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LEADING ARTICLE

Maternal Anti-Fetal Brain IgG Autoantibodies and Autism Spectrum Disorder: Current Knowledge and its Implications for Potential Therapeutics

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Abstract Several studies have found a correlation between the presence of circulating maternal autoantibodies and neuronal dysfunction in the neonate. Specifically, maternal anti-brain autoantibodies, which may access the fetal compartment during gestation, have been identified as one risk factor for developing autism spectrum disorder (ASD). Studies by our laboratory elucidated seven neurodevelopmental proteins recognized by maternal autoantibodies whose presence is associated with a diagnosis of maternal autoantibody-related (MAR) autism in the child. While the specific process of anti-brain autoantibody generation is unclear and the detailed pathogenic mechanisms are currently unknown, identification of the maternal autoantibody targets increases the therapeutic possibilities. The potential therapies discussed in this review provide a framework for possible future medical interventions.

Key Points

There is sufficient evidence that maternal autoantibodies are a viable risk factor for the development of autism spectrum disorder (ASD); however, little has been described regarding any potential options for therapeutic intervention.

Methods involving ex vivo autoantibody removal, in vivo autoantibody competition and removal, and inhibition of autoantibody generation to remove and prevent maternal anti-brain autoantibodies from binding to fetal brain antigens in the developing fetus have been discussed.

A better understanding of the mechanisms that drive autoantibody generation and autoantibody-mediated pathology is necessary to further translate this research into a clinical application; however, identification of the fetal brain antigens and the antigenic epitopes has significantly increased the translation of this research towards a clinical application.

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1 Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by deficits in social communication and interaction, and restricted repetitive behaviors, interests, and activities [1]. The estimates of ASD prevalence have been steadily rising for several years, and this increase in frequency cannot fully be attributed to diagnostic changes and improvements in detection [2].

Moreover, the etiology of ASD is not well-understood, but is thought to involve a complex interplay between both genetics and environment [2, 3]. Specifically, maternal antibodies transferred to the developing fetus during pregnancy are gaining interest in the field as a viable environmental exposure for autism risk [4].

The placental transfer of maternal immunoglobulin to the developing fetus is a specific adaptive mechanism that confers short-term immunity in the neonate by providing the immunologically naïve fetus with a subset of the maternal humoral immune system [5, 6]. Immunoglobulin G (IgG) crosses the placenta in part mediated by the neonatal Fc receptor (FcRn), an IgG transport protein [7, 8]. Most antibodies are acquired during the third trimester and IgG levels in full-term infants often exceed those in the maternal circulation [9, 10]. Additionally, maternal IgG is ingested by the newborn in its mother's milk and colostrum, which enables maternal IgG to persist and provide protection to the newborn through early infancy [8]. However, maternal antibodies are passed into the fetal compartment without regard to their specificity, and pathologically significant maternal autoantibodies might be delivered in addition to protective antibodies [11]. Several studies by our laboratory and others revealed a significant correlation between the presence of maternal autoantibodies reactive to fetal brain proteins and diagnosis of ASD in the child [6, 7, 12–18]. Recognizing that identification of the target antigens for maternal autoantibody-related (MAR) autism was a critical step towards advancing this area of research, our laboratory recently determined the identity of seven candidate autoantigens, including lactate dehydrogenase (LDH) A and B, stress-induced phosphoprotein 1 (STIP1), collapsin response mediator proteins (CRMPs) 1 and 2, cypin, and Y-box binding protein (YBX1) [17]. Each of these autoantigens is known to be present in abundance in the fetal brain, and all play an important role in neurodevelopment, which further supports the hypothesis of maternal autoantibodies interfering with critical processes in neurogenesis [17].

Currently, it is unclear how these maternal autoantibodies arise, but several potential mechanisms are possible. In addition to the protective antibodies needed to overcome infection, the generation of pathologically significant autoantibodies can result if loss of self-tolerance is facilitated by excessive immune activation [19]. Furthermore, molecular mimicry is thought to lead to a misguided immune response to self-antigens due to cross-reactivity between the infectious agent and self-proteins [19]. Some individuals have a genetic predisposition toward autoimmunity, which is often attributed to specific major histocompatibility complex haplotypes and polymorphisms in genes involved in establishing self-tolerance and immune regulation [20]. Interestingly, several studies have found an increased association between a family history of certain autoimmune diseases and ASD [21]. Lastly, there is evidence that the generation of particular anti-brain autoantibodies can be induced by systemic malignancies that express onconeural antigens, such as occurs with paraneoplastic disorders [22]. While this seems like the least likely cause of autoantibody generation, a couple of recent studies have found correlations between having a child with ASD and cancer; one study found a statistically significant increase in the incidence in endocrine-related (ovarian and uterine) cancers, tumors, or growths in mothers of children with ASD compared with mothers of typically developing children and women with ASD, while another found evidence of increased cancer mortality in mothers of children with ASD [23, 24]. Further, one of the identified antigens in MAR autism, YBX1, is a marker for aggressive breast carcinomas [25]. Thus, while we have no information regarding the generation of the antibodies associated with MAR autism, it remains an area of active study.

Prior to designing a therapeutic intervention, one must first demonstrate that the specific autoantibodies have pathological significance. Thus, while many studies have shown that the mere presence of autoantibodies with brain reactivity does not necessarily correlate with CNS disease or pathogenicity for several antibody-mediated diseases, this concept is convincingly established when passive transfer of autoantibodies associated with a particular autoimmune disorder induces disease in an animal model [26, 27]. Presently, we do not know if maternal autoantibodies, regardless of their generation, interfere with neuronal development, but animal model studies using gestational transfer of purified IgG from mothers of children with ASD, have shown that the autoantibodies associated with MAR autism induce long-term behavioral changes in gestationally exposed offspring [12, 28–32]. Specifically, in a study by Bauman et al. [31], rhesus monkeys gestationally exposed to IgG from mothers of children with ASD that have autoantibodies to the three major target proteins (LDH, CRMP1, and STIP1) led to heightened maternal protectiveness, deviation from species typical norms including inappropriate social approach with familiar and unfamiliar peers, lack of reciprocal social interaction, and enlarged brain volume compared with control IgG-treated animals. Further, a recent study performed in collaboration with Martínez-Cerdeño et al. [32] provided additional evidence supporting autoantibody pathogenicity in a mouse model. In this very recent study, we directly introduced autism-specific maternal autoantibodies into the developing cerebral ventricles of embryonic mice, which led to increased cellular proliferation in the subventricular zone, increased the size of adult cortical neurons, and increased adult brain size and weight

compared with animals exposed to autoantibody-negative control IgG [32]. Both of these studies corroborate the observation of abnormal brain growth and total cerebral volume in children with MAR autism [31, 32]. Such studies support the notion that pre-natal exposure to anti-brain autoantibodies alters the developmental trajectory of the offspring, while providing increased evidence that these antibodies are pathologically significant [33]. Furthermore, the transfer of these autoantibodies coincides with fetal neuronal development, which relies on the precise timing, functional levels, and anatomical localization of particular signaling molecules. Thus, the recently identified target proteins, each of which plays a critical role in normal neurodevelopment, could be altered by the exogenous autoantibodies transferred in utero [4]. In addition, during pre-natal development the blood–brain barrier (BBB) is not fully formed in the fetus and is permeable to these potentially pathogenic antibodies [34]. Moreover, many of the antigens targeted by these anti-brain antibodies are highly expressed early in brain development with decreased expression as the individual ages [17]. Combined, these factors help explain the contradictory findings associated with anti-brain autoantibodies; they seem to be innocuous to the fully developed maternal brain, but can lead to profound development deficits in the offspring.

While there is now ample evidence that maternal autoantibodies are a viable risk factor for the development of ASD, little has been described regarding any potential options for intervention. Therefore, based upon several studies of clinical populations and animal models for MAR autism, we discuss several potential treatments that could serve as a template for therapeutic intervention.

2 Mechanisms to Prevent Transfer of Pathogenic Autoantibodies

In this section, we address the three main mechanisms that we propose could be employed to prevent pathogenic antibodies from accessing the fetal compartment. First, pathogenic antibodies can be removed from maternal circulation, which can be done both specifically and non-specifically. Additionally, there are many therapies that promote the degradation of endogenous maternal antibodies. Finally, drugs that specifically stimulate the apoptosis of plasma cells are currently being tested for their ability to inhibit autoantibody generation. In contemplating potential treatment options, it should be emphasized that this review is meant to be merely a scientific discussion of future areas of interest in this realm. Further, there is of course the added issue of these treatments being administered during pregnancy. Before the proposed options could become viable treatments in MAR autism they would need to be

thoroughly tested to ensure the safety of both the mother and the fetus, and the benefits of any therapy must outweigh potential adverse effects. Thus, while we discuss the various possibilities, this discussion is clearly meant to provoke future studies into options for the prevention of MAR autism.

2.1 Ex Vivo Antibody Removal

Removing the offending antibodies from circulation alleviates many antibody-mediated diseases and is a relatively safe technique that can be exploited to eliminate maternal autoantibodies during pregnancy [35]. Early treatments in this category utilized therapeutic plasma exchange (TPE) or plasmapheresis, a procedure that separates and removes the patient's plasma from their blood cells and then reconstitutes their blood cells with plasma from a donor while returning their blood cells to circulation [36]. However, these treatments were limited by their non-selective removal of all plasma components, leading to the reduction of coagulation factors, albumin, and hormones in addition to the removal of pathogenic antibodies [19, 35]. Nevertheless, plasmapheresis has been found to dramatically improve symptoms in patients with Guillain-Barré syndrome, an autoantibody-mediated autoimmune disorder, and may provide protective benefits to the developing fetal nervous system in MAR autism [37].

Further, with the discovery of staphylococcal protein A (a bacterial protein with high affinity for certain immunoglobulins), the more selective technique of immunoadsorption was realized [38]. This method allows for the therapeutic removal of immunoglobulin from plasma without removing other important plasma proteins and has been proven to be a useful treatment option for a number of autoimmune disorders [35]. This practice was enhanced by the creation of sterile, synthetic immunoglobulin adsorbers, which eliminated the infection risks associated with biologically purified proteins [35]. Alas, the downside of this technique is that, in addition to the removal of harmful antibodies, protective antibodies are also removed and complete elimination of IgG could leave patients at risk for contracting opportunistic infections [19, 27]. Fortunately, this potential risk is overcome by the administration of intravenous immunoglobulin (IVIg) [35]. Even though the risks associated with this technique are minimal, it still does not specifically target autoantibodies for removal and would be more risky during pregnancy. A treatment that specifically removes the offending maternal autoantibodies may be more effective in MAR autism.

In certain diseases, specific epitopes can be defined for the corresponding pathogenic autoantibody, which allows the specific removal of antibodies in an antigen-specific

manner and spares irrelevant immunoglobulins and other plasma proteins from being depleted, thus reducing the titer of specific pathogenic antibodies and avoiding temporary immune suppression [27, 35]. With the recent identification of targeted fetal brain proteins, we are now finalizing the specific peptide sequences recognized by these potentially pathogenic maternal autoantibodies. Determination of the epitopes will enable the development of specific peptide ligands that can be used to selectively remove the anti-brain autoantibodies in an immunoadsorption device (Fig. 1). This approach seems to be the most logical, but the identification and isolation of a specific antibody and its target epitope do not guarantee the feasibility of an efficient column [27]. This approach is hampered by the possibility that there are several pathogenic antibodies present and the column may not express all the potential epitopes. Additionally, the column may not be efficient in removing low affinity antibodies [27]. Lastly, while many patients with antibody-mediated disorders experience remission following antibody removal, the number of patients treated with immunoadsorption remains small because repeated and prolonged treatments are needed and there is a lack of well-defined clinical trials using this

therapeutic approach [19]. However, unlike most autoimmune disorders where autoantibodies must be constantly removed from circulation for the life of an individual, these potentially pathogenic maternal autoantibodies would only have to be removed during the period of gestation when maternal antibodies are transferred to the fetus. Thus, this could be a very promising treatment for MAR autism. Several factors would determine the critical time periods when maternal autoantibody removal would be most successful. These include the timing of expression for the specific protein target, the critical pathways in neurodevelopment dependent on the antigens recognized by the autoantibodies, the titer of the maternal autoantibody, and the integrity of the BBB of the fetus/infant. Animal studies are currently underway to address these issues.

2.2 In Vivo Antibody Competition and Removal

In addition to mediating the transfer of maternal IgG across the placenta, the FcRn also plays an essential role in protecting IgG from catabolism and is responsible for prolonging the half-life of IgG antibodies and serum albumin [39, 40]. The FcRn maintains a constant level of IgG in the
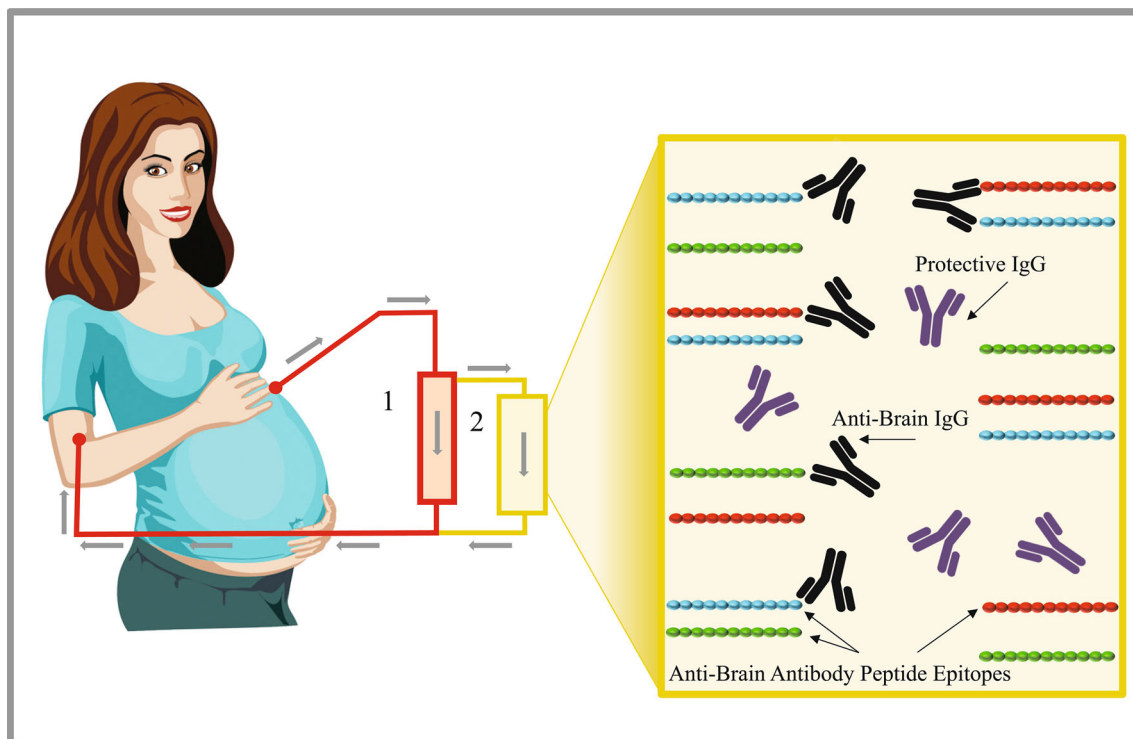

Fig. 1 Ex vivo maternal anti-brain autoantibody removal. The identification of the specific peptide epitopes targeted by maternal anti-brain autoantibodies enables the specific removal of these antibodies using plasmapheresis. First (*1*), the blood cells are separated from the blood plasma and returned to the maternal blood stream. Subsequently (*2*), the plasma is filtered using affinity chromatography. In this procedure, the anti-brain autoantibodies are selectively removed from the maternal blood stream by filtering the plasma through a peptide-bound column. Autoantibodies with reactivity to the peptide epitopes will bind to the column and are removed from circulation, while the remaining, unbound antibodies are returned to the maternal blood stream. *IgG* immunoglobulin G
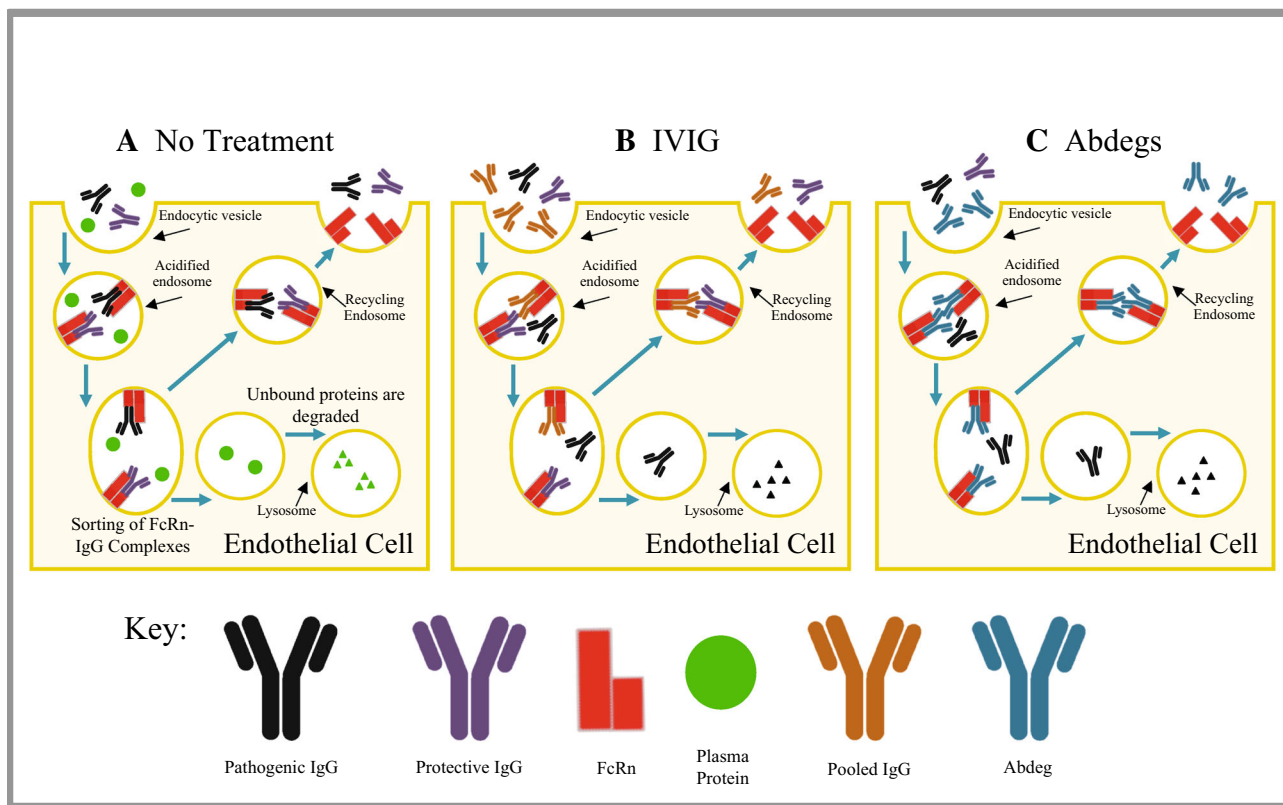
Fig. 2 In vivo maternal anti-brain autoantibody removal. Treatments that saturate the neonatal Fc Receptor (FcRn) increase the degradation of immunoglobulin G (IgG) and will potentially increase the degradation of maternal anti-brain autoantibodies. *a* Under normal conditions, the FcRn preferentially binds IgG and albumin to increase their half-life within the blood plasma. *b* Intravenous immunoglobulin (IVIg) therapy increases the amount of innocuous IgG within the blood plasma, leading to the dilution of anti-brain autoantibodies while also decreasing their half-life in the blood stream via FcRn competition. *c* Antibodies that enhance IgG degradation (Abdegs) are recombinant antibodies with high affinity for the FcRn, and are another potential therapeutic that could increase the clearance rates of anti-brain autoantibodies by out-competing endogenous IgG for binding to the FcRn

serum throughout the body by decreasing the level of IgG breakdown (Fig. 2a) [41]. Due to the saturable nature of the FcRn, the amount of IgG protected from degradation depends on the amount of available receptors; any unbound IgG molecules enter the lysosomal pathway and are digested [5, 41]. Therapies that compete with endogenous antibodies for binding to the FcRn receptor and therapies that block antibodies from binding the FcRn can lead to a decrease in serum autoantibody titers because they enhance IgG clearance rates.

Paradoxically, the same class of molecule that promotes pathology in a disease can also be used as treatment for the same disease [42]. IVIg therapy is the administration of large quantities of non-specific, pooled IgG antibodies from the serum of thousands of donors and is used to treat a number of immune-related diseases [42]. IVIg therapy has a dual function; in addition to saturating the FcRn and leading to the increased degradation of all endogenous IgG, it also results in the dilution of pathogenic antibodies by

increasing the concentration of innocuous IgG (Fig. 2b) [5, 40]. Although this treatment is not very specific, it is typically well-tolerated and the most frequent adverse effects include headache, fever, and nausea [42]. IVIg therapy is a desirable approach to prevent MAR autism, because it has minimal toxicity and is already approved as a treatment for antibody-mediated autoimmune diseases [42].

Recombinant antibodies, whose Fc regions have been specifically engineered to bind the FcRn with a higher affinity, also known as Abdegs, are another potential therapeutic that increases the clearance rate of IgG by out-competing any endogenous IgG for binding to the FcRn (Fig. 2c) [40, 41]. Additionally, by blocking the FcRn, Abdegs are a more attractive treatment for MAR autism because they might also inhibit the passage of deleterious autoantibodies to the fetus [41]. Similar to Abdegs, monoclonal antibodies directed toward the FcRn and peptides, which bind the Fc region of IgG, also lead to increased IgG degradation and potentially block the FcRn from mediating

Fig. 3 Inhibition of placental maternal antibody transfer. *a* Antibodies are transferred to the fetus during gestation to provide the neonate with a temporary immune system at birth. *b* This process can be inhibited with the use of the neonatal Fc Receptor (FcRn) blockers in order to prevent the transfer of maternal anti-brain autoantibodies during critical periods of neurodevelopment. However, this would not be a specific process and would block all immunoglobulin G
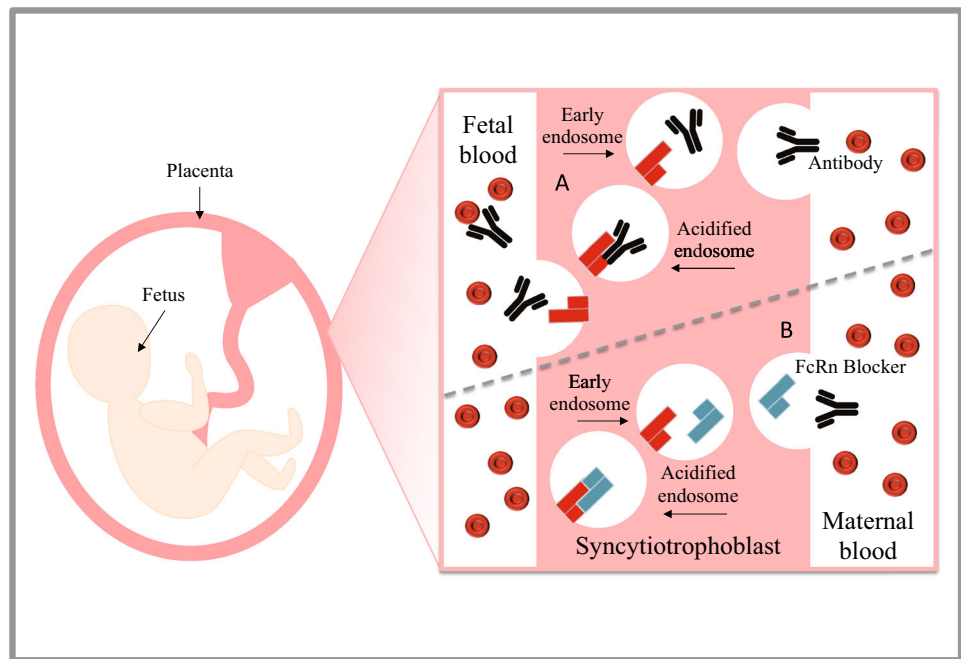
the placental transfer of IgG (Fig. 3) [40]. Unfortunately, all of the above-mentioned treatments could systemically induce the degradation of all IgGs because they are relatively non-specific [41]. Further, the aforementioned therapeutics would potentially prevent the transfer of all maternal antibodies, which may increase the risk of immunodeficiency in the infant. Determining the precise timepoint during which the BBB becomes impermeable to circulating maternal factors may allow these treatments to be utilized in a way that prevents anti-brain antibodies from entering the fetal compartment before BBB formation but permits the transfer of protective antibodies after early steps in fetal brain development have been completed. Research is ongoing to better understand the ontogeny of the BBB in primates.

Small-molecule inhibitors offer a more specific therapeutic approach. Defining the peptide epitopes recognized by maternal anti-brain autoantibodies will permit the generation of molecular mimeotopes, which share structural features with the peptide epitopes and can be orally absorbed by the mother [43, 44]. The peptide mimeotopes would act as a decoy antigens, competing with endogenous antigens expressed on the fetal brain [44]. These small-molecule inhibitors could potentially neutralize the maternal autoantibodies and prevent antibody-mediated damage in the fetus (Fig. 4). This technique is currently being explored as a therapy for antibody-mediated lupus brain disease [43, 44]. However, this therapy has not been tested in a pregnancy setting and, due to the experimental nature of this treatment, the adverse effects are currently

unknown. One possible drawback of this therapeutic is the potential for these small-molecule inhibitors to stimulate the formation of immune complexes, which can become deposited in small blood vessels, activating complement and phagocytic cells, resulting in inflammation and fever induction, vasculitis, nephritis, and arthritis [45]. Fortunately, many of these adverse effects are transient and resolve when the peptide mimeotope is cleared from the system [46]. Conversely, immune complex formation may be beneficial, because it might prevent anti-brain autoantibodies from binding the FcRn and would specifically clear these autoantibodies from maternal circulation. However, it is unclear if the benefits of small-molecule inhibitors outweigh their potential adverse effects, because like the maternal autoantibodies, inflammation and maternal immune activation during pregnancy has been associated with altered fetal brain development [47]. Designing a blocking system that provides the benefit of antibody blocking without the deleterious effects of immune activation is possible, but will require careful design of the blocking agent to render it non-immunogenic.

2.3 Inhibiting Antibody Generation

Broad-spectrum immunosuppressants, including glucosteroids, cyclophosphamide, and antibody therapies that selectively deplete B lymphocytes, have had a variable impact on the generation of autoantibodies [39, 48, 49]. These treatments normally require several months to significantly reduce antibody titers and often do not lead to

Fig. 4 Small-molecule inhibition of maternal anti-brain autoantibodies. *a* Anti-brain autoantibodies, which cross the placenta during gestation, can bind to fetal brain proteins and potentially inhibit important mechanisms in neurodevelopment. *b* Small molecules that mimic the protein antigens can be used to compete with the endogenous antigens expressed in the fetal brain and neutralize the maternal autoantibodies to prevent antibody-mediated damage. *IgG* immunoglobulin G
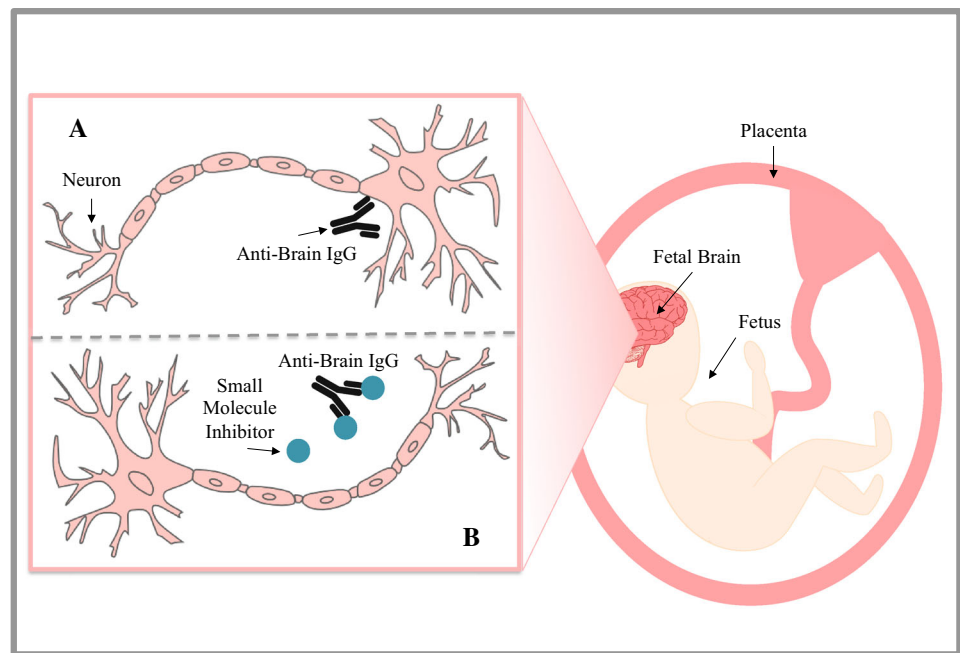

remission of autoantibody-mediated disease [48, 50]. The persistence of autoantibodies upon immunosuppression is most likely because autoantibodies are produced by long-lived plasma cells, which are resistant to immunotherapy and do not express the B cell marker targeted by anti-B cell antibodies [39, 48–50]. Plasma cells are highly differentiated B cells that synthesize and secrete several thousand antibody molecules per second and are essential for maintaining and regulating circulating antibody levels [39, 50]. It is currently thought that a therapeutic that specifically eliminates plasma cells might represent a new strategy for combating antibody-mediated diseases [48].

Proteasome inhibitors, which have demonstrated success in multiple myeloma, have been shown to deplete normal plasma cells without causing overt toxic effects [48, 49]. It was recently discovered that, in addition to targeting cancerous plasma cells, normal plasma cells are also hypersensitive toward proteasome inhibition due to their high rate of protein synthesis. Proteasome inhibitors promote the accumulation of misfolded proteins, which triggers the terminal unfolded protein response, leading to the activation of proapoptotic proteins and caspases, killing both long-lived and short-lived plasma cells [48–50]. These inhibitors specifically target plasma cells because as part of their differentiation from B cells, they up-regulate proteins related to the endoplasmic reticulum stress and unfolded protein response [50]. Further, proteasome inhibitors, such as bortezomib and carfilzomib, are thought to preferentially target autoreactive plasma cells; plasma cells secreting autoantibodies would most likely have a higher rate of antibody synthesis and secretion, because unlike

pathogenic antigens that are present temporarily during the course of an immune response, self-antigens are often present in vast quantities and are often consistently available (Fig. 5) [39, 49]. Also, there is competition between newly generated plasma blasts and old plasma cells for occupancy of survival niches, and plasma cells with reactivity for more recent antigens often out-compete plasma cells with reactivity for antigens that have not been encountered recently [39]. Although proteasome inhibitors have been shown to lead to a decrease in autoantibody levels, they only induce a moderate decrease in total serum IgG concentrations [48]. Therefore, it seems that proteasome inhibitors could be used to rapidly reduce autoantibody titers, without compromising the humoral immune system [50]. Unfortunately, these treatments are hampered by deleterious adverse effects. A large percentage of patients using bortezomib develop painful neuropathy [49]. However, carfilzomib has been shown to have a low rate of peripheral neuropathy and recent advances in administration and dose are reducing this risk [49, 50]. Proteasome inhibitors represent a promising treatment option for MAR autism, but their toxicity to the developing fetus is unknown and may prevent the use of these drugs during pregnancy. Clinical studies would clearly be needed to determine if these drugs are safe during pregnancy, as they are non-specific and there is a significant amount of protein synthesis during gestation. Moreover, the level and duration of suppression would also need to be established. If autoantibody levels were effectively suppressed long enough, which could be determined with the use of an assay to monitor maternal autoantibody status, proteasome

Fig. 5 Plasma cell depletion using proteasome inhibitions. *a* Autoreactive plasma cells are thought to have increased rates of antibody synthesis, because self-antigens are present in vast amounts and are not eliminated like antigens from pathogens. *b* Proteasome inhibitors, such as bortezomib, which selectively deplete plasma cells due to their high protein synthesis rates, may be a potential therapeutic to remove autoreactive plasma cells secreting anti-brain autoantibodies
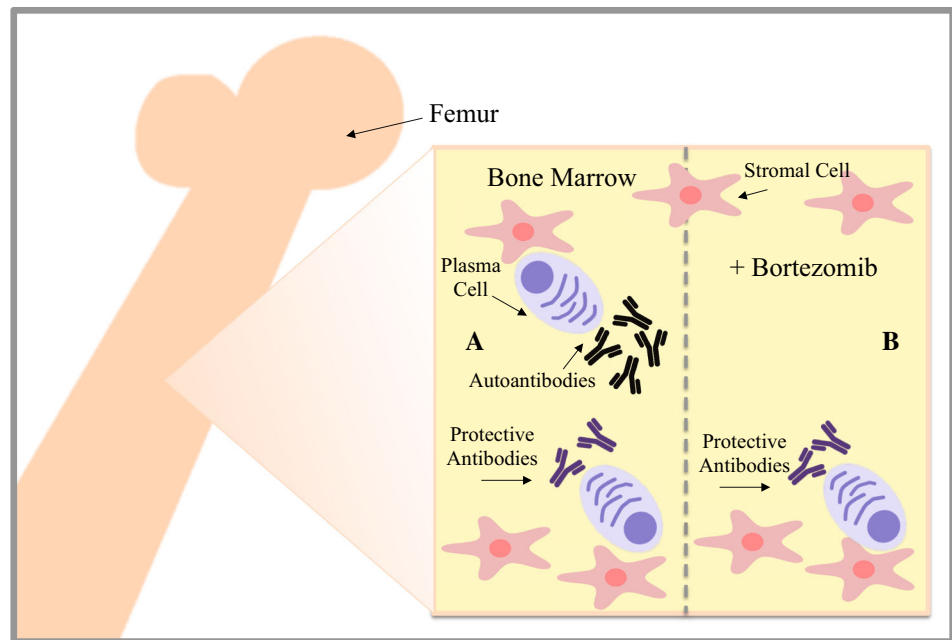
inhibitors could potentially be utilized to reduce autoantibody levels prior to pregnancy.

3 Conclusions

The proposed therapeutic strategies discussed in this review have the potential to prevent maternal autoantibodies, which are hypothesized to functionally interfere with and/or decrease the abundance of proteins critical for neurodevelopment, from gaining access to the fetal brain and thus preventing irreversible damage. However, the best method for the treatment for MAR autism may involve a combination of several of the above-mentioned techniques. If the autoantibodies are indeed responsible for the development deficits observed in ASD, determining the peptide epitopes will improve the specificity of these therapies. Work in this area is now underway. Further, the development of an autoantibody-based screening test will identify candidates in need of medical intervention. Nevertheless, studies are ongoing to determine if the maternal autoantibodies are mediating a pathological effect or if they are merely biomarkers of cell damage. A better understanding of the mechanisms that drive autoantibody generation and autoantibody-mediated pathology is necessary to further translate this research into a clinical application.

Compliance with Ethical Standards

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