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Oligoclonal bands in multiple sclerosis; functional significance and therapeutic implications. Does the specificity matter?

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Abstract

Since their discovery, the existence of secreted oligoclonal immunoglobulin in the central nervous system in people with multiple sclerosis has been the subject of scientific investigation and debate over several decades. Although autoantibodies can be detected in some individuals, probably secondary to release of neo-antigens after damage, evidence for a major, primary involvement of damaging antibodies is still relatively lacking. However it is possible to construct a working hypothesis that establishes the interaction of plasma cells, which is the source of oligoclonal bands, microglia and astrocytes to create a self-perpetuating activated phenotype. This may generate an environment conducive to long-term plasma cell survival and the initiation and perpetuation of neurotoxicity that may contribute to disease worsening in multiple sclerosis. Therapeutic strategies to re-establish a homeostatic environment conducive to repair/recovery are indicated to control progressive multiple sclerosis.

Keywords

Oligoclonal bands, plasma cells, microglia, astrocytes, neurodegeneration, multiple sclerosis.

Highlights

- Immunoglobulins in oligoclonal bands secreted by plasma cells in the CNS can contribute to worsening pathology in MS
- Secreted immunoglobulin can interact with microglial Fc receptors in an antigen non-specific manner.
- Microglia and astrocytes may create a survival niche for long-term plasma cell survival.
- Plasma cells, microglia and astrocytes may interact to establish a locally neurotoxic or dystrophic environment.
- Bruton’s tyrosine kinase inhibitors are may be therapeutic agents for the potential elimination of plasma cells and OCB from the CNS in MS.

Introduction

Oligoclonal bands (OCB) are clonally restricted immunoglobulins (Ig), detected by isoelectric focusing (Freedman et al. 2005), which are produced by cerebrospinal fluid (CSF) and parenchymal B lymphocytes (Obermeier et al., 2011). These are a key hallmark of ongoing inflammatory events in the central nervous system (CNS) and have been reported in a number of neuroinflammatory conditions and viral infections such as: chronic infectious encephalitis; paraneoplastic syndromes, neuromyelitis optica spectrum disorders, acute disseminated encephalomyelitis, Behcet Disease, optic neuritis and multiple sclerosis (Chu et al., 1983, Psimara et al., 2010, Juryńczyk et al., 2015). More recently, the potential role of OCB in the perpetuation of immune responses and the establishment of a neurodegenerative environment in MS is increasingly indicated.

Oligoclonal bands and multiple sclerosis.

For many years the accepted dogma has been that multiple sclerosis (MS) is an autoimmune disease mediated by T cells. This is primarily based on experimental evidence from rodent models, where any role for the B cell arm of the immune response is often regarded as being of lesser importance. More recently, a pivotal role of B cells in the development of MS is increasingly indicated from the study of responses to immunomodulatory therapies in MS (Baker et al., 2017, Lehmann-Horn et al., 2017, Hauser et al., 2017, Ceronie et al. 2018). These notably include inhibition of active MS by CD20-depleting antibodies such as; rituximab, ocrelizumab and ofatumumab (Gelfand et al. 2017). One of the diagnostic hallmarks of MS is the presence of OCB in people with MS (pwMS), which are detected early in the disease process (Matute-Blanch et al., 2018). These bands indicate the presence, in the CNS compartment, of a restricted number of B cells, notably, plasma cells, secreting Ig into the CSF (Obermeier et al., 2011). The pattern of these OCB is characteristic for each individual and tends to remain unchanged over a long duration, despite therapeutic intervention (Olsson and Link, 1973, Walsh and Tourtellotte, 1986, Link and Huang, 2006). Up to 95% of pwMS in Northern Europe are positive for OCB (Link and Huang, 2006), lower levels reported in other countries may reflect less sensitive detection methodology (Dobson et al., 2013).

The presence of OCB in CSF may be associated with a more severe disease course and development of disability due to neurodegeneration, compared to OCB negative pwMS (Rojas et al., 2012). A more recent study revealed also that the presence of OCB at MS onset led to; a greater level of grey matter pathology, a more severe level of disability and cognitive impairment compared to OCB negative pwMS over a ten year study period. Farina et al., 2017). There has been reported to be a lower incidence of OCB positivity in primary progressive MS than relapsing-remitting MS, although they have a higher level of CSF Ig (Lourenco et al., 2013). Yet despite decades of study, convincing targets for these OCB to either myelin antigens (van Haren et al., 2013) or any other CNS target specific to MS (Srivastava et al., 2012, Navas-Madroñal et al., 2017)have yet to be reproducibly demonstrated (Owens et al. 2009; Willis et al., 2015; Navas-Madroñal et al. 2017, Bashford-Rogers et al. 2018). Indeed OCB could bind

to 'epiphemomenic' infectious agents or other targets, as such some OCB are targeted ubiquitious, intracellular targets (Brändle et al., 2016; Gastaldi et al. 2017, Bashford-Rogers et al. 2018). This suggests that the Ig may develop secondary to CNS damage (Winger and Zamvil 2016), rather than being of primary pathogenic importance. However, some antibodies in MS are clearly pathogenic as seen by the benefit exhibited by some pwMS following plasma exchange and immunoadorption (Keegan et al., 2005, Faissner et al. 2016, Lehmann-Horn et al., 2017) and the damage induced by MS-derived Ig in ex-vivo experimental assays (Elliot et al. 2012, Blauth et al. 2015). However, antibodies may have an immune stimulating role following Fc receptor interactions that is not dependent on the antigen-binding region. These would occur concurrently with effects mediated via direct antigen binding.

Perpetuation of plasma cells in MS and cellular interactions in the CNS.

Activation of microglia is a pathological feature of MS (Zrzavy et al. 2017). Human microglia express receptors to detect and bind Ig (FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIa) at very low levels under normal conditions. The expression of these Fc receptors is reported to be increased on microglia in the CNS of pwMS (Ulvestad et al., 1994a). Activation of FcγR on microglial cells, via immunoglobulin and immune complexes, leads to phagocytosis, endocytosis, release of inflammatory mediators, oxidative bursts, neurotoxicity and the regulation of B cell activation and antibody production (Coggeshall, 2002, Ulvestad et al. 1994b, Teeling et al., 2012). Interferon-gamma (IFN-γ) treatment of adult rat microglia resulted in enhanced expression of FcR and increased the production of superoxides (Woodroofe et al., 1989). Importantly, the Fc binding capacity of microglia was found to be significantly greater than that of peritoneal macrophages, underlining the potential role of microglia in immune-mediated neurodegeneration in MS (Woodroofe et al., 1989).

After the development of inflammatory lesions in the CNS in MS, a local population of microglia that have been activated due to the secretion of pro-inflammatory cytokines by invading lymphocytes at lesion onset, may persist for some time after the initial inflammatory lesion has resolved and overt lymphocytic infiltrates are no longer present (Zrzavy et al. 2017). In addition, the presence of OCB, indicates the presence of long-lived plasma cells in the CNS in both the meninges and brain parenchyma (Ligocki et al., 2010, Lovato et al., 2011), which continue to secrete Ig over a long period of time and which may persist for decades.

This locally secreted Ig may interact with the previously activated microglial population to not only maintain an activated phenotype via the expression of immunoglobulin Fc receptors on microglia in an autocrine manner but may also stimulate the release of neurotoxic factors by this population.

The expression of the chemokine CXCL12, the ligand for the CXCR4 receptor expressed on B and plasma cells, which is involved in not only extravasation but also plasma cell persistence, as CXCR4 expression is maintained during plasma cell differentiation, has been detected in lesional areas of CNS tissue in MS and the experimental autoimmune encephalomyelitis (EAE) model of MS (Krumbholz et al., 2006, Pollok et al., 2017). CXCL12 expression has also been

reported to be present in inactive/quiescent lesions (Krumbholz et al., 2006). In addition, strong expression of the chemokine CXCL13 has been reported in MS lesions and a high level of B cell expression for its receptor CXCR5. This CXCL13 expression strongly correlated with intrathecal Ig production (Krumbholz et al., 2006).

The source of CXCL12 appears to be from activated astrocytes in the inflamed tissue (Pollok et al., 2017). CXCL12 is involved in the migration of plasma cells to their physiological niche in the bone marrow and the expression of CXCL12 in the parenchyma may result in the establishment of a micro-niche in the CNS contributing to the long-term survival of these cells in the CNS (Pollok et al., 2017). Astrocytes, both pre-activated and in their basal state can also promote the survival of isolated human B cells *in vitro* by the release of as yet unidentified soluble factors and by implication, contribute to the long-term survival of potentially pathogenic B cell responses in the CNS (Touil et al., 2018). Astrocytes and microglia may also promote B cell activation and survival via the secretion of; B cell activating factor (BAFF), (Krumbholz et al., 2005), a proliferation-inducing ligand (APRIL), (Thangarajh et al., 2007) and interleukin 15, which can stimulate proliferation and Ig secretion by B cells (Rentzos et al., 2006).

These plasma cells, in areas associated with previous inflammatory lesion activity, may be of particular significance as there will be a population of demyelinated neurons under conditions of metabolic stress that renders them particularly susceptible to the release of neurotoxic factors from these localised plasma cell niches. It is likely that the majority of the detectable CSF Ig is likely to arise from outside the parenchyma in B cell and plasma cell rich infiltrates in ectopic leptomeningeal/subarachnoid areas (Serafini et al., 2004, Magliozzi et al. 2007). These ectopic B cell follicles have similarities to tertiary lymphoid organs and may secrete Ig into the CSF and immunoglobulin may also arise from plasma cells detectable in the CSF and meninges. It is also likely and perhaps of more direct pathological significance, that the presence of plasma cells in areas of the brain parenchyma at sites of previous inflammatory lesion activity is important. In these areas there is an already activated population of reactive microglia and where microglia, astrocytes and plasma cells will interact in a self-perpetuating feedback loop, where locally secreted Ig reacts with microglial Fc receptors, maintaining an activated phenotype and the release of neurotoxic factors in addition to maintaining an environment conducive to long-term plasma cell survival. The presence of an activated microglial population may also induce, via the production of the cytokines including interleukin one alpha (IL-1α), tumour necrosis factor (TNF) and the complement component C1q, an activated astrocyte population (designated A1 as opposed to neuro-supportive A2) that lose the ability to; promote neuronal survival, outgrowth and synaptogenesis and induce neuronal and oligodendrocyte death via the secretion of a yet to be identified toxic factor that has specificity for neurons and oligodendrocytes (Liddelow et al., 2017). Astrocytes may promote excitoxicity and block lactate transport that can contribute to redox and energy deficits that are neurotoxic in nerves (Bolanos 2016). These activated neurotoxic astrocytes, characterised by complement component C3 expression are detected in demyelinating MS lesions and are closely associated with CD68 positive, activated microglia (Liddelow et al., 2017). Astrocytes,

may also secrete factors such as IL-33 that drive microglia to cause nerve damage (Vainchtein et al., 2018).

It has also been reported that B cells in the CNS may be intrinsically neurotoxic. B cells isolated from pwMS can release as yet unidentified factors that can not only be toxic to oligodendrocytes but also neurotoxic and these factors are unrelated to secreted Ig, not complement-mediated and induce apoptosis (Lisak et al., 2012, 2017). B cells isolated from normal, normal control subjects did not secrete such factors toxic to oligodendrocytes or neurons.

Although, TNF is a pleotrophic pro-inflammatory cytokine, which can be generated by microglia (Liddelow et al., 2017). Peripheral inhibition of TNF can worsen MS and may relate to augmentation of memory B cell responses, which appear to contribute to the pathogenesis of relapsing MS (Leandro 2009; Baker et al. 2017). However, TNF is also a plasma cell survival factor and supports the formation of B cell follicles (Leandro 2009, Paulino et al. 2018). Inhibition of TNF can inhibit ectopic follicle formation and treat disease in rheumatoid arthritis (Cañete et al., 2009, Leandro 2009). However, this may not occur in MS, as antibody is unlikely to neutralise centrally-active TNF activity due to poor penetration of antibodies into the CNS (Freskgård, and Urich 2017). Thus although, thisindicates that inflammation during MS is complex, it further suggests the importance of targeting the immune response within the CNS.

Potential therapeutic strategies.

To date, of the new generation of highly-effective, licensed disease-modifying drugs used in MS, few will significantly enter and act with the CNS, notably the antibodies and protein-based treatments due to the action of the blood brain barrier (Freskgård and Urich 2017). Therefore many are unable to target plasma cells within the CNS. Indeed and surprisingly, the only one reported, in some cases, to show an effective reduction or in some cases extinction of OCB in CSF is the lymphocyte migration blocker natalizumab (von Glehn et al., 2012, Harrer et al., 2013, Mancuso et al., 2014). Whilst showing promise, natalizumab therapy is currently limited due to the risk progressive multi focal leukoencephalopathy in individuals with John Cunningham virus (Ho et al., 2017). Furthermore, the effectiveness in the reduction of secreted Ig from plasma cells located deep in the brain parenchyma and the clinical response has yet to be effectively determined and the depletion of OCB does not always occur (Warnke et al. 2015). In contrast, treatment with the lymphocyte migration blocker fingolimod did not show any reduction in OCB level, within the duration of observation (Kowarik et al., 2011). Likewise, no reduction in OCB has been reported following peripherally-administered rituximab (Piccio et al., 2010, von Büdingen et al., 2016). Peripheral-rituximab induces ineffective deletion of B cells in CNS tissue compared to effective deletion in CSF, which was observed in some instances following intrathecal rituximab (Studer et al., 2014, Komori et al., 2016). However, as plasma cells do not express CD20 (the target antigen of rituximab) deletion of plasma cells, following rituximab use, would not be expected. This suggests that any influence on CNS-derived plasma cells by rituximab would be secondary to: depletion of plasma cell precursors, depletion of survival factors or destruction of B cell niches rather than a direct influence on plasma cells. The persistence of OCB has been reported after treatment with the lymphocyte-depleting

agents, alemtuzumab (Hill-Cawthorne et al., 2012) and cladribine (Sipe et al., 1994). However, there was a reported stabilisation of OCB level or decrease with cladribine treatment in chronic progressive MS compared to a continued increase in OCB level in the placebo group and also clinical improvement or stabilisation compared to a continued clinical deterioration in the placebo arm (Sipe et al., 1994, Beutler et al., 1996). Cladribine, in contrast to monoclonal antibody-based therapies, has a good CNS penetration across the blood:brain barrier and after oral delivery in normal subjects the concentration in the cerebrospinal fluid is 25% of that in plasma (Lillemark, 1997) and is likely to be higher in pwMS, where blood:brain barrier integrity is likely to be compromised, with the reduced expression of drug efflux pumps (Al-Izki et al., 2014). The recent approval of an orally-delivered cladribine derivative for MS may help to determine whether cladribine therapy can produce a robust reduction or elimination of OCB after treatment, although again plasma cells may escape effective depletion as they appear to contain lower levels of the enzymes required for cladribine-induced cytotoxicity than other B cell subsets (Ceronie et al. 2018). Importantly, there was no reported major effect on OCB after autologous haematopoietic stem cell transplant following high dose immunosuppressive therapy, using agents with limited CNS penetration and activity (Saiz et al., 2001, Bowen et al., 2012). This further supports the view that CNS-directed immunotherapy may be required to target OCB in MS.

Bruton's tyrosine kinase (BTK) is a Tec-family kinase that is expressed in most haematopoietic cells but not T cells (Satterthwaite and Witte, 2000). BTK-dependent activation of NF-kappa B is essential for reprogramming the expression of genes that control B cell survival and proliferation (Khan, 2001). Mutations in BTK result in the B-cell immunodeficiencies X-linked agammaglobulinemia in humans and X-linked immunodeficiency in mice. These diseases are characterized by blocks in B-cell development at multiple stages and impaired function of residual mature B cells (Satterthwaite and Witte, 2000, Khan, 2001). BTK has been shown to be a key factor in B cell and plasma cell development and in the negative selection of autoreactive cells and overexpression of that leads to increased plasma cell numbers and autoimmunity in a mouse model of systemic lupus erythematosus, which is alleviated by treatment with a BTK inhibitor (Kil et al., 2012, Katewa et al., 2017). Thus, BTK inhibitors can be used to target plasma cells (Katewa et al., 2017). Importantly, some BTK inhibitors, such as ibutrinib, can cross the blood:brain barrier and are CNS active(Goldwirt et al., 2018; Lionakis et al., 2017). This is evidenced by successful treatment of B cell lymphoma within the CNS (Bernard et al., 2015, Lionakis et al., 2017). Thus, such agents may have utility to target OCB within MS.

Although BTK is a key mediator of B cell receptor signalling in B cells, it is also important in FcγR signalling in myeloid cells and may represent a novel key therapeutic target for the removal of pathogenic intrathecal plasma cells and also potentially activated macrophages/microglia in the treatment of MS. Indeed, BTK inhibition is beneficial in alleviating EAE (Menzfeld et al., 2015). As EAE is primarily a T cell-mediated disease with limited B cell requirements (Sefia et al. 2017), and as T cells do not express BTK, the disease amelioration

effect in EAE seems to be a direct effect on microglial activation/cytokine secretion via BTK and a novel malonitrile-sensitive target (Menzfeld et al., 2015).

Blockade of colony stimulating factor one can inhibit microglial development and can inhibit neuroinflammatory disease (Chitu et al. 2016). However, such agents have yet to enter the clinic for the treatment of MS. Minocycline is a tetracycline antibiotic that also inhibits migroglial activity and appears to promote neuroprotection in experimental models (Garrido-Mesa et al. 2013). Whilst trials in MS have been undertaken and show that minocycline has no or marginal activity, compared to current disease modifying treatments, as an immunosuppressive agents in MS (Sørensen et al. 2016; Metz et al., 2017). These have yet to adequately address whether minocycline has neuroprotective potential in humans.

In addition, there is the potential for non-steroidal anti-inflammatory drugs (NSAID) such as aspirin to reduce pro-inflammatory prostaglandin release from chronically-activated, peri-lesional microglia via the inhibition of the cyclooxygenase (COX) family of enzymes. Aspirin is of particular interest here as it has the unique ability to covalently acetylate and inactivate COX enzymes (Roth et al., 1975), in contrast to other competitive reversible NSAID COX inhibitors (Stanford et al., 1977) and penetrates readily across the blood:brain barrier. Aspirin and its derivatives have been shown to block microglial activation and the release of pro-inflammatory mediators and confer neuroprotection in an *in vitro* model of neurotoxicity, probably at levels relevant to human use (Lee et al., 2013). Aspirin may also block the generation of reactive astrocytes in response to inflammatory mediators and the release of cytotoxic factors such as nitric oxide via COX2 inhibition and blocking signalling pathways that induce a reactive astrocyte phenotype (Lee et al., 2013, Yao et al., 2014). In addition, aspirin has also shown to block COX/prostaglandin-mediated astrocytic release of the potential excitotoxic neurotransmitter glutamate (Cali et al., 2014) indicating the potential pleiotropic properties of aspirin therapy in MS.

This strategy may also aid the reversion to a quiescent microglial and neuro-supportive astrocytic phenotype and in combination with the removal of plasma cells after a short course of treatment with a BTK inhibitor, may restore cellular homeostasis in lesional areas of the brain parenchyma and aid the establishment of endogenous repair processes that are impaired by inflammatory activity.

Conclusions

Whilst the existence of OCB in the CNS of pwMS has been long recognised, it is only in recent years that experimental evidence points to their potentially important role in the pathological events driving neurodegeneration and the perpetuation of immunological responses in MS. Evidence from MS and animal models points to the intimate involvement of Ig-secreting plasma cells with microglia and astrocytes to create not only a survival niche for plasma cells in the CNS, but also generating an activated phenotype in the associated microglia and astrocytes, which have the capability to foster a locally self-perpetuating neurodegenerative environment,

which hampers endogenous repair processes and results in glial scarring which precludes lesion repair.

Whilst some of the current highly-effective disease modifying drugs used in MS have shown some ability to reduce OCB, new therapies such as the BTK inhibitors show promise in not only effectively modifying MS, but also in the effective eradication of plasma cells from the CNS, which may have long-term positive consequences on disease progression and re-setting the MS brain to a more homeostatic state. Combination of a course of BTK inhibitor therapy with longer term use of an NSAID such as aspirin may also be useful in re-establishing microglial and astrocyte quiescence.

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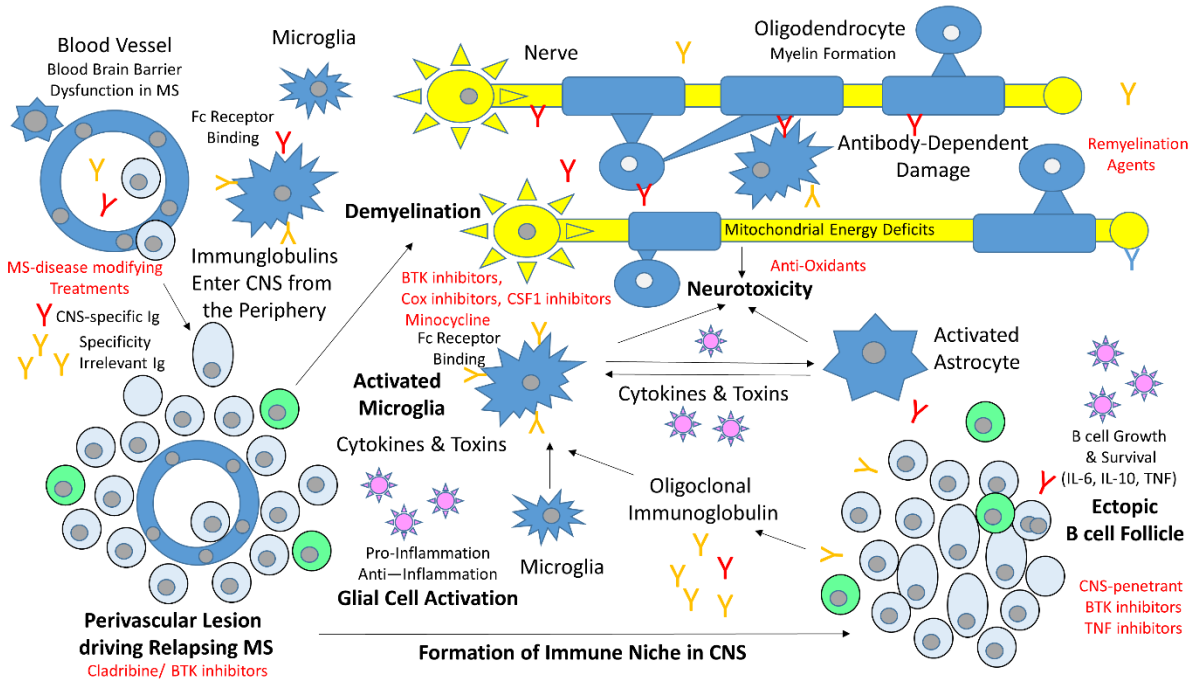
Figure 1.



Activation of microglia to drive neurodegenerative disease in MS. The MS disease process leads to the accumulation and activation of lymphocytic immune cells in the CNS. These produce cytokines and other factors that induce blood brain barrier dysfunction leading to the accumulation of monocytes and more B and T lymphocytes within perivascular cell space and the entry of immunoglobulins from the periphery. These cells and antibodies induce demyelination and relapsing clinical attacks. Whilst they can produce damage, they also release growth factors that promote glial activity. These infiltrates may allow the formation of immunological niches within the CNS that can generate plasma B cells and B cell follicles. These produce oligoclonal immunoglobulins with the CNS. These plasma cell niches become self-sustaining and long-lived and are outside the control of most peripherally-acting disease modifying drugs, currently used in MS. These may be a central part of the neurotoxic cascade that drives progressive neurodegeneration, notably of demyelinated nerves. Demyelinated nerves are particularly sensitive to toxicity due to the high metabolic demands required to sustain neurotransmission. This may be because of the formation of more energy-dependent, ion channels that must redistribute from the node of Ranvier after demyelination for nerve transmission to occur. *(A) Direct neuro-toxic effect of antibodies*. Some antibodies may have specificity for targets within the CNS. These can promote direct immune damage to oligodendrocytes and nerves, via complement activation and antibody-dependent killing mechanisms driven by infiltrating macrophages and microglia. In addition there is probably a concomitant (B) *Indirect neurotoxic effect of antibodies.* Fc receptor binding of immunoglobulins, with a specificity that is CNS-irrelevant, may provide a source of continued stimulation that generates or perpetuates chronically-activated microglia, especially once perivascular lesions have resolved Activated microglia are probably the central mediators of neurotoxicity in neuroinflammatory conditions and can stimulate astrocytes to become neurotoxic, such via secretion of IL-1 and TNF. Likewise, astrocytes produce factors such as IL-33 that can further activate microglia to become neurotoxic. These multiple neurotoxic mechanisms, occurring concomitantly during disease, may be the basis for damage in progressive MS. Current disease modifying treatments act to block the peripheral immune response from accumulating in the CNS to inhibit relapsing MS. Additional targeting of neuroinflammation in the CNS, to block B cell activation, differentiation and plasma cell formation, along with inhibitors of microglial activation may be necessary to block accumulating nerve loss. This is the substrate of progressive disability in MS. Agents (in red) may target these processes. Bruton's tyrosine kinase inhibitors may be able to target both plasma cell and microglia and may be a novel route to therapy in MS, which can be complemented by existing and novel therapies.