [95].

3.2. T cells

In contrast to other autoimmune diseases, such as MS or paraneoplastic autoimmunity, in which T cells are strongly implicated in pathogenicity [96,97], they have classically not been considered a primary driver in AE. Histopathological studies rarely observed $CD3^+$ T cells around small vessels or within the brain parenchyma [66,96,98] which were commonly negative for CD8 or cytotoxic markers such as granzyme B [34,66]. Additionally, in a mouse model of NMDARE, cytotoxic T cells were not prominently detected in histological examination [18].

Currently, T cells are more and more recognized in supporting B cell maturation and promoting inflammation in AE. In NMDARE several findings suggest a T cell contribution: histopathological studies showed scattered $CD4^+$ T cell infiltration [34,66,98] and cytokine signatures, particularly Th1 and Th17 cytokines, were elevated throughout disease, especially in the most severely affected patients [76]. In addition, in the active immunization mouse model [18], mice with TCRα knockout (lacking mature $CD4^+$ and $CD8^+$ T cells) did not develop disease.

$CD4^+$ follicular helper T cells are particularly relevant for helping in B cell maturation and class switching during GC reactions [99]. Moreover, $CD4^+$ T cells can transiently open the BBB allowing lymphocytes to enter immunoprivileged sites [100]. Given this role, one might expect elevated antigen-reactive $CD4^+$ T cells in the peripheral blood of NMDARE patients. Surprisingly, a study of patients with NMDARE ($n = 24$) reported reduced numbers and reduced cytokine secretion of NR1-specific circulating T helper cells ($CD4^+/CD154^+$) compared to age- and sex-matched healthy controls ($n = 33$) [55]. In the same study – for the first time in humans – LGI1-specific T cells were detectable, but their frequencies were not different compared to healthy controls. The reduced circulating T helper cell numbers in NMDARE might reflect migration to lymphoid tissues or the brain, where they participate in GC responses, but these compartments were not examined in the study. Alternatively, these findings may point to T helper cell-independent mechanisms of autoantibody production in NMDARE, which would be consistent with the weak or absent association of specific HLA class II alleles in NMDARE compared to other forms of AE. Another T cell subset, naïve T regulatory cells (Tregs) were reduced in the peripheral blood of patients with NMDARE ($n = 4$) when compared to the levels in age- and sex-matched controls [101]. Interestingly, this reduction was accompanied by an increase in memory Tregs, leading the authors to hypothesize a higher turnover from naïve Tregs to memory Tregs. The memory Tregs exhibited a trend toward lower CCR6 expression, a chemokine receptor critical for both suppressive function and migration to inflamed tissues. However, as this study focused solely on peripheral blood, it remains unclear whether the observed reduction in naïve Tregs and lower CCR6 expression in memory Tregs reflects a systemic deficiency or preferential migration to lymphatic or brain tissue. The latter hypothesis is supported by elevated levels of CCL20, the ligand of CCR6, in the CSF of NMDARE patients ($n = 60$) [90] suggesting that Tregs could specifically migrate to the brain compartment in NMDARE. Treg cells are closely linked to Th17 cells, as naïve T cells can differentiate into Treg cells under the influence of TGF-β, but in the presence of additional cytokines, such as IL-6 or IL-21, they are redirected toward a Th17 phenotype [87]. Given the elevated IL-6 levels in the CSF of NMDARE patients, a conversion from Tregs to Th17 cells is possible [74,95]. Supporting this hypothesis, Th17 cells ($CD4^+/IL\text{-}17^+$) were significantly increased in the CSF of a large cohort of NMDARE patients [90]. Given that immune cell migration to the brain is a hallmark of AE, future research should not be limited to peripheral blood but include analysis of lymph nodes and CNS compartments to distinguish whether observed peripheral changes reflect true cellular deficiencies or redistribution due to tissue migration.

A multicenter single-cell transcriptome study In LGI1 and CASPR2 encephalitis patients identified $CD4^+$ (and to a lesser extent $CD8^+$) clonally expanded, activated T cells [73] with shared clones found both in the CSF and peripheral blood. They might promote intrathecal B cell expansion and class switching, but the same study replicated that B cells in LGI1 and CASPR2 encephalitis matured mainly in the periphery before CNS infiltration. Therefore the exact pathogenic roles of these dysregulated T cells in the CSF needs to be elucidated in future studies. Interestingly, the study further reported a reduction in mucosal-associated invariant T (MAIT) cells in both the peripheral blood and CSF of patients. MAIT cells, an "innate-like" subset of T cells, have been implicated in many autoimmune diseases. The authors therefore proposed that a deficit of peripheral innate regulatory mechanisms might unleash the interaction of autoreactive B cells with autoreactive T cells which then results in intrathecal infiltration and autoantibody production.

These studies illustrate that distinct T cell subsets, previously underappreciated, could play a more prominent and distinct role in the different forms of AE. A detailed investigation of each subset within specific AE forms is warranted and might uncover new therapeutic targets.

3.3. Microglia

Microglia, the resident immune cells of the CNS [102] contribute to neuroinflammation, for example through chemokine secretion [103]. Histopathological studies in NMDARE have demonstrated pronounced microglial activation, with upregulation of activation markers such as HLA-DR and CD68 [66]. In the CSF of patients with NMDARE (n = 29) markers of microglial activation were elevated compared to controls [104]. In a brain biopsy of a patient with NMDARE, perivascular microglia and macrophages expressed CXCL13, a chemokine critical for recruiting immune cells to the CNS, suggesting their active role in immune cell trafficking [77]. Furthermore, a neuron-microglia co-culture model demonstrated that patient-derived NMDAR autoantibodies engaged microglia via Fc receptors, leading to phagocytosis of autoantibody-tagged NMDA receptors [105]. Despite these intriguing findings, the detailed role of microglia in AE has not been the primary focus of research.

4. Triggers and predisposition in autoimmune encephalitis

Certain triggers and genetic predispositions are associated with AE which might explain how *peripheral tolerance* mechanisms are bypassed.

4.1. Tumor

Tumors are often associated with AE and their prevalence varies by subtype [22]. Ovarian teratomas (OTs) are found in 30–40 % of NMDARE cases [6] and were shown to harbor GC-like structures with lymphocytes producing anti-NR1 autoantibodies [32,43]. While OTs can contain ectopic nervous tissue, potentially triggering the anti-neuronal immune responses in the inflammatory tumor environment [106], 40–66 % of OTs from neurologically healthy individuals also contain nervous tissue, suggesting its mere presence is insufficient for tolerance breakdown [30]. Autoantibody development might involve tumor-intrinsic factors (e.g., abnormal neuroglial features or NMDA receptor composition have been described) [30], although a recent cohort study found no genetic or histopathological differences except for GC formation in encephalitis-associated OTs [107]. Alternatively, susceptibility to developing an autoimmune response to OT may also stem from genetic alterations, such as a polymorphism in a gene regulating type I IFNs that was linked to tumor-associated cases but not non-tumor cases [108]. Also concomitant infections of the tumor tissues acting as adjuvants can be discussed ("ASIA" [109]).

Another mechanism of tumor-associated tolerance breakdown is exemplified by thymomas. These tumors are strongly associated with autoimmune diseases, particularly myasthenia gravis [110] and patients frequently exhibit a broad immune defect with multiple autoantibodies [110,111]. The thymus is central to the negative selection of autoreactive T cells and this mechanism can be disturbed by thymomas, with altered presentation of self-antigens, allowing autoreactive $CD4^+$ T cells to evade tolerance checkpoints and assist GC B cells but also by reducing Treg cells [112]. Some AE, including $GABA_AR$ [113]; AMPAR [114], LGI1 [115] and CASPR2 encephalitis [36], can have underlying thymomas, though no such link has been described for NMDARE.

It is important to recognize tumor-associated cases of AE, as patients usually respond to surgical tumor removal [116] in addition to immunotherapy. In their analyses, researchers must clearly distinguish between AE with and without underlying tumors as the underlying pathophysiology and thus druggable pathways likely differ.

4.2. Virus

It is well recognized that infections can trigger autoimmune responses but the causal mechanisms are not clearly understood. With the increased testing for specific autoantibodies, an increasing number of antigen-specific autoantibodies after viral infections have been described and represent one line of explanation (other than persistent infection or persistent organ damage) for post-viral sequelae [117]. Among these, NMDAR autoantibodies stand out due to their frequent and consistent associations with multiple viruses. Approximately 30 % of patients develop NMDARE within three months after HSV-1 encephalitis (HSVE), with CSF NMDAR autoantibodies (absent prior to infection), negative HSV PCR (arguing against persistent infection), and responsiveness to immunosuppressive therapy (speaking against virus-induced organ damage [118,119]). In addition, NMDAR autoantibodies have been reported after infections with other members of the Herpesviridae family [120], HIV [121], influenza A [122], Japanese encephalitis virus (JE) [123], and tick-borne encephalitis virus [124]. Less commonly, other associations have been reported, such as $GABA_AR$ autoantibodies after HSV-1 and HHV-6 infections [125] or dopamine-2 receptor (D2R) autoantibodies after HSV-1 infections [126].

Three primary hypotheses on how viruses trigger autoimmune response in AE have been proposed.

Molecular mimicry: This mechanism occurs when viral proteins share structural similarities with self-antigens, potentially inducing cross-reactive autoantibodies [127]. An example for this is the presence of EBV autoantibodies in MS that cross-react with a glial cell adhesion molecule [128]. While similar molecular mimicry has been hypothesized for HSV-1 and the NMDA receptor, direct evidence supporting this hypothesis is lacking.

Antigen exposure through tissue damage: HSV-1 infection may cause direct neuronal damage and disrupt the BBB, exposing previously hidden NMDAR antigens [129]. This damage, coupled with transient abnormal antigen expression and inflammatory signals, could mount an autoimmune response [130].

Polyclonal B cell activation: During certain viral infections, B cells can become non-specifically activated. While this is a complex and possibly agent-specific process, multiple mechanisms of T cell-independent polyclonal B cell activation via virus-induced Bruton kinase, secretion of IL-17, upregulation of AID enzymes or TLR signaling have been described [131]. Such polyspecific B cell activation has been reported in MS following Epstein-Barr virus infection [132]. This is reflected by the "MRZ reaction", i.e. the simultaneous production of antibodies against measles, rubella, and varicella zoster virus, a parameter tested in MS patients. The presence of the MRZ reaction was recently found in 19 % of patients in a small NMDARE patient cohort [133], hinting at possibly similar mechanisms in AE that warrant further exploration.

The site of autoreactive B cell priming in NMDARE secondary to HSVE remains to be elucidated. One hypothesis points to peripheral immunization in cervical lymph nodes, suggesting exposure of NMDAR fragments to the peripheral immune system during acute CNS injury. However, a case study comparing BCR repertoires in CSF and blood of an HSVE patient revealed early clonal B cell expansion within the CSF, indicating that autoreactive ASCs may also arise intrathecally from a local adaptive immune response of infiltrated B cells [134].

4.3. Genetics: HLA-class II association

Autoantibody-driven autoimmune diseases are often strongly associated with HLA class II genes which encode MHC class II molecules. These are expressed on antigen-presenting cells (APCs) and present peptides to $CD4^+$ T cells. Specific alterations in this interaction might include the escape of autoreactive T cells from thymic selection or preferential display of antigens in the binding groove leading to cross-reactivity of T cell receptors with microbial and self-antigens or preferential binding of modified "neoantigens" [135]. Some HLA associations confer protective effects, which may be explained by correct thymic selection of T cells [136]. In addition, HLA polymorphisms have been linked to preferential IL-10 and IgG4 production [137]. While the exact mechanisms are complex, HLA class II associations in autoantibody-mediated autoimmune disease hint at a contribution of

T-B cell interactions in autoantibody production (Fig. 1).

A prominent example of an HLA class II association is LGI1 encephalitis. Studies have consistently reported a strong association with HLA-DRB1 * 07:01, with up to 90 % of LGI1 encephalitis patients testing positive across ethnicities [46–49]. In CASPR2 encephalitis, HLA-DRB1 * 11:01 has been implied [46,138]. In IgLON5 disease 85 % of patients carry HLA-DQ5 haplotypes and DRB1 * 10:01 has been reported [41,138,139]. Notably, HLA-DRB1 * 10:01-carriers were more likely to exhibit intrathecal IgG4 production than non-carriers [41], which highlights the need for experimental studies to establish causal explanations.

HLA class II associations in NMDARE are less consistent. Studies that identified HLA associations in LGI1 encephalitis within Korean and Caucasian populations found no such associations in NMDARE patients (n = 17 and n = 96 patients, respectively; [48,49]). Some studies have identified weak associations such as HLA-DRB1 * 16:02 and HLA-DQB1 * 05:02 in a Chinese Han population [140,141], which other studies could not replicate [142], or HLA-DRB1 * 15:02 in Thai children [143]. As genetic studies are influenced by population-specific genetic predispositions the overall low frequency of the specific alleles in Korean and Caucasian populations may explain these contrasting findings. It could also hint at heterogenous pathophysiological groups within the cohort of patients with NMDARE of which some are potentially less dependent on T cell help.

4.4. Genetics: susceptibility genes outside of HLA genes

The genetic risk factors of AE extend beyond HLA associations. With thousands of loci involved in the immune system [144], mutations or variations in one or more of these loci can predispose individuals to autoimmune diseases. Today, next-generation sequencing can identify such genetic alterations on an unprecedented scale [145]. These genetic associations are different to classical genetic diseases where a single mutated gene leads to a phenotype. Rather, they lower the threshold for the breakdown of immune tolerance, so that triggering events, such as viral infections or tumors, can induce autoimmunity in genetically predisposed individuals, while those without such predispositions or those who simply do not encounter triggers are spared [146].

In NMDARE risk loci were found in B cell development and pro-inflammatory cytokine production pathways of microglia and astrocytes associated with BBB integrity [147]. Other studies in NMDARE detected genetic variations in type I interferon signaling pathways, innate immunity [140] and genes specifically associated with cancer, herpesviridae infections and B cell differentiation [108]. Non-HLA risk loci in LGI1 encephalitis were located in B cell activation and Th17 cell differentiation pathways [148].

As genetic research progresses, additional associations emerge. Future research should prioritize functional studies of these genes to describe causal roles in the immunobiology of AE, which might identify new therapeutic targets.

5. Therapeutic implications and future directions

While immunosuppressive therapy has revolutionized the treatment of AE [5], sequential aggressive immunosuppression in treatment-refractory cases still poses a risk of serious infections. And even among responders, only 30 % of NMDARE patients achieve pre-disease functional levels in sensitive neuropsychological assessments [149]. Therefore, optimized treatment approaches are needed. Future therapeutic developments should address two key questions: What can the successes and failures of current treatments tell us about the underlying pathophysiology, and how can immunological insights guide the design of novel therapies?

5.1. Standard of care

Combinations of high-dose corticosteroids with intravenous immunoglobulin (IVIG) and/or plasmapheresis to “wash out” the autoantibodies constitute the first-line therapy [150], but are either very broadly targeted or only a downstream approach (Fig. 2). Second- and third-line strategies for AE target the drivers of the disease more specifically by depleting B cells and plasma cells (Fig. 2 and Table 1).

5.2. Targeting B cells

Histopathological findings of B cells and plasmablasts [34,98], alongside early immunophenotyping studies that identified intrathecal B cells ($CD19^+$) [151] and the proof of autoantibody pathogenicity [8], had led to the adoption of rituximab, a CD20 directed B cell depleting mAb, as second-line therapy [150]. In our center, it is already integrated as a first-line agent. Rituximab depletes plasma cell precursors in the periphery (Fig. 2), thereby indirectly reducing autoantibody production and preventing further B cell migration into the lymph nodes and CNS. A meta-analysis of NMDARE treatments [152] and large retrospective cohort studies of the most common subentities of AE [5,6] suggest that rituximab treatment is associated with better outcomes and prolonged time to relapse [153].

Nonetheless, 6–20 % of patients with neuronal surface autoantibodies do not respond favorably to rituximab (as defined with the modified Rankin Scale (mRS) ≤ 2 at follow-up) and up to 20 % of patients relapse [5]. This raises the possibility that treatment failure may be due to other pathogenic cell populations that are not targeted by $CD20^+$ depletion, such as plasmablasts and plasma cells. Rituximab fails to target plasma cells directly, as CD20 expression diminishes during the differentiation from plasmablasts to plasma cells (Fig. 2). But also early $CD20^-$ autoreactive B cell precursors might not be targeted by rituximab and repopulate autoreactive B cells [154].

One strategy to address this problem is to target CD19, which is expressed more widely in the B cell lineage and on a subset of plasma cells (Fig. 2) [155]. The mAb inebilizumab targets $CD19^+$ cells and reduces the relapse risk and disability progression in patients with NMOSD [156]. A phase IIb, double-blind, randomized controlled trial is underway to investigate its safety and efficacy in patients with NMDARE (ExTIN-GUISH (NCT04372615)).

5.3. Targeting plasma cells

The CD38 mAb daratumumab might have advantages over CD20 or CD19 mAbs as it targets short- and long-lived plasma cells [157]. Additionally, daratumumab exerts broader immunomodulatory effects as CD38 is expressed on various hematopoietic cells, including subsets of B cells, plasmacytoid dendritic cells, and T cells (Fig. 2) [158]. A case series of five patients with refractory AE reported a decrease in CSF and serum autoantibody levels and improved disease severity in one patient with NMDARE and two patients with CASPR2 encephalitis [159].

Another plasma cell-directed agent is bortezomib, which like daratumumab was originally developed for the treatment of multiple myeloma. It targets short- and long-lived plasma cells by inhibiting the 26S proteasome, leading to the accumulation of misfolded proteins [160]. The high antibody production in plasma cells, secreting thousands of antibodies per second [161], renders them especially susceptible to bortezomib. A systematic review of case reports found that bortezomib treatment in 29 patients with NMDARE refractory to secondary immunotherapy was associated with favorable clinical outcomes in 55.2 % of cases [162]. Currently, a phase IIb, double-blind, randomized controlled trial in Germany is enrolling AE patients refractory to rituximab (including but not limited to NMDARE) to evaluate the potential benefits of adjunctive bortezomib therapy (Generate-boost (NCT03993262), [163]).

Plasma cell depleting rescue therapies (daratumumab: n = 5,

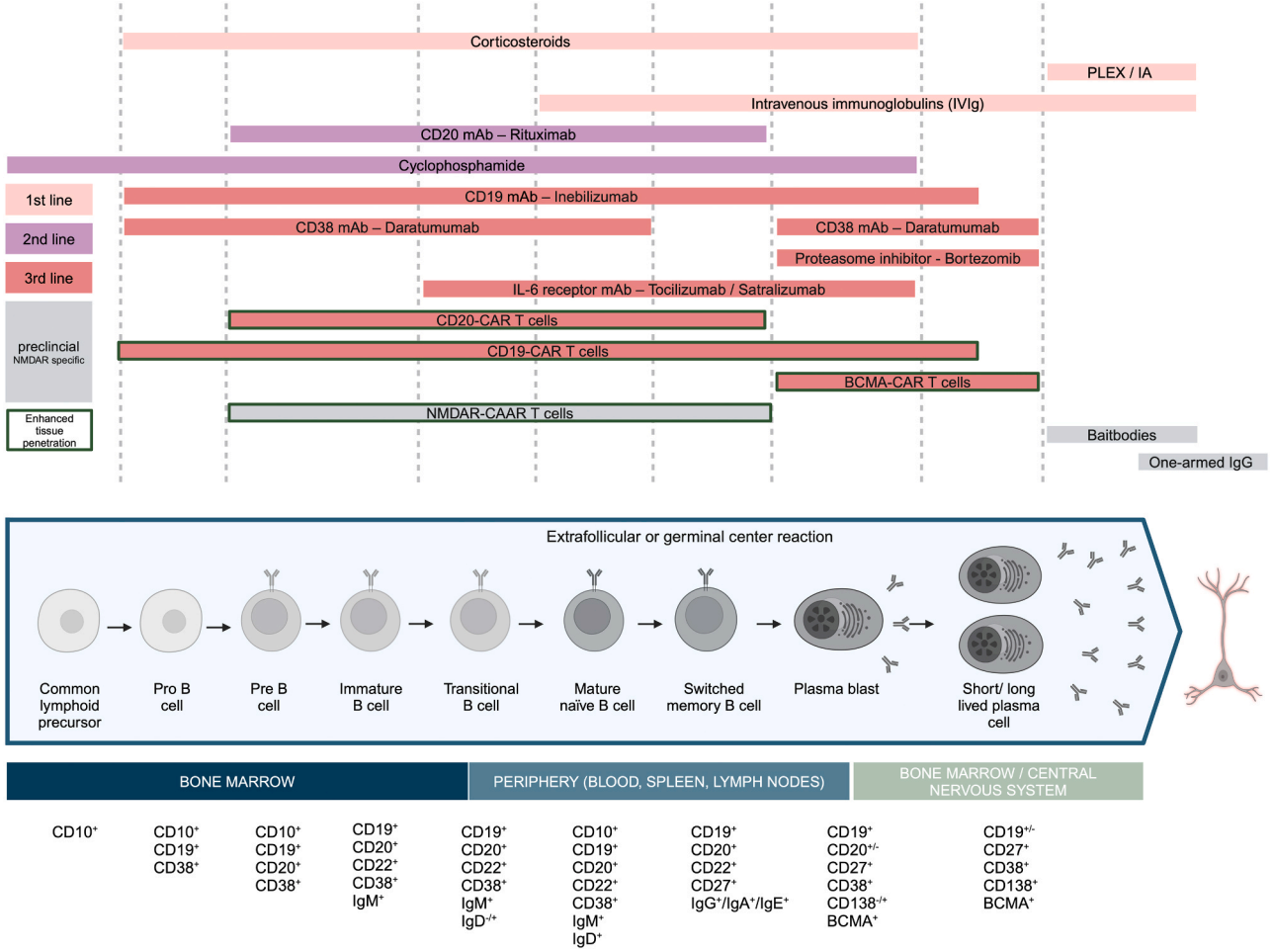

Fig. 2. Therapeutic targets in autoimmune encephalitis. In the development from lymphoid precursors in the bone marrow to plasma cells that secrete autoantibodies, B cells can be differentiated by certain surface markers, as indicated. Therapeutic interventions are depicted based on their targets within this developmental pathway as first- (light red), second- (purple) and third-line (dark red). Emerging preclinical NMDAR-specific immunotherapies (grey) comprise CAAR T cells that identify and deplete NMDAR specific autoreactive B cells through their BCR [180], "baitbodies" that neutralize autoantibodies [184] and one-armed antibodies that compete with autoantibody binding (ART5803). Therapies with enhanced tissue penetration are highlighted (green border). BCMA = B cell maturation antigen; PLEX = plasmapheresis; IA = immunoadsorption; mAb = monoclonal antibody; CAR = chimeric antigen receptor; CAAR = chimeric autoantibody receptor. Created in BioRender https://BioRender.com/t06k732.

bortezomib; n = 9) led to comparable clinical outcomes and decline in CSF and serum autoantibody titers compared to patients who initially responded to rituximab in a retrospective analysis of 36 intensive care unit (ICU) patients with severe AE mediated by neuronal surface autoantibodies [164]. This is remarkable as patients requiring escalation therapy presented with higher disease burden, spent a longer time in the ICU and exhibited a median interval of 119 days between treatment initiation and response [164].

Although targeting plasma cells after initial B cell depletion using agents such as daratumumab or bortezomib shows promise for refractory AE cases, combined immunosuppressive therapy increases the risk of infections and persistent autoantibodies in treatment-refractory cases, despite combined B cell *and* plasma cell depletion, require further investigation.

5.4. Targeting compartmentalized B cells and plasma cells

Refractory disease courses after B cell and plasma cell depletion may be explained by the *compartmentalization* of pathogenic cells where they are less accessible to mAb- and large molecule-based therapies. Such compartments may include the bone marrow, lymph nodes, tumor tissue and, crucial in the context of AE, the CNS protected by the BBB. Whether lymph nodes present a compartment where rituximab insufficiently disrupts the GC reaction remains debated. In NMOSD patients, deep cervical lymph node aspirates showed a 430-fold reduction in $CD19^+$ B cells after rituximab, indicating an effect on this compartment [165]. However, no structural analysis of the lymph node architecture was performed in this study. The recent rise of CAR T cell therapies in autoimmunity suggests that a deeper depletion may be needed. Indeed, in lymph node biopsies, only CAR T cell treatment — not rituximab — disrupted follicular structures and completely eliminated $CD19^+$ and $CD20^+$ B cells [166]. Similar analyses are needed in NMDARE, LGI1, and CASPR2 encephalitis to determine whether residual or compartmentalized B cells underlie treatment resistance and poor outcomes. In NMDARE, even after rituximab treatment, $CD20^+$ cells (albeit in reduced numbers) were found in patients' teratomas [107], indicating that "minimal residual" autoreactive B cells could persist in the tissue. In addition, considering CNS infiltration and intrathecal autoantibody production in AE these CNS-compartmentalized cells might not be sufficiently depleted. Along those lines, sustained autoantibody presence in the CNS after one year correlated with earlier relapses and poor outcomes, as shown in a cohort of 69 NMDARE patients, two-thirds of whom received rituximab [20].

CAR T cell therapy is a transformative approach in the treatment of B cell-mediated autoimmune diseases due to its success in treatment refractory cases [167]. A patient refractory to multiple

Table 1
Overview of clinical trials and case reports evaluating second- and third-line therapies in autoimmune encephalitis.

Target		Substance	AE Subtype	Evidence	Reference
B cells	CD20	Rituximab	NMDAR	Metanalysis, cohort study	[6,152,153,185]
			NMDAR, LGI1, CASPR2, GAD65	Cohort study	[5]
			LGI1	Case series	[186]
B cells and plasma cells	CD19	Inebilizumab	AQP4 (NMOSD)	Phase II/III RCT	[156]
			NMDAR	Phase-IIB RCT *ongoing*	ExTINGUISH trial (NCT04372615)
		CD19 CAR T cells *KYV−101*	GAD65 (Stiff-person-syndrome)	Case report	[169]
Plasma cells	BCMA	BCMA CAR T cells	Unspecified	Case series *ongoing*	CARTinNS trial (NCT04561557)
		CT103A	AQP4 (NMOSD)	Phase I open-label *preliminary results*	[171]
	CD38	Daratumumab	NMDAR, CASPR2, Unknown epitopes	Case series	[159]
	26S protea-some	Bortezomib	NMDAR	Case series	[187]
			Severe AE (not specified)	Phase II RCT *ongoing*	Generate-Boost trial (NCT03993262) [163]
IL−6	IL−6 receptor	Tocilizumab	NMDAR	Cohort study	[116]
			NMDAR, LGI1, Amphiphysin, seronegative AE (66 %)	Cohort study	[173]
			CASPR2	Case report	[174,175]
		Satralizumab	NMDAR	Phase III RCT	CIELO trial (NCT05503264)
			LGI1	*ongoing*	

immunosuppressive medications with CNS manifestations of SLE showed clinical improvement and decline of (slightly elevated) CSF B cell numbers [168] only after the treatment with CD19-CAR T cells. Similarly, remarkable clinical improvement was observed in a patient with treatment-refractory (rituximab and bortezomib) stiff-person syndrome treated with CD19-CAR T cells [169]. Preliminary results from a phase I open-label trial targeting the B cell maturation antigen (BCMA) in 12 treatment-refractory (including rituximab in some cases) patients with NMOSD showed drug-free remission in $>$ 90 % of patients with decreased serum autoantibody levels (CARTinNS (NCT04561557), [170,171]). A patient with unspecified AE has recently been treated with CD19-CAR T cells as part of a series of 20 patients with various autoimmune diseases, although a detailed report of the clinical outcome is pending [172]. It is encouranigng that in the limited amount of studies no serious adverse events were reported. Thus the application of CAR T cells might be a successful strategy for treatment-refractory AE. To learn whether deep depletion fills a gap in AE treatment, its application should be combined with detailed characterization of B cell counts and GC structures across peripheral blood, lymph nodes and CNS compartments.

5.5. Targeting other parts of the immune system: IL-6 receptor blockade

Another approach to treatment failure after B cell and/or plasma cell depletion is targeting other parts of the immune system. The humanized mAb tocilizumab binding to IL-6 receptors exemplifies this potential. IL-6 is notably elevated in patients with NMDARE during the acute phase and is correlated with disease severity (see Section 3.1: Cytokines). Cohort studies in NMDARE patients [116,173] and case reports in CASPR2 [174,175] and LGI1 encephalitis [176] have consolidated tocilizumab as a therapeutic option for refractory AE. A phase III randomized, double-blind, placebo-controlled, multicenter basket study currently investigates the efficacy and safety of IL-6 receptor targeting mAb satralizumab in NMDAR and LGI1 encephalitides following first-line therapy (CIELO (NCT05503264) [177].

There is not yet enough evidence to universally recommend tocilizumab for AE, but it exemplifies how the humoral immune system can be modulated outside of B cell/ plasma cell targeted therapies. Considering the cytokine signatures and the involvement of T cells and potentially microglia in AE, this highlights opportunities for further immunomodulatory strategies. For example CXCL13 targeting mAbs and interventions aimed at restoring the Th17/Treg balance could be promising approaches [178]. Additionally, the convergence of cell therapies as vehicles for CNS delivery of cytokines presents an exciting avenue for future exploration [179].

5.6. Enhancing targeted therapies

Generalized immunosuppression via pan-B cell or pan-plasma cell depletion carries the risk of severe to fatal infections, particularly in patients undergoing sequential treatments or prolonged stays in the ICU [159]. For such patients, an even more targeted approach avoiding general immunosuppression should be considered. One innovative, but still experimental strategy is the use of chimeric autoantibody receptor (CAAR) T cell therapy in NMDARE [180], which has demonstrated efficacy in a mouse model and is progressing toward a phase I clinical trial. This approach selectively targets autoreactive B cells through their BCR, while sparing all other B cells. As a cell therapy, in contrast to therapeutic mAbs, it would be able to traverse the BBB and deplete intrathecal autoreactive B cells. A first-in-human (FIH) study with CAAR T cells for the autoantibody-mediated skin disease pemphigus vulgaris (RESET-PV (NCT04422912)) began recruitment in October 2022 and final data on its safety and efficacy remain forthcoming. The development of such targeted therapies is a huge leap toward increasingly precise and effective therapeutic strategies in the future.

6. Conclusion

This review summarizes the current knowledge on the pathophysiology of AE with neuronal surface autoantibodies and analyzes how immunological findings can stimulate the selection and development of immunotherapies and – vice versa – how the response to immunotherapies teaches the field on the underlying autoimmune mechanism. Collectively, these data demonstrate that AE patients harbor autoreactive B cells and ASC across the B cell lineage (including naïve B cells) with converging evidence that often these cells initially mature outside of the CNS in GC reactions. CNS infiltration of ASC and intrathecal antibody production is a frequent feature, especially observed in NMDARE. While B cell and plasma cell directed therapies are effective in second- and third-line treatments, sequential depletion of B cells and ASC has its limits by risking severe infections and still yields suboptimal outcomes in many cases. In our view, future therapeutic approaches should prioritize strategies that inhibit B cell transmigration to compartments or reach compartmentalized ASC residing in tissues and behind the BBB. In addition, as growing evidence implicates additional

pathophysiological mechanisms — including the involvement of specific T cell subsets, potential extrafollicular reactions, cytokine pathways and microglia — further investigation may open avenues for novel, targeted interventions beyond the B cell/ASC axis. With evidence for diverging pathophysiologies within AE subtypes, each one must be dissected along the outlined pathways individually and bidirectionally — from bench to bedside and back again.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4o in order to make linguistic improvements. No content was created by artificial intelligence. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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