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Review

How type I interferons shape myeloid cell function in CNS autoimmunity

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RECEIVED JANUARY 30, 2012; REVISED APRIL 30, 2012; ACCEPTED MAY 17, 2012. DOI: 10.1189/jlb.0112043

ABSTRACT

The precise mechanisms underlying the effects of IFN-I in CNS autoimmunity remain poorly understood despite the long-standing use of these cytokines as first-line disease-modifying drugs in the treatment of RRMS, a chronic demyelinating CNS autoimmune disease. Systemic use of IFN-I results in pleiotropic immunomodulation linking the innate and adaptive immune responses. Recent research has demonstrated that in the setting of CNS autoimmunity, IFNs-I have multiple effects on myeloid cell subsets, such as circulating monocytes, granulocytes, DCs, and tissue macrophages, such as microglia. These diverse effects include changes in cell activation, maturation, antigen presentation, and cytokine production, thus influencing T cell differentiation and expansion, as well as the regulation of executive functions, such as apoptosis and phagocytosis. Moreover, current data suggest that the engagement of the IFNAR on myeloid cells changes the activation status of the inflammasome in a cell type-specific manner. Whereas most reports support primarily immune-suppressive effects of IFN-I on myeloid cells, endogenously produced, exogenously induced, and peripherally administered IFNs-I exert complex differential spatial effects during CNS autoimmune inflammation. Clearly characterizing the molecular and cellular basis of these effects promises to yield viable targets for a more directed, localized, cell type-specific IFN-I-based therapeutic approach. This kind of approach would allow for replacing the current treatment strategy in MS of broadly and unselectively altering all immune responses, regardless of their beneficial or detrimental nature. *J. Leukoc. Biol.* 92: 479–488; 2012.

Introduction

IFNs-I are a group of cytokines recognized for their pleiotropic effects, which include antiviral and antitumor activities, as well as numerous immunomodulatory functions in innate and adaptive immunity, often providing an essential link between the two [1]. The various IFNs-I in humans are comprised of the IFN-α family, encoded by more than 13 genes, as well as IFN-ε, IFN-κ, and IFN-ω [1]. The most important subtypes, from an immunological perspective, however, are IFN-α and IFN-β [2]. IFNs-I can be produced by all nucleated cells in response to a variety of stimuli, including viral pathogens and recognition of host danger signals [2]. Under physiological conditions, IFNs-I are constitutively expressed at low levels. But, during CNS inflammation, the production of endogenous IFN-I is locally up-regulated in the brain [3]. All IFNs-I signal through the ubiquitously expressed heterodimeric IFNAR, thereby activating signaling pathways involving JAKs and STAT transcription factors, which ultimately culminate in the downstream transcription of IFN-I-inducible genes [2]. IFN-I has been used for the treatment of MS for two decades, and despite the development of other therapies, IFN-β remains a widely used, first-line disease-modifying drug, especially in RRMS [4]. MS is a chronic neurodegenerative, demyelinating T cell-mediated autoimmune disease of unknown etiology and heterogeneous clinical symptoms and course, characterized by CNS inflammation, resulting in axonal damage with subsequent neurological disability [5]. IFN-β markedly attenuates the clinical course and severity of CNS inflammation in RRMS and EAE, the well-established animal model of MS [6–8]. Accordingly, the deletion of *Ifnb* in mice significantly enhances the severity of EAE and increases the influx of mononuclear cells to the CNS [9]. However, IFN-β treatment exacerbates disease in neuromyelitis optica, a demyelinating CNS autoinflammatory disorder whose clinical manifestations resemble MS but whose IFN signature was recently observed to be similar to lupus erythematodes [10]. Among MS patients, therapeutic responses to IFN-I may also vary greatly, even proving inefficient in some and causing severe, undesirable side-effects in others [11]. Despite their wide-spread clinical use, the mo-

Abbreviations: AIM2=absent in melanoma 2, ASC=apoptosis speck-like protein containing a caspase recruitment domain, EAE=experimental autoimmune encephalomyelitis, FoxP3=forkhead box P3, GITRL=glucocorticoid-induced TNFR ligand, IFNAR=IFN-α/βR, iNKT=invariant NK T cell, mDC=myeloid dendritic cell, MS=multiple sclerosis, NLRP1b/3=nucleotide-binding ATPase oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein, OPN-i= intracellular osteopontin, RLH=retinoic acid-inducible gene I-like helicase, RRMS=relapsing-remitting multiple sclerosis, sIL-1R=soluble IL-1R, Treg=regulatory T cell, TRIF=Toll/IL-1R domain-containing adaptor-inducing IFN-β

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lecular mechanisms underlying the immunomodulatory effects of endogenous and exogenously induced or administered IFN-I remain elusive [12]. Recent reports have implicated myeloid cell subsets as important targets for mediating the immune-suppressive actions of IFN-I in CNS autoimmunity [3, 13, 14]. With the use of a series of cell type-specific IFNAR knockout mice, the distinct, protective effects of IFN-I, produced locally in the CNS during EAE, were shown to be mediated by myeloid cells [3]. Thereby, the impact of IFN-I on these immune cell subsets was diverse but ultimately induced a shift from a proinflammatory to a more regulatory immune environment ameliorating EAE disease severity and course. These findings delineate a crucial function of IFN-I-mediated effects on myeloid cells for promoting protective immunomodulation, which might be exploited selectively using novel therapeutic approaches to avoid the adverse effects of nonspecific immunoregulation. This review will therefore focus on the differential but distinct effects of IFN-I on and mediated by myeloid cells during the course of CNS autoimmunity.

IFNs-I AS MODULATORS OF APCs

DCs and macrophages are considered APCs. These MHC-II-expressing innate immune cells are capable of eliciting an adaptive immune response by T cell priming, which leads to the activation and differentiation of naïve $CD4^+$ T cells into distinct effector or regulatory subsets characterized by their particular cytokine production [15]. Additionally, the expansion and survival of certain T cell lineages are induced by APC-mediated signals [16]. APCs thereby link the innate and adaptive immune response through at least three major functions: antigen cross-representation to T cells, along with costimulatory molecule expression; production of soluble messengers, such as cytokines and chemokines, which influence the developing adaptive response; and in the case of macrophages, phagocytosis [15, 17]. In recent years, DCs and macrophages have been recognized as key regulators of CNS autoimmunity [18]. These APCs are required for the peripheral stimulation and central reactivation of T cells [18]. Thereby, IFNs-I have been shown to be vital in modulating the interaction of DCs and macrophages with the adaptive immune system [19–21].

Antigen presentation

DCs are considered the most effective APCs pivotal for the priming of naïve T cells in the periphery during the initial phase of CNS autoimmunity, and additionally, especially mDCs appear to be regulators of the local immune environment directly in the brain during subsequent stages of the disease [15, 18, 22, 23]. In turn, CNS macrophages (microglia) appear to play a more important role in furthering the secondary activation and expansion of T cells already primed in the periphery, whereas their importance in the priming of naïve T cells during CNS autoimmunity currently remains an object of debate [17, 18, 24].

The nature and effectiveness of naïve T cell priming depend on the APC phenotype, meaning its activation and maturation status, which denotes a stimulus-dependent, functional differentiation [25]. This phenotype may vary considerably within a wide range, from tolerogenic to stimulatory, depending on the signals received [26]. These signals constitute pathogen components or endogenous danger signals, such as IFN-I, which lead to APC activation and maturation [26]. This process in turn coincides with the increase and modulation of the expression of costimulatory molecules that are required for efficient priming [27].

In the case of DCs, IFNs-I appear to preferentially induce a phenotype that prompts Treg responses [19–21, 28] (**Fig. 1**). IFN-β significantly increases the maturation and thus, the antigen-presenting capacity of immature mDCs in vitro, as well as in the blood of MS patients to iNKT cells [19]. iNKT cells present a T cell subset that can exhibit strong immune-suppressive properties when receiving regulatory activation signals and has been shown to ameliorate, prevent, but also exacerbate autoimmune disease in preclinical MS models, depending on the biological context of their interaction with myeloid APCs [7, 29]. In turn, iNKT cells can also influence the immunomodulatory capacity of APCs [30]. DC maturation is thereby associated with the up-regulation of two key costimulatory molecules—CD40 and CD80—and the restriction molecule CD1d for iNKT cells [7, 19]. This alteration in DC phenotype in turn furthers iNKT-cell polarization toward a regulatory phenotype, producing IL-4, IL-5, IL-10, and IFN-γ upon TCR stimulation, and promotes their growth and function [19].

Moreover, IFN-β has been demonstrated to mediate the expansion of the naturally occurring $CD4^+CD25^+FoxP3^+$ regulatory, anergic T cell population in an EAE model [21]. Hereby, IFN-β induces the up-regulation of GITRL on DCs and an associated down-regulation of CTLA-4 on Tregs, making them more susceptible to stimulation. This finding provides a possible mechanistic explanation for the increased quantity of Tregs and marked up-regulation of peripheral $CD14^+$ mononuclear cells observed in MS patients treated with IFN-β [21].

Furthermore, in vitro IFNAR engagement on immature DCs and monocytes from MS patients and healthy controls strongly induces the expression of B7-H1, a costimulatory factor and negative regulator of T cell inflammatory responses [18, 31–33]. In turn, an increased expression of B7-H1 leads to the inhibition of APC-induced autologous and antigen-specific $CD4^+$ T cell activation [20], implicating IFNs-I as regulators of the B7-H1/programmed death-1 pathway in CNS autoimmunity.

In contrast, IFNs-I may also bias DCs toward boosting proinflammatory T cell responses. IFN-I-mediated maturation and activation of human and murine DCs in vitro, in the absence of pathogen-related signals, have been observed to increase the expression of MHC-I and -II and the costimulatory molecules CD40, CD80, CD86, and CD83, which are usually associated with a heightened capacity to promote $CD8^+$ T cell responses [34–37].

In the case of macrophages, much less is known to date about their interactions with and modulation by IFNs-I during CNS autoimmunity regarding their ability to activate and reactivate naïve and primed T cells, respectively. However, a primary innate immune response of macrophages upon IFN-β challenge in vitro is suggested, as numerous genes encoding chemokines, cytokines, costimulatory, and antigen-presenting molecules, as well as macrophage-related activation markers,

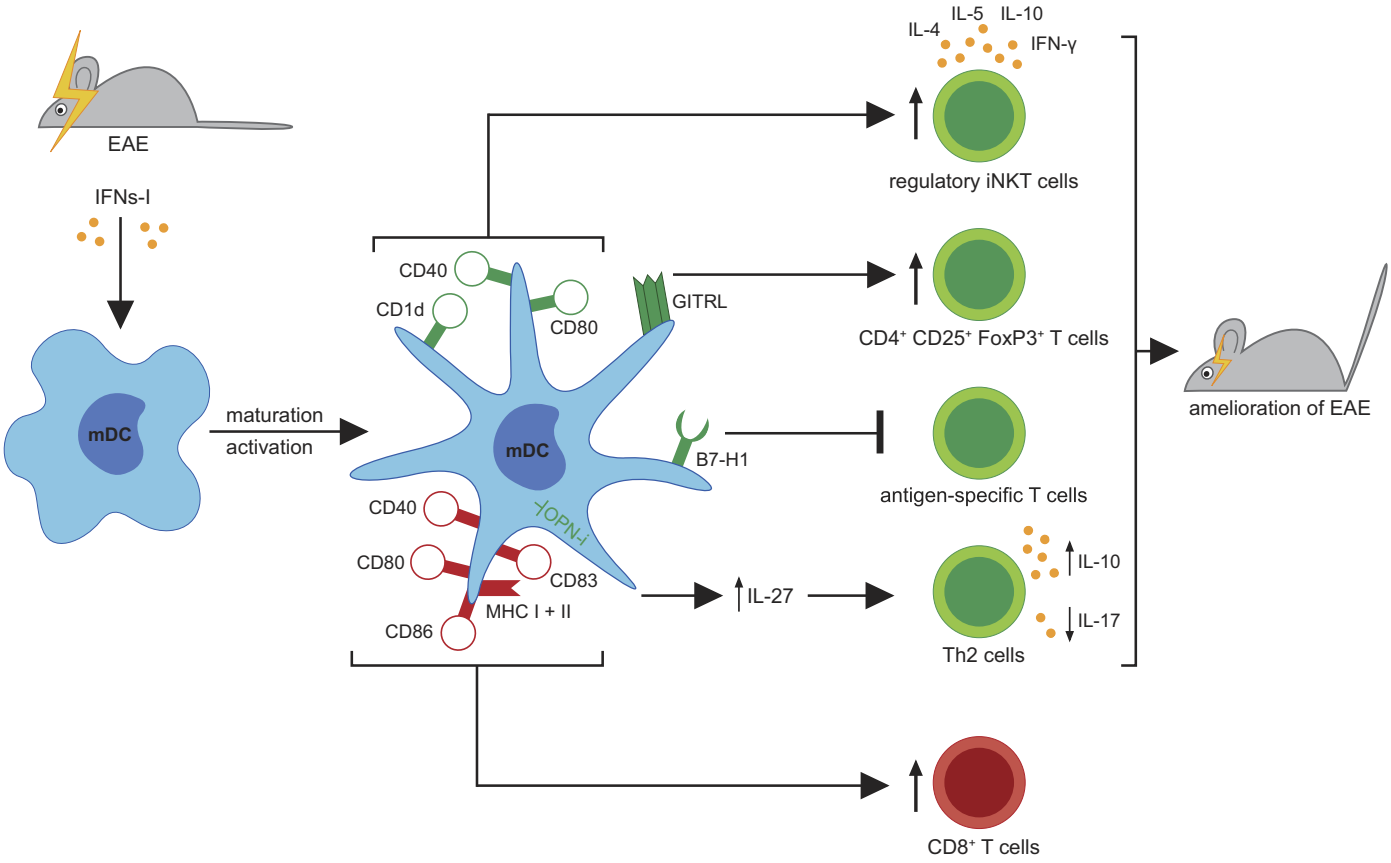

Figure 1. The complex IFN-I-induced effects mediated by mDCs during CNS autoimmunity. During EAE, IFN-I leads to an activation and maturation of resting, immature mDCs. Key costimulatory and surface molecules, such as CD1d, CD40, CD80, GITRL, and B7-H1, are up-regulated in an IFN-I-dependent manner. Additionally, intracellular OPN is inhibited, which allows for a derepression of IL-27 expression. A primarily regulatory myeloid cell-mediated T cell response is thus prompted, whereas proinflammatory, antigen-specific T cell responses are inhibited, ultimately leading to an amelioration of disease. However, an up-regulation of costimulatory molecules, the combined expression of which is usually associated with a heightened $CD8^+$ T cell response, has also been shown.

but no genes representative of a Th cell shift, show a significant change in expression [3]. Furthermore, an altered expression of the chemokines CXCL1 and CXCL2 upon stimulation with LPS and IFN-β of IFNAR-deficient compared with WT macrophages in vitro is observed, indicating an enhanced chemokine response in the absence of IFNAR on this myeloid cell subset [3].

Cytokine and chemokine secretion

DC and macrophage cytokine production substantially influences the expansion and survival of pathogenic T cell populations crucially involved in the pathogenesis of MS and EAE, especially proinflammatory T_H17 cells [38, 39]. In several studies, the inhibition or down-regulation of this T cell subset has led to a marked reduction of disease severity in EAE [40, 41]. The development, expansion, and survival of T_H17 cells are regulated by an intricate network of cytokines [42]. Additionally, a number of cytokines have been implicated in the inhibition of T_H17 cell responses, among these, IL-4 and IFN-γ, which inhibit IL-23-driven T_H17 cell expansion, as well as IL-2, IL-12, IL-10, and IL-27, a cytokine that has notable anti-inflammatory functions and is a potent negative regulator of T_H17 cell development [40, 43].

Whereas IFN-β has been observed to exhibit proinflammatory effects in T_H17-induced inflammation, as it exacerbates T_H17-polarized EAE [14, 44], recent research has demonstrated that IFN-I is able to suppress the T_H17 cell response in CNS autoimmunity [13, 45, 46]. Thereby, IFNAR engagement by IFN-β on DCs and macrophages induces IL-27 production, which subsequently prevents a productive T_H17 response [13]. In vitro and in vivo deficiency of IFNAR or the TRIF, an adaptor that responds to activation of TLRs, leads to enhanced T_H17 cell-mediated disease development with markedly increased CNS inflammation and IL-17A production [13]. IFN-I-mediated IL-27 induction has been shown to involve the inhibition of OPN, a multifunctional cytokine important in chemotaxis, activation, and differentiation of immune cells and critical to the inflammatory processes in MS, EAE, and other autoimmune conditions [47–50]. An increased expression of OPN is found in DCs isolated from MS patients, as well as brain lesions in EAE and MS, and has been shown to promote the survival of autoreactive T cells [16]. In vivo IFN-I inhibits

OPN-i, an isoform of OPN in DCs and microglia, the brain endogenous macrophages, which in turn, suppresses the generation of T_H17 cells through the derepression of IL-27 [45]. As a result, the clinical onset of disease as well as the infiltration of lymphocytes and macrophages into the spinal cord and brain are delayed [45].

The direct suppressive effect on T_H17 cells in vitro and in vivo is most likely mediated by IL-10, which is released by $CD4^+$ T cells in response to the increased production of IL-27 by APCs [44]. The inhibition of OPN and subsequent suppression of IL-17 through engagement of IFNAR on $CD4^+$ T cells, accompanied by a decrease in IL-23 production by $CD14^+$ PBMCs, have also been reported and likely present a synergistic mechanism to the myeloid cell-mediated OPN-i inhibition [48].

The analysis of human blood samples implies that these findings are relevant for our understanding of IFN-I-mediated effects in human CNS autoimmunity [46, 48]. IFN-β-treated MS patients show considerably reduced blood serum levels of OPN [48]. Moreover, in vitro IFNAR engagement on DCs derived from MS patients leads to an increase in IL-12 and IL-27 but a decrease in IL-1β and IL-23 levels [46]. These effects are conveyed by STAT1- and STAT3-mediated pathways, respectively [46]. Additionally, T cells cultured with the supernatants of these IFN-β-stimulated DCs were observed to exhibit a reduced expression of T_H17 cell-related molecules, such as retinoic acid receptor-related orphan receptor c, IL-17A, IL-23, and CCR6, indicating an effective suppression of T_H17 cells [46]. This study also finds IFN-β to directly inhibit T_H17 cell expansion and survival, as evidenced by a down-regulation of the T_H17 molecules and an up-regulation of IL-10 gene expression.

Overall, the expression of IL-27 by DCs and macrophages appears to constitute an important immunoregulatory mechanism to restrict a productive T_H17 immune response. However, there are notably also IFN-β-mediated effects on DCs limiting T_H17 cells that are clearly independent of IL-27 [51]. IFNs-I derived from RLH-stimulated DCs have been shown to inhibit encephalitogenic T_H17- and T_H1-mediated immune responses, even in IL-27-deficient mice [51].

Phagocytosis

Macrophages exhibit properties as tissue phagocytes in innate and adaptive immune defense [17]. During the course of CNS autoimmunity, activated macrophages can be found in the inflamed brain [18]. It has been suggested that IFN-β, produced locally in the CNS during autoimmune inflammation, reduces the activation status of activated macrophages, as characterized by the down-regulation of MHC-II molecules [3, 9]. This effect is associated with a significant decrease in their ability to phagocytose myelin in vitro [3]. Phagocytosis of degraded myelin has been associated with an altered functional macrophage phenotype, resulting in immunoregulatory, thus beneficial, and proinflammatory, thus detrimental, effects in CNS autoimmunity [52]. While myelin-phagocytosing macrophages show an augmented expression of MPOs, which cause neuronal damage [52] and most likely increase the presentation of myelin antigens to autoreactive, encephalitogenic T cells, furthering their reactivation and thus epitope spreading in the CNS [18, 52], in vitro myelin-phagocytosing macrophages have been shown to suppress T cell reactivity by producing NO [53]. Hence, phagocytosis by macrophages most likely fulfills dual functions. However, the effects of macrophage phagocytosis during CNS autoimmunity and especially the effects of IFN-I on this process remain poorly characterized and thus ambiguous.

IFNs-I AS INDUCTORS OF MYELOID CELL-MEDIATED T CELL APOPTOSIS

TRAIL, which exists in a membrane-bound and a soluble form, is a member of the TNF superfamily [54]. TRAIL mediates its activity by interacting with an intricate system of two death receptors (TRAILR1 and TRAILR2) and three decoy receptors (TRAILR3, TRAILR4, and osteoprotegerin), which lack the cytoplasmatic tail necessary to trigger apoptosis. Thus, TRAIL, which is known to be expressed on various cell types, is capable of inducing apoptosis in susceptible cells [54]. TRAIL deficiency is associated with an increased susceptibility to autoimmune diseases in mice [55].

IFN-I has been shown to up-regulate the secretion of soluble and the expression of membrane-bound TRAIL in normal human PBMCs in vitro. In these experiments, the supernatants of the IFN-α or -β-stimulated PBMCs are capable of inducing apoptosis [56, 57]. However, IFN-I is not found to up-regulate TRAIL in T cells. Significant differences in IFN-I-mediated TRAIL induction can also be seen among blood samples from IFN-β treatment responders, nonresponders, and untreated MS patients [58, 59]. Whereas TRAIL mRNA is increased significantly in monocytes from patients clinically responsive to IFN-β, this is not the case in nonresponders. Moreover, the expression of the decoy receptor TRAILR3 on autoreactive T cells is elevated in untreated RRMS patients, whereas IFN-β reverses this effect. Thus, IFN-β may be able to promote the apoptotic elimination of autoreactive T cells by increasing the amount of TRAIL available to activate TRAIL death receptors, while at the same time, reducing the number of TRAIL decoy receptors [59].

When human PBMCs are exposed to IFN-I in vitro, only monocytes and granulocytes respond with an up-regulation of TRAIL expression, thus selectively sensitizing these cells to apoptosis [58]. Furthermore, differential STAT, p38 MAPK, and NF-κB activation in myeloid cells and leukocyte subsets in response to IFN-β is measured in this study. The demonstration of differential cell type-specific, IFN-I-mediated effects offers up a possible mechanistic explanation to, at least in part, explain the difference in responsiveness to IFN-β therapy among MS patients. This notion is underscored by additional reports that the IFN-I pathway appears to be dysregulated selectively in peripheral blood monocytes of MS patients nonresponsive to IFN-β, as evidenced by an altered IFN-I gene signature, increased baseline expression levels of endogenous IFN-β and IFNAR1, as well as the inability of IFN-β to induce its own expression [60, 61].

T cell apoptosis is pivotal in establishing self-tolerance and preventing autoimmunity [38]. Thus, TRAIL signaling in myeloid cells might support the immunoregulatory effects of

IFN-I in CNS autoimmunity by eliminating primary autoreactive, encephalitogenic T cells that are present as a result of a breach in self-tolerance. At the same time, supplementary IFN-I-mediated signaling pathways, leading to selective, cell type-specific apoptosis, are most likely active [62]. Moreover, it remains to be determined whether differential TRAIL expression could help explain the discrepancies in responsiveness to IFN-β treatment among MS patients and might therefore be used as a clinical treatment marker in MS therapy [58].

MODULATION OF THE INFLAMMASOME IN MYELOID CELLS BY IFNs-I

IL-1β and IL-18 are proinflammatory inflammasome-derived cytokines involved in T cell differentiation and activation, including T_H17 cell development in inflammatory conditions [63]. Excessive production of IL-1β and IL-18 is associated with autoinflammatory and autoimmune conditions [63]. These cytokines also appear to play an important role in MS, where they are produced by myeloid cells in and around demyelinating brain lesions [64]. IFN-β, in turn, has been observed to suppress the intracellular production of IL-1β in myeloid cells in vitro and in MS patients [28, 46]. The biologically active forms of IL-1β and IL-18 are generated via caspase-1-dependent maturation within the inflammasome, which is a cytoplasmatic multiprotein complex whose assembly is triggered by sensory proteins [NLRP1, NLRP3, IL-1β-converting enzyme-protease-activating factor (nucleotide-binding oligomerization-like receptor family caspase recruitment domain-containing protein 4), AIM2] in response to certain stimuli, such as pathogens and danger signals [65].

Inflammasome activation is crucial in host defense but has also recently been implicated in the pathogenesis of autoinflammatory and autoimmune disorders [66, 67]. Whereas IFN-I-mediated activation of the inflammasome in macrophages is reported as part of the host defense mechanism during bacterial infection [68], there is evidence that IFN-I limits inflammasome activity and subsequent IL-1 production in autoimmunity and autoinflammation [69]. Thus, IFN-β has been demonstrated to suppress the production of mature IL-1β through the inhibition of inflammasome activation in monocytes in vitro and in vivo, which is achieved via two distinct STAT1-mediated mechanisms [69]. First, STAT1 inhibits the inflammasome sensors NLRP1 and NLRP3, thus inhibiting the caspase-1-dependent cleavage of pro-IL-1β. Second, STAT1 induces the expression of IL-10, which in turn, reduces the levels of pro-IL-1α and -β.

Moreover, an IFN-β-dependent decrease in inflammatory cell recruitment to the site of inflammation is seen during alum-induced, IL-1-dependent peritonitis, in which IFN-β is induced by poly(I:C) [69]. The same study then recapitulates the suppressive effects of IFN-I clinically by the finding that monocytes, isolated from the blood of IFN-β-treated MS patients, produce less IL-1β upon ex vivo stimulation with LPS than those from healthy donors [69]. Additionally, IFN-I inhibits the activation of caspase-1 within the NLRP3 and also AIM2-ASC inflammasomes via the induction of IFN-γ-inducible protein 16 expression, a p200-family protein, in a monocytic cell line in vitro [70]. This observation provides one possible molecular mechanism of IFN-I-mediated anti-inflammasome activity.

Caspase-1-, ASC-, and NLRP3-deficient mice show reduced EAE incidence and disease severity [66, 67, 71]. Caspase-1 deficiency thereby correlates with a defective development of anti-myelin oligodendrocyte glycoprotein IFN-γ-producing T_H1 cells [71], whereas ASC deficiency impairs the peripheral survival of mature $CD4^+$ T cells [67], and NLRP3 deficiency presents with reduced inflammatory infiltrate in the spinal cord and decreased IFN-γ, IL-17, and IL-18 production [66]. Additionally, an IFN-I-mediated inflammasome-independent pathway of IL-1β inhibition in monocytes based on the induction of the sIL-1R antagonist has been described in vitro [72, 73].

IFN-I-mediated alteration of inflammasome and thus, caspase-1 activation appears to require a precise balance. Excessive inflammasome inhibition, which occurs in response to viral exposure, is associated with immune suppression, thereby increasing susceptibility to secondary infections with pathogens such as *Candida albicans* and *Listeria monocytogenes* [69]. On the other hand, inflammasome overactivation may favor an excessive stimulation of the immune system and hence, production of the inflammatory cytokines IL-1β and IL-18, which are associated with several autoimmune conditions [69]. It seems possible that endogenous IFN-I counteracts danger signals that are potentially released during EAE development and would otherwise induce excessive activation of certain inflammasomes. However, which inflammasomes are affected during CNS autoimmunity and might thus be targeted therapeutically remains controversial at present [66, 67]. Nonetheless, these data suggest that the suppression of inflammasome-dependent cytokine maturation and activity, notably the IL-1-inflammasome axis, contributes to the therapeutic efficacy of IFN-β in MS treatment.

THE EFFECTS OF IFNs-I ON MICROGLIA

Microglia are brain endogenous myeloid cells of yolk sac origin and key players of the immune response in the CNS [74–76]. Activated microglia present a characteristic feature in many neuroinflammatory disorders [18, 77, 78]. In fact, these cells become activated early in the process of CNS autoimmune inflammation before the onset of disease symptoms and infiltration of inflammatory cells into the CNS [77]. Moreover, activated microglia are found in actively demyelinating EAE lesions [77, 79]. Indeed, microglia are important modulators of CNS autoimmune disease, as the reduction of these cells by use of the CD11b-herpes simplex virus-thymidine kinase approach represses the development of EAE [80]. Further corroborating this assertion, the inhibition of microglial activity, using minocyclin or microRNA-124, also leads to a marked suppression of the disease [81, 82]. Importantly, there is a significant up-regulation of endogenous IFN-β produced locally in the brain during EAE that is also present before inflammatory cells from the periphery begin to infiltrate [3]. Therefore,

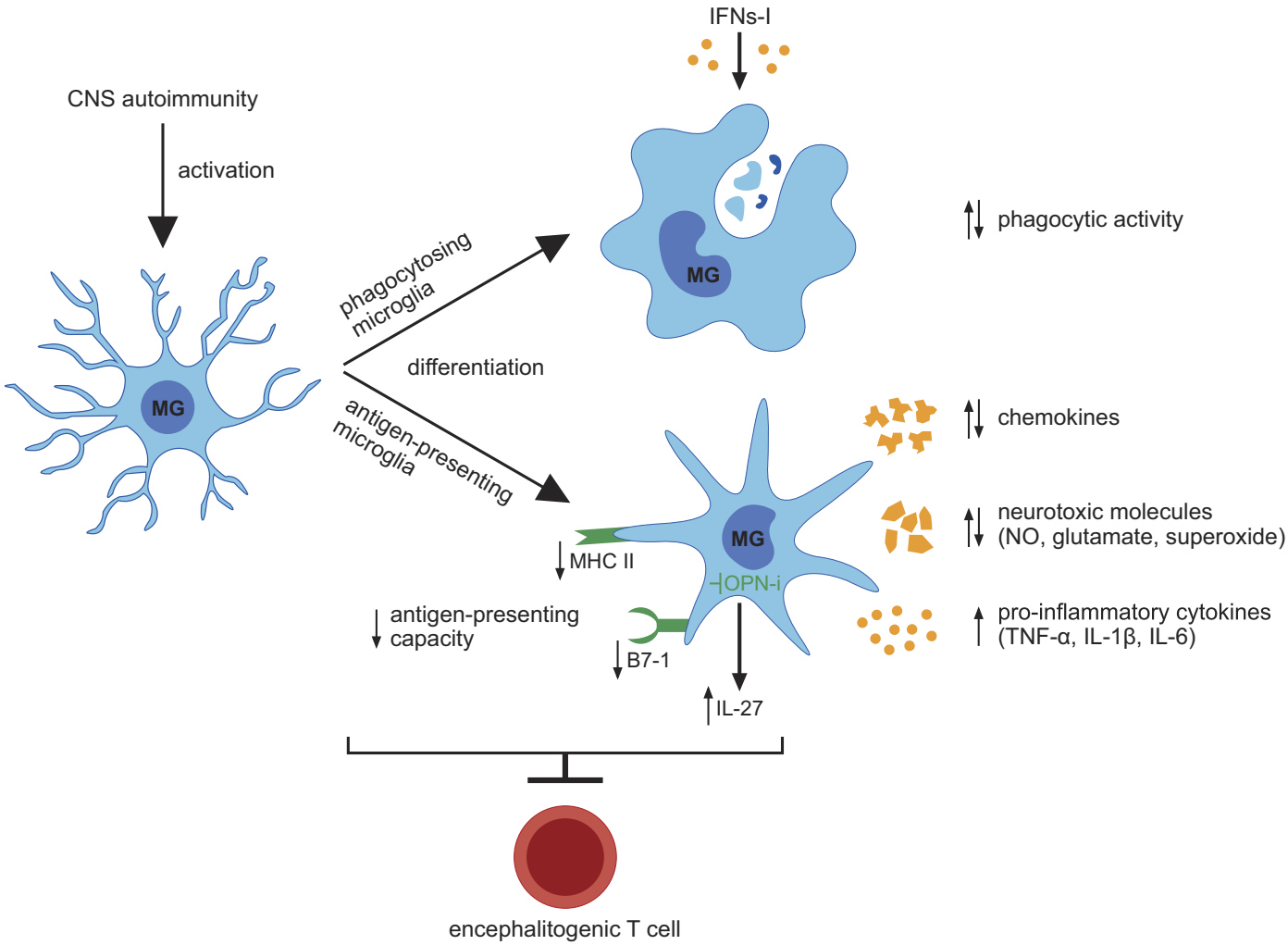

Figure 2. Intricate, differential, microglial-mediated responses to IFNs-I have been described during CNS autoimmunity. The activation of microglia (MG) during CNS autoimmune disease most likely leads to their differentiation into antigen-presenting and phagocytosing microglia, exhibiting distinct effector properties. Whereas IFNs-I have been observed to alter the phagocytic capacity of activated microglia in differing ways, the effects of IFNs-I on APC-like microglia appear to be even more complex. IFN-I reduces the antigen-presenting capacity of microglia, likely through a down-regulation of MHC class II and B7-1 molecules, as well as the inhibition of OPN-i, thus suppressing a productive encephalitogenic T cell response. On the other hand, proinflammatory cytokines are increasingly expressed after IFN-I stimulation. Furthermore, the expression of chemokines, as well as neurotoxic molecules, has been observed to be affected in differing ways.

the modulation of microglia-mediated effects by IFNs-I likely constitutes an important immunomodulatory mechanism in shaping CNS autoimmune disease.

Current research, in fact, points to quite complex, divergent activities of microglia in autoimmunity, mediating protective and detrimental effects on the surrounding tissue. These effects are mediated by activated microglia, which can function as APCs, producers of cytokines and chemokines, and as phagocytes [83]. Hence, when activated, microglia are thought to adopt a proinflammatory phenotype resembling APCs or a more regulatory macrophage-like phenotype exhibiting phagocytic activity [83]. Antigen-presenting microglia thereby appear to contribute primarily to the reactivation of primed rather than the activation of naïve T cells, thus potentially assisting in the progression of relapsing EAE [18, 83].

IFN-β, however, may reduce the antigen-presenting capacity of microglia in vivo, which in turn limits epitope spreading and inhibits the effector function of encephalitogenic T cells [3, 84]. The precise mechanism by which IFN-β decreases the antigen-presenting capacity of microglia remains unknown, although a down-regulation of the expression of MHC-II molecules, which are usually highly up-regulated in activated microglia during EAE, and costimulatory molecules, such as B7-1, has been observed [3, 18, 84, 85]. Whereas IFN-β promotes the IL-27-mediated, OPN-i-dependent suppression of T_H17 cell expansion in EAE in microglia [45], it also up-regulates proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6 in vitro, which might help explain the flu-like symptoms observed as a major adverse effect in IFN-β-based MS therapy [85]. In vitro IFN-I appears to differentially influence the expression of NO,

TABLE 1. Overview of the Major Studies Delineating the Complex Effects of IFN-I on Myeloid Cell Subsets

Myeloid cell subset	Method/model	Species	Effect/finding	Reference
Monocytes, DCs	EAE in IFNAR-deficient mice	Murine	Exacerbated EAE symptoms in IFNAR-deficient mice	[3]
Macrophages, microglia	EAE in IFNAR/TRIF-deficient mice	Murine	Exacerbated EAE symptoms in IFNAR/TRIF-deficient mice	[13]
DCs	PBMC cell culture	Human (HD, MS)	Induction of regulatory iNKT cells	[19]
DCs	EAE in IFNAR-deficient mice PBMCs of MS patients analyzed for GITRL	Murine Human (MS)	Up-regulation of GITRL on DCs → Expansion of regulatory $CD4^+CD25^+FoxP3^+$ T cells	[21]
DCs Macrophages, microglia	EAE in spp1-deficient mice	Murine	Inhibition of OPN-i → derepression of IL-27 → Suppression of T_H17 cell differentiation	[45]
DCs	PBMC cell culture	Human (HD, MS)	Up-regulation of IL-12 and IL-27 and down-regulation of IL-1β and IL-23 → Suppression of T_H17 cell differentiation	[46]
Monocytes, DCs	PBMC cell culture	Human (HD, MS)	Up-regulation of B7-H1 on APCs → Inhibition of antigen-specific T cell differentiation	[20]
Monocytes	PBMC cell culture	Human (HD, MS)	Up-regulation of costimulatory molecules CD80, CD86, and CD40	[27]
Monocytes	Sterile peritonitis/*C. albicans* infection in WT mice PBMC cell culture	Murine Human (HD, MS)	Inhibition of NLRP1 and NLRP3 inflammasomes	[69]
Monocytes	Cell culture of THP-1 monocytic cell line, frozen PBMCs, and purified $CD14^+$ monocytes	Human (HD)	Inhibition of NLRP3 and AIM2-ASC inflammasomes	[70]
Monocytes	PBMC cell culture	Human (HD)	Increased secretion of sIL-1R → inhibition of IL-1β secretion	[73]
Monocytes, granulocytes	PBMCs and granulocyte cell culture	Human (MS)	TRAIL up-regulation → increased apoptosis of monocytes	[56] [57]
Monocytes Granulocytes	Whole blood sample analysis	Human (MS)	Differences in TRAIL induction among responders, nonresponders, and nontreated MS patients	[58]
Monocytes	Whole blood sample analysis	Human (MS)	Decrease of TRAIL decoy receptor expression on T cells and up-regulation of TRAIL → increased apoptosis of autoreactive T cells	[59]
Monocytes	PBMC cell culture Whole blood sample analysis	Human (MS)	IFN-β pathway dysregulation	[61] [60]
Microglia	EAE in IFN-β-deficient mice Primary mixed glial cell culture of B10.RIII mice	Murine	Reduction of antigen-presenting capacity Inhibition of encephalitogenic T_H1 cell effector functions	[84]
Microglia	Microglia and macrophage cell culture of C57BL/6 mice	Murine	Down-regulation of MHC-II and B7-1 molecules Suppression of antigen-specific T_H1 cells Enhanced production of TNF-α, IL-1β, IL-6, and NO	[85]
Microglia	Primary human fetal microglia cell culture	Human (HD)	Modulation of IFN-β signaling cascades Induction of genes encoding for chemokines (RANTES, MIP-1α/β, IFN-inducible protein 10, MCP-1)	[87]
Microglia	Microglia and neuronal cell (co)culture of C57BL/6 mice	Murine	Enhanced production of TNF-α, IL-1β, and NO Repressed production of glutamate and superoxide → Reduction in microglia-induced neuronal cell death	[86]

HD, Healthy donors; spp1, secreted phosphoprotein 1.

while moderately reducing the secretion of neurotoxic glutamate and superoxide, which in turn, decreases the incidence of microglia-mediated neuronal cell death [85, 86]. Additionally, IFNs-I have been observed to alter the expression of chemokines by microglia, thereby potentially influencing the influx of immune cells into the inflamed brain [3, 87].

The phagocytic activity of microglia is affected by IFN-I in differing ways as well. IFN-I increases phagocytosis, especially of apoptotic encephalitogenic T cells in vitro, which is crucial for the safe and efficient resolution of an inflammatory infiltrate [88]. However, in the absence of IFNAR signaling, the phagocytic activity of microglia is also increased in an EAE model, as evidenced by an increased amount of degraded myelin protein found within the cells [3, 88]. While phagocytosis of degraded myelin, apoptotic inflammatory cells, and neuronal debris are conducive to the clearance of inflammation, the effect of microglial phagocytosis on disease progression thus remains elusive [89].

Current data point to various important IFN-I-mediated alterations of microglia functions in CNS autoimmune inflammation (**Fig. 2**), although the significance of these findings is limited due to the fact that most results were obtained in an in vitro setting. The nature of microglia activation by IFN-I is most likely highly context-sensitive, depending on host conditions, disease phase, the distinct, additional activation signals that they receive, and potentially, the type of microglia cell activated.

CONCLUDING REMARKS

Most findings support predominantly protective, immunosuppressive effects of IFNs-I, which are used as disease-modifying drugs in the treatment of MS with varying therapeutic success [4]. Recent research demonstrates distinct in vivo functions of IFNAR engagement on myeloid cell subsets and thus, delineates an important role of myeloid cell-mediated IFN-I effects in limiting CNS autoimmune disease [3]. These effects make use of different cell type-specific mechanisms to shape the innate and adaptive immune responses in a chiefly regulatory manner (**Table 1**). It has remained difficult, however, to assess the differential effects of IFNs-I on brain endogenous versus CNS-infiltrating myeloid cells during CNS autoimmunity, as not all peripheral myeloid cells can be readily distinguished from activated brain endogenous ones using the currently available diagnostic tools, which is largely due to the marked plasticity of CNS-endogenous microglia. Yet, considerable and striking differences in the mechanisms by which IFNs-I suppress CNS autoimmunity have emerged. IFN-β, produced locally in the CNS during autoimmune inflammation, elicits effects distinct from IFN-β induced or administered in the periphery. Thus, CNS endogenous IFN-β has been shown to suppress autoimmunity by inhibiting macrophage activation without altering the nature of the T cell response [3], whereas increased IFN-β in the circulation, which can be induced by RLHs, limits EAE by inhibiting T_H1/T_H17 expansion via DC stimulation [51]. These differential regulatory effects are likely a result of the specific regional distribution of immune cells and distinct temporal immune cell-mediated actions and effector functions in MS and EAE. Thus, the location and mode of IFN-I induction or administration define the impact of these cytokines on the immune response. Inducing endogenous IFN-β production, for example, via RLH ligands [51], could therefore present a promising therapeutic approach by providing the possibility of eliciting local, compartmentalized, and cell type-specific IFN-I responses. This approach would allow for selectively targeting certain immune cell subsets that are actually involved in disease pathogenesis and are differentially, spatially distributed within the body. Thus, one could avoid administering a suppressive, sweeping blow directed at all immune responses, irrespective of their immunomodulatory nature, causing a great deal of collateral damage, as is the current prevalent treatment strategy for MS and many other autoimmune diseases.

OUTLOOK

Despite considerable advances made in the field of CNS autoimmunity, important questions regarding the complex differential interactions of IFNs-I and the various components of the peripheral and central immune system, such as myeloid cells, remain to be answered. IFNs-I all signal through the heterodimeric IFNAR, which is assembled identically on all cells. The effects of IFNAR engagement by IFNs-I, however, vary greatly among different cell types and even among cells of the same subset, depending on their functional and activation state and also on the neighboring microenvironment. Deciphering how these cell type-specific, differential immunomodulatory responses to IFNs-I are achieved poses one of the current outstanding challenges in IFN research. This knowledge would ultimately not only permit a highly selective modulation of IFN-I-mediated immune responses but also provide a novel appreciation of basic immunoregulatory mechanisms, the understanding of which, at least in part, will most likely be transferable to other regulatory mechanisms in immune system disorders.

AUTHORSHIP

S.M.B. and M.P. contributed to the preparation of this manuscript.

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KEY WORDS:
MS · EAE · microglia · inflammasome · TRAIL