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New Insights into the Role of IL-1β in EAE and MS

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Abstract

Multiple sclerosis, and its animal model experimental autoimmune encephalomyelitis, are neuroinflammatory diseases driven by autoreactive pathogenic T_H cells which elicit demyelination and axonal damage. How T_H cells acquire pathogenicity and communicate with myeloid cells and cells of the central nervous system remain unclear. IL-1β is recognized to play an important role in EAE and perhaps MS. Clinical EAE is significantly attenuated in IL-1 receptor-deficient and IL-1β-deficient mice, and IL-1β is found in the blood, cerebrospinal fluid, and CNS lesions of MS patients. Here, we will focus on new reports which elucidate the cellular sources of IL-1β and its actions during EAE, in both lymphoid tissues and within the CNS. Several immune cell types serve as critical producers of IL-1β during EAE, with the cytokine inducing responses in hematopoietic and non-hematopoietic cells. These findings from the EAE model should inspire efforts towards investigating the therapeutic potential of IL-1 blockade in MS.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the brain and spinal cord that presents clinically with different temporal and pathologic patterns and results in a variety of neurologic signs and symptoms. Immune cell invasion of the CNS in MS induces both demyelination and axon loss, and involves communication between the invading leukocytes and astrocytes, glia, and neurons. Autoreactive $CD4^+$ T cells play an important role in driving MS pathology, although γδ T cells, $CD8^+$ T cells, and B cells also appear to contribute to disease (1–5). How autoreactive T_H cells acquire pathogenicity and how they mediate CNS damage remain important outstanding questions. Current MS therapies mainly target the functions of lymphocytes, but are not universally effective.

Experimental autoimmune encephalomyelitis (EAE) serves as an animal model of MS and can be elicited in several species through active immunization with myelin antigen or via adoptive transfer of T lymphocytes (passive EAE). In recent years the C57BL/6 mouse model of EAE has become the most popular, as it has allowed the use of knockout and transgenic mouse strains on this genetic background. In the most commonly used version of the C57BL/6 EAE model, mice are immunized with a Complete Freund's Adjuvant (CFA)-based emulsion containing a peptide from murine myelin oligodendrocyte glycoprotein

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(MOG_{35-55}) (6). Although this immunization elicits peptide-specific T_H cells, mice must also be systemically injected with pertussis toxin (PTX) as a coadjuvant to induce a monophasic, paralytic clinical disease (7, 8). Following EAE induction, priming and differentiation of MOG-specific T_H cells take place during the first week in secondary lymphoid organs. Over subsequent days, these T_H cells and blood-derived myeloid cells traffic through the meninges and across the blood-brain barrier (BBB), with clinical signs of disease typically apparent by 10 days post-induction. T_H cells are thought to re-encounter their cognate antigen (MOG_{35-55}) in the context of MHC class II-expressing antigen presenting cells both in the meninges and the CNS parenchyma, with these interactions resulting in the production of pathogenic cytokines by the T_H cells, notably granulocyte-macrophage colony-stimulating factor (GM-CSF) (9–11).

Established associations between IL-1 and autoimmune neuroinflammation

The IL-1 family of cytokines displays pleiotropic effects on a variety of hematopoietic and non-hematopoietic cells relevant to neuroinflammation. IL-1α is generated constitutively by epithelial cells and induced upon stimulation of most immune cell types (12). IL-1β is produced via both inflammasome-dependent and -independent pathways upon activation of a variety of leukocytes (13–17). Both of these IL-1 family members bind to a single activating receptor complex, composed of the IL-1R1 and IL-1RAcP (the IL-1R accessory protein, also called IL-1R3) chains, each containing a cytosolic Toll/interleukin-1 receptor homology (TIR) domain (18). Cytokine binding by this receptor engages the MyD88 signaling cascade, including IRAK1/2/4, TRAF6, and TAK1, to ultimately result in AP-1 and NF-κB activation and proinflammatory gene transcription. Separately, another IL-1 family member, IL-1Ra (also called IL-1RN), functions as a soluble receptor antagonist, capable of binding to IL-1R1.

Several members of the IL-1 family of cytokines have been studied in the context of EAE and MS, with initial work in EAE beginning in the late 1980s. In 1987, Symons et al. found increased levels of IL-1 activity, measured at the time by a mouse thymocyte proliferation assay, in the plasma and cerebrospinal fluid (CSF) of guinea pigs immunized with spinal cord homogenates to induce a chronic relapsing form of EAE (19). In the same year, using a rat model of passive EAE, Mannie et al. showed lymph node cells from EAE-induced rats treated with human IL-1β were more encephalitogenic, and suggested that this effect was via the action of IL-1β on T lymphocytes (20). Two studies later found evidence for IL-1α within the spinal cord of mice with EAE (21, 22), and one report showed that IL-1β protein could be detected in rats with EAE within meningeal macrophages, parenchymal infiltrating macrophages, and activated microglia (23). Subsequent studies in rats showed that recombinant human IL-1α treatment after EAE induction exacerbated clinical disease and that treatment with soluble recombinant murine IL-1 receptor or IL-1Ra could ameliorate disease (24–27). Schiffenbauer et al. first reported that IL-1R-deficient mice (on a mixed genetic background) were resistant to active EAE induction (28). Their results have been confirmed by several other groups using IL-1R-deficient mice on the C57BL/6 background (29–34), although the degree to which these mice were protected from clinical disease was somewhat variable. Despite one report to the contrary (35), IL-1β appears to be the critical mediator of EAE, rather than IL-1α, as IL-1β-deficient mice were seen to resist EAE by two

groups (33, 36), while IL-1α-deficient mice remained susceptible (33, 35). For this reason, the remainder of this review will focus on IL-1β, although whether IL-1α plays any role in MS remains an open question. Consistent with a critical requirement for IL-1β for EAE susceptibility, mice deficient in the inflammasome components NLRP3 (37–41), ASC (36, 39, 42), caspase 1 (42, 43), and caspase 11 (44) were also at least partially resistant to EAE, as were mice treated with inhibitors of NLRP3 (45, 46) or caspase 1 (47). It is worth noting that in some reports (40–42), mice immunized with larger amounts of heat-killed *Mycobacterium tuberculosis* (*Mtb*) (usually greater than 300 micrograms per mouse) as part of the MOG_{35-55}/CFA emulsion developed an NLPR3- and ASC-independent form of aggressive EAE. However, this form of EAE still appears to be IL-1β- and IL-1R-dependent, given that the experiments in IL-1β- and IL-1R-deficient mice which demonstrated EAE resistance were typically performed with large amounts of heat-killed *Mtb* (29–34, 36).

Beginning in 1990, reports emerged showing that IL-1β protein or *IL1B* transcript could be detected in the CSF (48, 49) or within CNS lesions of MS patients (50–55). More recently, these findings were extended by Seppi et al. who showed that CSF levels of IL-1β correlate with the number and volume of brain cortical demyelinating lesions (56), and by Rossi et al. who showed that relapsing-remitting MS (RRMS) patients with detectable IL-1β in the CSF at the time of clinical remission had a more severe course of disease (57). In addition, transcript levels of *IL1B* and two inflammasome components (*CASP1* and *NLRP3*) were more highly expressed by peripheral blood mononuclear cells from MS patients compared to healthy controls (58–60). Collectively, while these results indicate that IL-1β expression in the CNS and blood is associated with disease activity in MS, they do not establish a causal role for the cytokine in disease pathogenesis. This review will therefore focus on the mouse model of EAE, where several groups have begun to elucidate the mechanism of action of IL-1β (Fig. 1).

Cellular sources of IL-1β in EAE

Mononuclear phagocytes and neutrophils

Over two decades ago it was first suggested that CNS macrophages and microglia express IL-1β in rats with EAE (23), although more recent mouse experiments demonstrated that CNS-infiltrating Ly6C-positive macrophages but not resident microglia were producers of this cytokine (61). Examining IL-1β production in the CNS more carefully using pro-IL-1β reporter mice, Levesque et al. identified neutrophils and monocyte-derived macrophages as the primary cell subsets expressing IL-1β in the spinal cord after clinical disease onset (33). These authors also found that transmigration through the blood-spinal cord barrier triggered pro-IL-1β expression by neutrophils, and that at day seven after EAE induction, IL-1β-producing neutrophils were found in the blood. We and others also found IL-1β-producing myeloid cells in peripheral lymphoid organs at days five through eight following EAE induction (31, 32, 36, 62). These reports collectively identified a population of $CD11b^{+}Ly6C^{mid\text{-}hi}MHC\ II^{lo\text{-}hi}$ monocyte-derived DC/macrophages (moDCs/Macs) as the main source of IL-1β in draining lymph nodes (DLNs), and showed that these cells increase dramatically following MOG_{35-55}/CFA immunization given with PTX coadjuvant. We and the laboratories of Sallusto and Waisman explicitly showed a requirement for PTX to yield

IL-1β production from this DLN cell population, by comparing MOG_{35-55}/CFA immunizations with and without PTX (32, 34, 36). While the details of how PTX induces DLN cells to generate IL-1β are not clear, Dumas et al. had previously shown that intraperitoneal PTX alone was sufficient to induce IL-1β production by macrophages and neutrophils in the peritoneum within a few hours after injection (63). It is noteworthy that in our experiments (32), we found that DLN cells collected at day seven from mice that were immunized with MOG_{35-55}/CFA produced little IL-1β, even when re-exposed to the immunogenic component of CFA, heat-killed *Mtb*, ex vivo. In contrast, DLN cells collected from mice immunized with MOG_{35-55}/CFA given with systemic administration of PTX produced a small amount of IL-1β ex vivo, which was greatly augmented by re-exposure to heat-killed *Mtb*. Overall, these results suggest that PTX is essential for the generation of IL-1β-producing cells in vivo in the C57BL/6 EAE model, and help to explain the requirement for this coadjuvant to yield clinical disease.

Another recent finding relevant to IL-1β production by myeloid cells came from Gao et al. (64) who confirmed that CD47-deficient mice were resistant to EAE (65) and showed that CD47's role was hematopoietic cell-intrinsic. CD47 is a transmembrane protein of the immunoglobulin superfamily that can associate with integrins in cis and can bind the membrane ligand SIRPα in trans or the soluble ligand thrombospondin-1 (TSP-1). In vitro experiments showed that LPS plus ATP treatment resulted in less caspase 1 activation and less IL-1β production by CD47-deficient macrophages, and serum from CD47-deficient mice contained less IL-1β following EAE induction. Mechanistic studies demonstrated that CD47 appears to repress nitric oxide production in macrophages which in turn allows full inflammasome activation and mature IL-1β generation. These data highlight the fact that there are likely several signaling pathways which integrate to result in maximal IL-1β production by myeloid cells during EAE.

Mast cells

In 2000, Brown and colleagues showed that mast cells play an important role in the MOG_{35-55} model of EAE based on studies with mast cell-deficient WBB6F1-$Kit^{W/Wv}$ mice, which displayed a reduced incidence and severity of disease (66). Selective reconstitution of meningeal mast cells by intracranial injection of bone marrow-derived mast cells (BMMCs) could restore EAE susceptibility in these mice, pointing to a particular role for mast cells at this anatomic location (67). Analysis of meningeal responses to EAE induction found that *Il1b* transcripts in the meninges of wild-type (WT) mice increased after EAE induction, with mast cells as a likely source, given that this increase was not seen in mast cell-deficient mice (68). More recently, the Brown group showed that reconstitution of meningeal mast cells with BMMCs from caspase 1-deficient mice could not restore EAE susceptibility or $CD4^+$ T cell encephalitogenicity, likely indicating that IL-1β from these cells contributes to disease pathogenesis (69, 70). A recent in vitro study also showed that activated human mast cells secrete IL-1β and thus promote IL-17 production by $CD4^+$ T cells (71).

T cells

IL-1β production by T cell has recently been appreciated. Using flow cytometry, McCandless et al. first showed that a majority of spinal cord-infiltrating $CD4^+$ T cells, $CD8^+$

T cells, and γδ T cells express pro-IL-1β during early EAE (72). A second study showed that in the cerebellum during EAE, $CD3^+$ T cells expressed IL-1β as assessed by immunofluorescent microscopy, and that splenic T cells secreted IL-1β (73). T_H cells from EAE-induced mice found in secondary lymphoid organs analyzed at day 7 after immunization produced IL-1β after antigen restimulation in the presence of either IL-12 or the combination of IL-23 and IL-1β (74). A true requirement for T_H cell-intrinsic production of IL-1β during EAE was elegantly shown through the use of ASC conditional knockout mice (*Asc*$^{fl/fl}$*Lck*-Cre), in which T cell-specific deletion of ASC resulted in almost complete resistance to active EAE (75). This was corroborated by the fact that *Rag1*-deficient mice reconstituted with *Il1b*-deficient $CD4^+$ T cells also did not develop EAE after immunization. EAE induction in *Asc*$^{fl/fl}$*Lck*-Cre mice resulted in normal $CD4^+$ T cell priming and cytokine production in DLNs at day 10 after immunization, suggesting that non-T cell sources of IL-1β were sufficient before this time point to instruct priming. When in vivo primed *Asc*$^{fl/fl}$*Lck*-Cre $CD4^+$ T cells were cultured with MOG_{35-55} in T_H1 polarizing conditions, they were fully capable of adoptively transferring EAE, but culture of these cells in T_H17 conditions resulted in non-pathogenic cells. These results highlighted a surprising role for intrinsic IL-1β production specifically by T_H17 cells during the effector phase of EAE, probably through autocrine action of this cytokine within the CNS. Interestingly, T_H17 cell production of mature IL-1β was stimulated by ATP and required a caspase 8-containing inflammasome, rather than caspase 1. Taken all together, following EAE induction, multiple immune cell types at different times and anatomic locations must secrete IL-1β to promote clinical disease development.

IL-1β acts on T_H cells to promote pathogenicity in EAE

Unlike naïve T_H cells, in vitro polarized T_H17 cells express high levels of the IL-1 receptor (T_H1 and T_H2 cells express only low levels) (76, 77). After EAE induction, IL-17A-producing as well as IFN-γ- and GM-CSF-producing $CD4^+$ T cells in the DLN show higher IL-1R1 expression compared to $Foxp3^+$ regulatory T cells (34). Because IL-1R1 knockout mice resisted active EAE induction but were susceptible to EAE when they served as recipients for adoptively transferred IL-1R-sufficient MOG-specific T_H17 cells, Sutton et al. reasoned that T_H17 cells themselves must be critical responders to IL-1β (29). Furthermore, *Rag1*-deficient mice reconstituted with IL-1R1-deficient $CD4^+$ T cells (77) and mice with T cell-specific ablation of IL-1R1 (*Il1r1*$^{fl/fl}$*Cd4*-Cre) developed milder clinical EAE after immunization (34), confirming a T_H cell-intrinsic role for IL-1 responsiveness. Ghoreschi et al. demonstrated that IL-1β in combination with IL-6 and IL-23 was critically required for the generation of pathogenic T_H17 cells using a system of adoptively transferred in vitro polarized MOG-specific 2D2 TCR transgenic T_H cells (78). Tracking IL-17A-producing cells during EAE through a fate mapping approach confirmed that T_H17 cells, but not T_H1 cells, expressed IL-1R1, and that these cells responded to IL-1β by producing large amounts of IL-17A (79). Interestingly, this approach also revealed an abundant population of IL-1R1-expressing exT_H17 cells that increased with disease progression and which no longer produced IL-17, but instead secreted IFN-γ in response to IL-1β.

Given that adoptive transfer studies had shown that neither IL-17 nor IFN-γ were absolutely required for passive EAE development (80, 81), the above studies did not provide a clear

explanation for how IL-1 responsiveness led to T_H cell encephalitogenicity. Two reports provided evidence that T_H cell-derived GM-CSF was essential for pathogenicity in adoptive transfer EAE models, even in the combined absence of IL-17A and IFN-γ (80, 81), and one of these (81)showed that IL-1β strongly enhanced GM-CSF production by T_H17 cells. Lukens et al. soon thereafter showed that T_H and γδ T cells from EAE-induced IL-1R1-deficient mice (which were highly resistant to EAE) failed to produce GM-CSF (30), although it remained unproven that IL-1R signaling was cell-intrinsically required by T_H cells for production of GM-CSF. This final point was made by Croxford et al. who showed that following EAE induction, IL-1R-deficient T_H cells were less represented amongst the GM-CSF-producing T_H cell population in IL-1R1 wildtype:IL-1R1-deficient mixed bone marrow chimeric mice (31).

Work from Jeffrey Bluestone's group (82) and our own lab (83) has shown a T_H cell-intrinsic requirement for the basic helix-loop-helix transcription factor Bhlhe40 (also known as DEC1, Stra13, Sharp2, and Bhlhb2) for EAE susceptibility. In each of these reports, Bhlhe40-deficient T_H cells were found to produce less GM-CSF, consistent with the aforementioned work linking GM-CSF to T_H cell encephalitogenicity. As a follow up to these studies, our lab analyzed the expression of Bhlhe40 in T_H cells during EAE using Bhlhe40 BAC transgenic GFP reporter mice (*Bhlhe40*^{GFP}) (32). GFP expression was notable in cytokine-producing T_H cells within secondary lymphoid organs and the CNS during EAE, but was poorly induced if PTX was not administered at the time of immunization. In vitro cultures of T_H17 cells revealed that IL-1β served as a strong stimulus for Bhlhe40 expression, and in vivo IL-1 neutralization or IL-1R1 deficiency impaired expression of the GFP reporter. More recently, to further test whether T_H cell-intrinsic IL-1R signaling was required for optimal Bhlhe40 expression in autoreactive cells, we co-transferred congenically-marked 2D2.*Bhlhe40*^{GFP} and 2D2.*Bhlhe40*^{GFP}.*Il1r1*$^{-/-}$ T_H cells to wildtype recipients and immunized these mice with MOG_{35-55}/CFA given along with PTX (unpublished data). At seven days post-immunization, IL-1R1-deficient 2D2 cells expressed significantly less GFP than IL-1R1-sufficient cells in the DLN. Overall, these data indicate the presence of a pathway whereby PTX induces IL-1β which acts on autoreactive T_H cells to induce Bhlhe40 expression and subsequent encephalitogenicity (Fig. 1).

Given the importance of IL-1R signaling for T_H17 cell pathogenicity it is interesting to consider which pathways regulate expression of this receptor by these cells. Among the cytokines required for T_H17 cell differentiation in vitro, IL-6 but not TGFβ or IL-23 strongly induced *Il1r1* transcripts in naïve $CD4^+$ T cells activated by anti-CD3 and anti-CD28 (77). Not surprisingly, IL-1R expression was severely impaired in T_H cells lacking STAT3, the primary transcription factor downstream of IL-6 receptor signaling. Recent reports have identified three novel T_H17 cell-intrinsic positive regulators of IL-1R expression, including the signaling regulator Spry4 (84), microRNA cluster miR-183-96-182 (85), and IL-1R signaling itself (64). Fukaya et al. found that Spry4-deficient mice were partially resistant to active EAE and that T_H17 cells from these mice were unable to elicit passive EAE (84). Spry4-deficient T_H17 cells expressed lower levels of IL-1R, and overexpression of Spry4 increased expression of the *Il1r1* transcript. Spry4 may carry out this regulation via inhibition of MEK and PKC pathways. Ichiyama et al. found that the microRNA cluster miR-183-96-182 (miR-183C) was expressed specifically in T_H17 cells

cultured in conditions that favor encephalitogenicity (IL-1 + IL-6 + IL-23) (85). T_H17 cells from miR-183C-deficient mice produced less IL-17 and GM-CSF and were less pathogenic. The 3′UTR of the transcription factor Foxo1 was found to be a target of all 3 miRs in this cluster such that miR-183C-deficient T_H17 cells expressed increased levels of Foxo1, which in turn directly repressed expression of *Il1r1*. Lastly, Gao et al. found that addition of IL-1β to T_H17 cells led to increased expression of *Il1r1*, supporting the existence of a feed forward circuit that reinforces T_H17 cell pathogenicity (64).

IL-1β action on non-T_H cells in EAE

Several lines of evidence indicate that cells other than T_H cells also respond to IL-1β to promote EAE pathogenesis. Ronchi et al. tracked transferred 2D2 cells in MOG_{35-55}/CFA-immunized hosts treated with systemic PTX and found that these autoreactive T_H cells were less abundant and less frequently expressed both IFN-γ and GM-CSF in the DLNs of IL-1R-deficient recipients when compared to IL-1R1-sufficient recipients (36). Likewise, Mufazalov et al. found that mice globally deficient for IL-1R were more resistant to clinical EAE than those with only T cell-specific ablation of IL-1R1 (*Il1r1*$^{fl/fl}$*Cd4*-Cre) (34). Finally, bone marrow chimera studies have shown that IL-1R signaling by radioresistant cells contributes to EAE pathogenesis (33, 72). Collectively, these studies suggest the possibility that hematopoietic non-T_H cells, radioresistant microglia, and/or radioresistant non-hematopoietic cells all may respond to IL-1β to enhance neuroinflammation during EAE. Future studies using *Il1r1*$^{fl/fl}$ mice (34, 86–88) crossed to additional Cre-expressing strains should be useful to dissect the roles of the aforementioned cell types.

With regard to non-hematopoietic cell types, data exist supporting the notion that IL-1β acts directly on astrocytes and/or CNS endothelial cells to result in leukocyte recruitment and BBB or blood-spinal cord barrier disruption, processes that may contribute to neuroinflammation in EAE. Argaw et al. identified a pathway whereby IL-1β promoted BBB permeability, possibly through its action on astrocytes to induce their production of VEGF-A (54). More specific actions of IL-1β on astrocytes were also shown by others to include the stimulation of chemokine production (CCL2, CCL20, CXCL2) which might recruit and activate leukocytes (89, 90). Work from the groups of Quan and Lacroix, however, did not observe expression of IL-1R1 on GFAP-expressing astrocytes, and instead found its expression largely restricted to CNS endothelial cells (33, 91). Lacroix's group further showed that this receptor was present specifically on venules at the pial venous plexus, corresponding to a site of myeloid cell infiltration during EAE (33, 92). Action of IL-1β on endothelial cells appears to make them receptive to firm adhesion with neutrophils (93) and induces their secretion of a variety of cytokines and chemokines (33). Specific knockdown of IL-1R1 on Tie2-positive endothelial cells attenuates clinical EAE, further supporting the pro-encephalitogenic action of IL-1β on these cells (94).

IL-1β in MS

While experiments in EAE have provided significant insight into the pathogenic role of IL-1β in this disease model, less is known about the contribution of this cytokine to the pathogenesis of MS. Numerous studies have detected IL-1β or its transcript in the brain,

CSF, or blood of MS patients, although the cellular sources of IL-1β are not clear. Likewise, whether a specific environmental stimulus drives IL-1β production in MS, akin to how PTX acts in EAE, is unknown. Some reports have analyzed the actions of IL-1β on human cells, and these serve as a framework for understanding its potential pathogenic role in MS. IL-1β can act on subsets of human T_H cells expressing the IL-1R (95), and receptor expression can be increased by IL-7, IL-15, and TGFβ (96). In vitro polarization of naïve human T_H cells in a cocktail containing IL-1β induces *IL17A*, *IL17F*, *IL21*, *IL22*, *IRF4*, *RORC*, *IL1R1*, and *IL23R* expression in an IL-1R-dependent manner (97). Furthermore, IL-1β treatment of activated human T_H17 cells increases the fraction of GM-CSF/IFN-γ/IL-17 multi-cytokine-producing cells (98), which are thought to play a pathogenic role in several autoimmune disorders including MS, rheumatoid arthritis, and inflammatory bowel disease. Recently, both naïve and memory T_H cell subsets from MS patients were found to express higher levels of *IL1R1* than cells from healthy controls, potentially suggesting increased responsiveness to this cytokine in MS (97). In addition, human astrocytes express *CXCL12*, *IL6*, *CCL2*, *CCL5*, *PTGS2*, and *TLR2* in response to IL-1β treatment (99, 100). Future studies should aim to more fully determine whether IL-1β plays a pathogenic role in MS, perhaps in specific patient subsets or at specific stages in the disease process.

Many studies have observed that therapeutic agents used to treat MS affect IL-1Ra and/or IL-1β production. These include the commonly used drugs type I IFN, glatiramer acetate (GA), and natalizumab (anti-VLA-4). Treating RRMS and progressive MS patients with IFN-β significantly increased IL-1Ra in the serum (101–103). In vitro, IFN-β treatment of human PBMCs or monocytes promoted IL-1Ra but inhibited IL-1β production (104, 105). Using murine bone marrow-derived macrophages, Guarda et al. showed that IFN-β indirectly limited pro-IL-1β abundance by inducing IL-10 expression and directly prevented IL-1β maturation by repressing inflammasome activation (106). Inoue et al. also found an alternative mechanism whereby IFN-β reduced IL-1β maturation in macrophages, through induction of SOCS-1 and subsequent inhibition of Rac1 (40). Rac1 inhibition led to reduced ROS generation, and thus less activation of the NLRP3 inflammasome. Like IFN-β, GA increased serum IL-1Ra levels in RRMS patients, and stimulated IL-1Ra but suppressed IL-1β production when applied to human monocytes in vitro (107, 108). The regulation of IL-1Ra by GA in monocytes required both MEK/ERK and PI3Kδ pathways, while IFN-β relied on a MEK2/PI3Kδ pathway to induce IL-1Ra (109, 110). Natalizumab is a monoclonal antibody targeting the integrin very late activation antigen (VLA)-4 and thus prevents the entry of peripheral leukocytes into the CNS. Treating MS patients with natalizumab led to lower levels of IL-1β in the CSF (111, 112). Collectively, these findings suggest that regulating IL-1 family proteins may serve as one mechanism of action used by several currently approved treatments.

Numerous studies have shown that inflammasome inhibition or IL-1R signaling blockade ameliorates EAE severity and/or delays disease onset (24–27, 45, 46, 73, 93, 113). It has been proposed that drugs interrupting IL-1R signaling may be therapeutically useful as treatment for MS (92, 114). While no small molecule inhibitors have been generated to specifically block this signaling pathway, anakinra (recombinant IL-1Ra) has been approved by the U.S. Food and Drug Administration (FDA) to treat rheumatoid arthritis and appears to be relatively safe with few serious adverse reactions (115, 116). We suggest that targeting

the production or actions of IL-1 in both secondary lymphoid organs and within the CNS be considered as new therapeutic opportunities for MS treatment.

Conclusions

This review has highlighted recent reports demonstrating the production of IL-1β in EAE by myeloid cells, mast cells, and T cells, and the response to this cytokine by both immune and non-hematopoietic cells. Several unanswered questions remain open to further experimentation. For example, how does PTX induce IL-1β production by monocytes and neutrophils, and what other stimuli can trigger IL-1β production by these cells? Also, it will be interesting to determine whether myeloid cells themselves respond to this cytokine in an autocrine and/or paracrine manner to facilitate disease progression. The anatomic location of these cells during different phases of disease should also be considered. As recent reports have shown T cells to produce IL-1β during EAE, it will be important to understand more fully the signals inducing this source of the cytokine. Lastly, many questions remain about the pathogenic role of IL-1β in MS and whether autoreactive subsets of human T cells respond to this cytokine to express GM-CSF or other proinflammatory cytokines.

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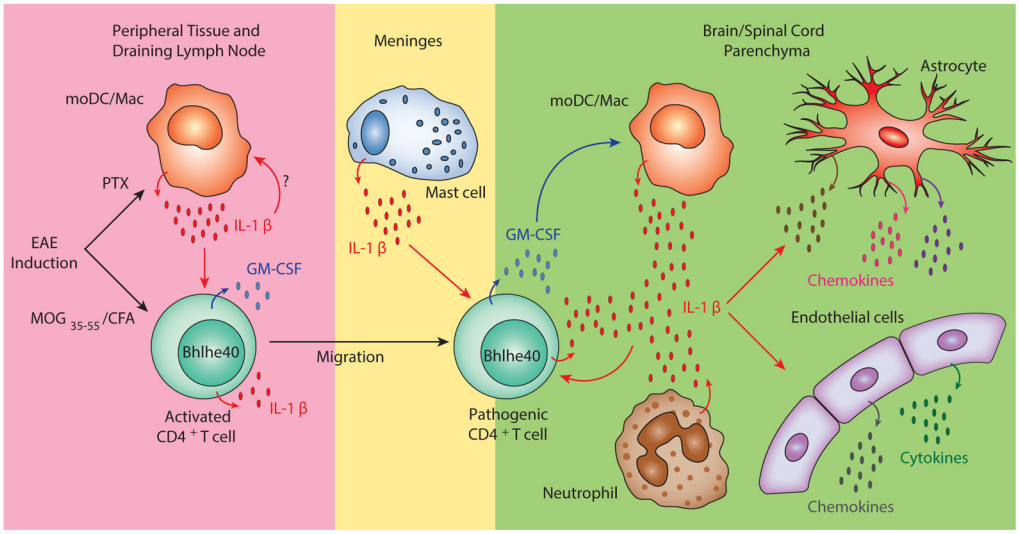

Figure 1. The Cellular Sources of IL-1β and Its Target Cells during EAE

In the EAE model in C57BL/6 mice, animals are immunized with MOG_{35-55}/CFA subcutaneously and treated with pertussis toxin (PTX) systemically. Five to eight days after immunization, IL-1β is primarily produced by $CD11b^{+}Ly6C^{mid\text{-}hi}MHC\ II^{lo\text{-}hi}$ monocyte-derived DC/macrophages (moDCs/Macs) in the peripheral DLNs. Activated $CD4^{+}$ T cells have also been recently appreciated to be cellular sources of IL-1β. Although T cell-derived IL-1β is dispensable for $CD4^{+}$ T cell priming in DLNs before disease onset, IL-1β derived from pathogenic T cells may be important to initiate inflammation within the CNS. IL-1β production from meningeal mast cells has also shown to be critical for EAE susceptibility and $CD4^{+}$ T cell encephalitogenicity. Neutrophils and moDC/Macs also produce IL-1β in the CNS. Multiple cell types respond to IL-1β during EAE. IL-1β enhances Bhlhe40 expression and GM-CSF production by $CD4^{+}$ T cells in both the DLN and the CNS and promotes T cell pathogenicity. Most of the myeloid cell subsets in the DLNs express IL-1R but whether they respond to IL-1β to facilitate disease progression is unclear. In the CNS, IL-1β can stimulate astrocytes to secrete chemokines which may recruit and activate leukocytes. Action of IL-1β on CNS endothelial cells facilitates cytokine production and neutrophil adhesion. Small arrows indicate cytokine or chemokine production. Large red and blue arrows indicate the actions of IL-1β and GM-CSF, respectively.