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Antibodies and myelination: facts and misacts

Abstract Polyreactive (auto)antibodies are frequently found in healthy subjects and are bona fide considered to be non-pathogenic. However, autoreactive B cells and circulating (auto)antibodies have been associated with several neurological syndromes, including demyelinating disorders. Whether these antibodies can have a real impact on disease development is still a matter of debate. Here, we briefly summarize some of the most recently published data on both the deleterious and the protective effects of antibodies in autoimmune demyelinating disorders of the central nervous system.

Key words Autoantibodies • Demyelination • Remielination • IVIg • Multiple sclerosis

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B cell characteristics

Mature B lymphocytes represent about 5–15% of the circulating lymphoid pool and include both naive and memory B cells as well as terminally differentiated plasma cells. Following antigen recognition in peripheral lymphoid organs, naive B cells expand, undergo somatic mutations leading to secretion of high-affinity antibodies, and switch immunoglobulin (Ig) isotype. This sequence of events leads to the generation of memory B cells – long-living cells capable of rapidly generating specific high-affinity antibodies upon recall antigenic stimulation – as well as plasma cells, which constitutively secrete large amounts of antibodies [1, 2]. In rodents and humans, naive long-lived B lymphocytes are heterogeneous in phenotype, topography, and function. Follicular re-circulating B cells populate follicles in spleen and nodes, whereas static marginal zone (MZ) B cells are enriched in the MZ of the spleen, and B1 cells re-circulate between blood and body cavities [1].

Pathogenic autoantibodies and demyelination

Polyreactive (auto)antibodies are frequently found in healthy subjects and are considered to be nonpathogenic [1, 2]. However, autoreactive B cells and antibodies directed against neural-derived self-antigens have been associated with several neurological syndromes (i.e., Rasmussen's encephalitis, multiple sclerosis, multifocal motor neuropathy, Guillain-Barré syndrome, myasthenia gravis, etc.). Thus, specific humoral immune responses, resulting from the activity of antibody-producing B lymphocytes, may result in overt neuroimmunological disorders. It has been shown that (auto)antibodies may virtually recognize any neural element from the cortex to the muscular junction and may act as effector arm of the immune system via antibody-dependent cellular cytotoxicity (ADCC), opsonization, neutralization, and complement fixation (CDC) [3].

Table 1 Controlled trials of IVIg in MS

Study	Clinical status	Patients (n)	IVIg dosage	Primary endpoints	Result
Fazekas et al. [17]	RRMS	150	0.2g/kg per month	EDSS changes	Positive
Achiron et al. [18]	RRMS	40	2 + 0.4g/kg per 2 months	Relapse rate	Positive
Sorensen et al. [19]	RRMS	26	2 g/kg per month	New MRI lesions	Positive
Lewanska et al. [20]	RRMS	49	0.2 and 0.4 g/kg per month	Relapse rate	Positive
Hass [21]	Post partum	34	60 + 10 g/month	Relapses	Positive
ESIMS [22]	SPMS	318	1 g/kg per month	Time to progression	Negative
Noseworthy et al. [23]	Optic neuritis	55	2 + 0.4 g/kg prmonth	Visual acuity	Negative
Noseworthy et al. [24]	Fixed motor deficits	67	2 + 0.4 g/kg/ 2 weeks	Muscle strength	Negative
Stangel et al. [25]	Stable motor deficits	10	2 g/kg	MEP	Negative

RRMS, relapsing-remitting multiple sclerosis; *SPMS*, secondary progressive MS; *MEP,* motor-evoked potentials; *IVIg* intravenous immunoglobulins; *MRI*, magnetic resonance imaging

There is, however, no consensus on the role of (auto)antibodies in multiple sclerosis (MS). It is well known that the presence of few antibody-producing (i.e., IgG, IgM and IgA) auto-reactive long-living B cell clones within the CNS of MS patients represents a highly specific hallmark of the disease, even despite intense immuno-ablative treatments [4–6]. However, the pathogenic relevance of such antibodies in MS remains poorly understood. Indications that these antibodies might play a pathogenic role in MS arise from the facts that (a) both macrophages and complement fractions have been found at the edge of demyelinating plaques [7, 8] and (b) B-cell-secreted anti-myelin oligodendrocyte glycoprotein (MOG) (auto)antibodies bound to disintegrating myelin sheets have been recently shown within actively demyelinating lesions in MS [8]. On the other hand, there is experimental evidence suggesting that (auto)antibodies in demyelinating disorders may also play a beneficial role in tissue repair. B cell-deficient mice still retain a susceptibility to EAE induction [9] and EAE has been successfully treated using a serum extract, thus possibly acting via the inhibition of complement-mediated tissue damage [10–12]. Moreover, intravenously administered polyclonal immunoglobulins (IVIg) or monoclonal myelin-reactive antibodies have been shown to accelerate the remyelination rate in different animal models of CNS demyelination, such as Theiler's murine encephalomyelitis virus (TMEV) and lysolecitin-induced demyelination [13, 14]. Finally, systemic administration of polyclonal human IgM or monoclonal oligodendrocyte-binding antibodies in TMVE mice was able to increase significantly the remyelination rate within the CNS, when compared with commercial IVIg [15, 16].

Polyclonal IVIg have also been used to treat MS patients and several clinical trials have been performed in the last few years (Table 1). Although it seems that IVIg have a somewhat beneficial effect on relapses, disability, and magnetic resonance imaging (MRI) changes in patients with a relapsing-remitting form of MS [17–25], no convincing data about IVIg-mediated effects on disability progression (measured as sustained deterioration in the EDSS score or beneficial effects on the lesion load on T2-weighted MRI) have emerged from the above trials. Suddenly, studies describing IVIg-induced relapse rate changes did not use appropriate placebo groups, thus possibly overestimating the therapeutic effects of IVIg. Finally, it has been recently shown that IVIg have no effect in secondary progressive MS [22]. Although the therapeutic efficacy of antibodies in MS has to be further confirmed, we can argue that polyclonal IgG (IVIg) or IgM might, in theory, function in promoting remyelination in different ways, IVIg (a) inhibiting complement binding; (b) neutralizing certain pathogenic cytokines; (c) down-regulating antibody production, or (d) modulating Fc-receptor mediated phagocytosis, whereas IgM may selectively modulate some Ca^{++}-dependent oligodendrocyte remyelination pathways, as recently shown [26].

Conclusions

At present, no single mode of action has been identified as the crucial mechanism for either therapeutic or pathogenic circulating (auto)antibodies in MS. Based on the evidence discussed here, we can argue that circulating (auto)antibodies might *"physiologically"* fulfill different effector functions, thus being either protective or detrimental, depending on the disease state. The study of the molecular and the immunological characteristics of such (auto)antibodies, together with the study of the appropriate timing for therapeutic use of IVIg in MS patients, would indeed be of great importance to set appropriate conditions to safely treat CNS demyelinating diseases.

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