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EDITED BY  
Nancy Monson,  
University of Texas Southwestern  
Medical Center, United States

REVIEWED BY  
Jessica L. Williams,  
Cleveland Clinic, United States  
Horea Rus,  
University of Maryland, United States

\*CORRESPONDENCE  
Clio P. Mavragani  
kmauragan@med.uoa.gr

†These authors have contributed  
equally to this work

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# The role of type I IFN in autoimmune and autoinflammatory diseases with CNS involvement

Sylvia Raftopoulou<sup>1†</sup>, Anna Rapti<sup>1†</sup>, Dimitris Karathanasis<sup>2†</sup>,  
Maria Eleftheria Evangelopoulos<sup>2†</sup> and Clio P. Mavragani<sup>1\*†</sup>

<sup>1</sup>Department of Physiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece, <sup>2</sup>First Department of Neurology, National and Kapodistrian University of Athens, Aeginition Hospital, Athens, Greece

Type I interferons (IFNs) are major mediators of innate immunity, with well-known antiviral, antiproliferative, and immunomodulatory properties. A growing body of evidence suggests the involvement of type I IFNs in the pathogenesis of central nervous system (CNS) manifestations in the setting of chronic autoimmune and autoinflammatory disorders, while IFN- $\beta$  has been for years, a well-established therapeutic modality for multiple sclerosis (MS). In the present review, we summarize the current evidence on the mechanisms of type I IFN production by CNS cellular populations as well as its local effects on the CNS. Additionally, the beneficial effects of IFN- $\beta$  in the pathophysiology of MS are discussed, along with the contributory role of type I IFNs in the pathogenesis of neuropsychiatric lupus erythematosus and type I interferonopathies.

## KEYWORDS

type I IFN, central nervous system, multiple sclerosis, neuropsychiatric lupus (NPSLE), type I interferonopathies

## Introduction

Interferons (IFNs) are a group of functionally related cytokines of innate immunity with antiviral, antimicrobial, and immunomodulatory activities (1). Three major types of IFNs are recognized: type I, type II, and type III (2). Type I IFNs were first recognized by Isaacs and Lindenmann in 1957 (3) and since then, a growing body of evidence supports a central role for type I IFNs in antiviral immune responses and in the pathogenesis of various autoimmune diseases (4). Type I IFNs are partitioned into several subclasses (IFN- $\alpha$ ,  $\beta$ ,  $\delta$ ,  $\omega$ ,  $\epsilon$ ,  $\tau$ ,  $\zeta$ ,  $\lambda$ , and  $\kappa$ ) with the subgroup of IFN- $\alpha$  being further divided into 13 subtypes which are encoded by 13 homologous genes, located on chromosome 9 (9p22-9p21) (5). Upon viral infection, almost all cells secrete type I IFNs (typically IFN- $\alpha$  and IFN- $\beta$ ) with IFN- $\alpha$  being secreted primarily by plasmacytoid dendritic cells (pDCs), whereas epithelial cells, phagocytes, DCs, and fibroblasts can secrete IFN- $\beta$  (1).

Physiologically, membrane-bound or cytoplasmic pattern-recognition receptors (PRRs) are responsible for detecting microbial products such as lipopolysaccharide (LPS) and endogenous or exogenous nucleic acids (6). In pDCs, upon stimulation of the

endosomal PRRs such as the toll-like receptors (TLR)-7/8/9 the myeloid differentiation factor 88 (MyD88) is activated, forming a complex with interleukin-1 (IL-1) receptor-associated kinase 1 (IRAK1) and IRAK4 which in turn phosphorylates the interferon regulatory factor 5 (IRF5) and IRF7 acting as transcription factors for IFN- $\alpha$  production (7–9). In other cell populations such as fibroblasts, macrophages, and epithelial cells, cytosolic PRRs such as RIG1-like receptors (retinoic acid-inducible gene 1) and MDA5 (melanoma differentiation association protein 5) sense RNA, while cGAS (cyclic GMP-AMP synthase) is able to detect DNA, leading to the activation of stimulator of interferon genes (STING) and type I IFN- $\beta$  production (4, 10).

Upon their secretion, type I IFNs bind to the IFN- $\alpha/\beta$  receptor (IFN-AR), a cell surface receptor consisting of two subunits, IFNAR and IFNAR1 leading to the intracellular autophosphorylation and activation of the Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and the subsequent phosphorylation of signal transducer and activator of transcription 1 (STAT1) and STAT2. Ultimately, STAT1 and STAT2 form a heterodimer that binds to IRF9 leading to the formation of IFN-stimulated gene factor 3 (ISGF3), which in turn translocates to the nucleus and stimulates the upregulation of a plethora of interferon-stimulated genes (ISGs) (8). ISGs products are involved in controlling pathogens, while they are also found to be upregulated in many systemic autoimmune diseases (11). Given the magnitude of type I IFNs implication in health and disease, we sought to examine in this review, the complex relationship of type I IFNs and the central nervous system (CNS) under physiological conditions and in selected autoimmune and autoinflammatory diseases with CNS involvement such as multiple sclerosis (MS), neuropsychiatric systemic lupus erythematosus (NPSLE), and type I interferonopathies.

## Type I IFN in CNS: An overview

It is of utmost importance that the CNS, similarly to any tissue, is protected against exogenous or endogenous threats such as pathogens and tumors by a well-functioning immune system. Importantly, infection of the CNS is a major challenge since neurons constitute an irreplaceable cell population that should be maintained despite potential insults (12). To minimize neuronal damage as a result of an infection, the communication between peripheral blood and CNS is restricted by the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB) to prevent the entry of noxious stimuli in the brain (13, 14).

Type I IFNs have been implicated in various processes within the CNS, including the prevention of viral invasion. Endogenously produced type I IFN has been shown to confer neuroprotection by preventing viral entry in the CNS through

IFNAR-mediated regulation of BBB permeability (15, 16). Indeed, mice deficient for IFNAR were more susceptible to CNS infections when exposed to neurotropic viruses, compared to wild-type mice (17). Nevertheless, when CNS infections do occur, they are followed by type I IFN production, as these cytokines are involved in the first-line defense against infection in the periphery but also the CNS (18). These findings stress the highly protective and antiviral role type I IFNs have in the CNS.

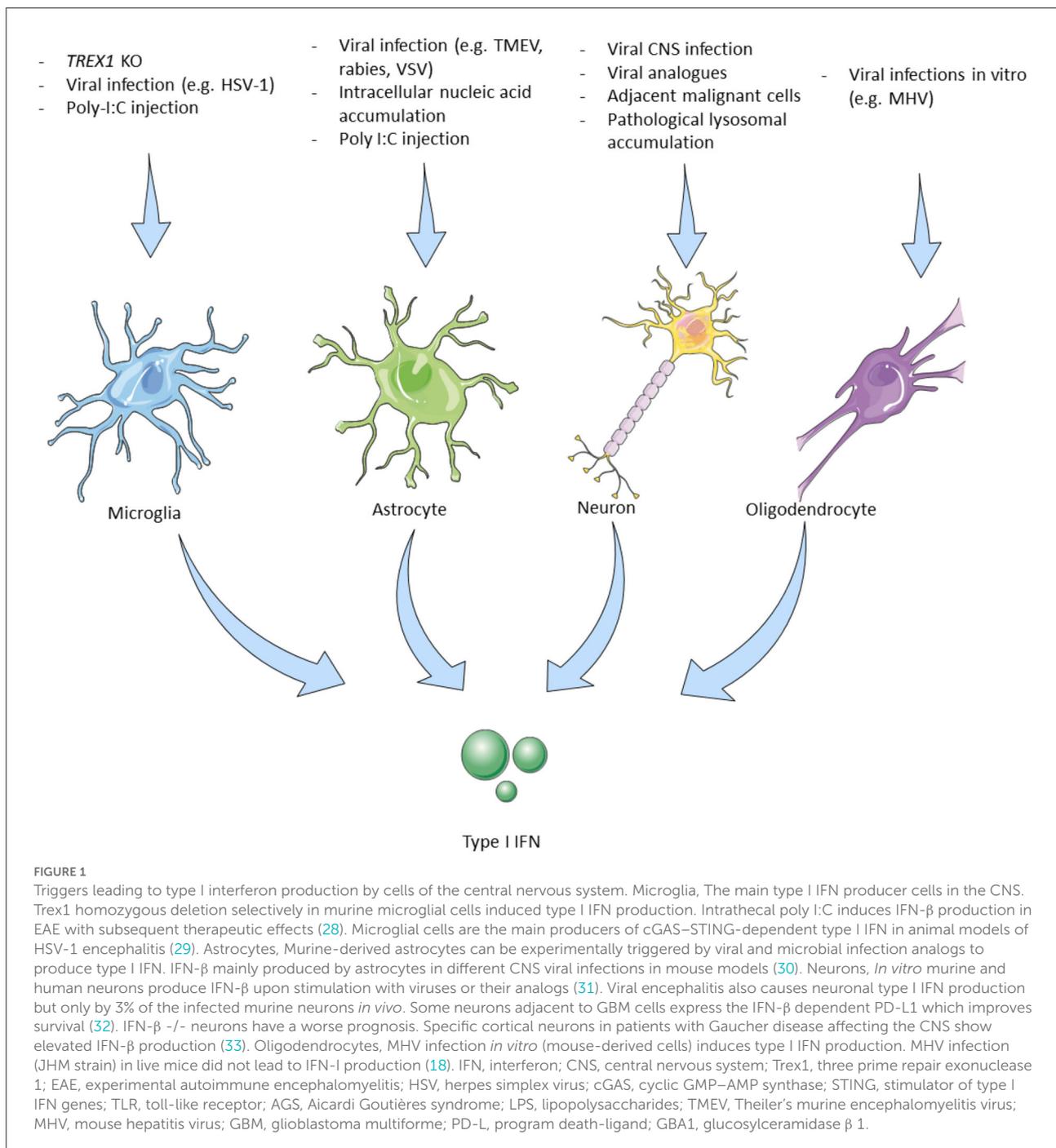
Beyond their antiviral properties, the type I IFN/IFNAR axis seems to play a key role CNS homeostasis and normal brain function suggested by the fact that mice deficient in IFNAR present defects in neuronal autophagy, cognitive function, and synaptic plasticity (19–22). In contrast, other reports suggested that induction of type I IFN signaling in the CNS hinders the vascular repair process following traumatic brain injury or cerebrovascular injury which is further associated with BBB leakage and failure to restore cognitive–motor function (23). Moreover, the overexpression of IFN- $\beta$  in the CNS of adult wild-type mice transforms the microglial transcriptional signature to induce a process similar to aging leading to impaired cognitive performance (24). Along the same lines, neuronal type I IFN expression was shown to be modulated by alpha-synuclein, a protein expressed predominantly in neurons, in association with neurodegenerative diseases such as Parkinson's disease (25). Taken together, these findings highlight the complex role of type I IFN in CNS pathophysiology.

## CNS cellular populations involved in type I IFN production

Plasmacytoid dendritic cells are the professional type I IFN-producing cells in the periphery, as they produce large amounts of IFN- $\alpha$  upon their activation by dedicating 60% of new transcriptional activity to make type I IFNs (26). However, it is reported that under physiological conditions, pDCs are absent from the brain, due to the CNS being an immune-privileged site (27). Even though the CNS lacks access to professional producers of type I IFN, these cytokines are still detected in the CNS, suggesting the ability of CNS cell populations to locally produce and respond to type I IFNs. In the following sections, we summarize the potential of CNS cells to locally produce type I IFNs under physiological conditions or upon stimulation (summarized in Figure 1).

## Microglia

Microglia are the resident immune cells of the brain that undergo rapid change states in response to their environment (34) and are one of the main type I IFN-producing cells in the CNS. In response to nucleic acid accumulation, either



due to a 3' prime exonuclease 1 (*Trex1*) gene deletion—which physiologically degrades dsDNA, ssDNA, and ssRNA (28)—or due to infection with the neurotropic herpes simplex virus 1 (HSV-1) in microglial cells (29), the cGAS-STING pathway is activated, resulting in type I IFN production. Kocur *et al.* studying the role of microglia in experimental autoimmune encephalomyelitis (EAE), the murine model of MS, demonstrated that a subpopulation of activated microglial cells

produces the largest amount of IFN- $\beta$  in EAE (35). Another experimental proof for the role of microglial cells as type I IFN-producing cells came by Khorrooshi *et al.*, they demonstrated that intrathecal injection of polyinosinic–polycytidylic acid (poly I:C) (a double-stranded RNA analog and TLR3 agonist and therefore a potent inducer of IFN- $\beta$ ), in mice with EAE, led to increased IFN- $\beta$  expression by parenchymal microglial cells and also had a disease remission effect (36) (Figure 1—Microglia).

## Astrocytes

Astrocytes are specialized glial cells that have a regulatory role within the brain and are implicated in processes such as neurogenesis and synaptogenesis, while they are also responsible for maintaining BBB permeability and controlling extracellular homeostasis (37). They express TLR3 and are also important producers of type I IFN in the CNS (18, 30). Murine astrocytes produce type I IFN upon stimulation with polyribonucleotide, cycloheximide, actinomycin D, and poly I:C (38, 39). Studying different neurotropic viruses in mice including rabies virus, Theiler's murine encephalomyelitis virus, and vesicular stomatitis virus, Pfefferkorn and colleagues showed that although these viruses mainly infect and reproduce in neurons, astrocytes are the main producers of IFN- $\beta$  in response to these infections. They also suggested that transiently infected astrocytes produce the majority of IFN- $\beta$  and that this production is mediated by the TLR and RIG-I-like receptors (RLR) signaling cascade (40). In mice infected with La Cross virus, astrocytes were also the major IFN- $\beta$  producing cells (41) (Figure 1—Astrocytes).

## Oligodendrocytes

Oligodendrocytes are primarily responsible for the maintenance and generation of the myelin sheath that surrounds axons. The precursors of oligodendrocytes have to undergo a well-orchestrated process of proliferation, migration, and differentiation to produce the myelin sheath of axons (42). They reportedly express TLR2 and TLR3, while their ability to produce type I IFN is rather conflicting (18, 43). Li et al. showed that MHV-infected oligodendrocytes express IFN- $\alpha/\beta$  via RIG-I activation *in vitro* (44). On the contrary, overexpression of MDA5, RIG-1, and TLR3 following MHV infection in the JHM strain *in vivo* did not result in type I IFN production, while poly I:C stimulation was not able to induce type I IFN production (43) (Figure 1—Oligodendrocytes).

## Neurons

Neurons, the fundamental units of the nervous system, have also been implicated in the production of type I IFN upon stimulation with various triggers, while they express TLR3, similarly to microglial cells and oligodendrocytes (18, 30). *In vitro* studies demonstrated that murine and human neurons stimulated with poly I:C or viruses (Sendai, rabies viruses), produced IFN- $\beta$ , (45, 46). In experimental mice, CNS infection with several viruses (Theiler's virus, La Crosse virus encephalitis) led to type I IFN production (31), while rabies virus, although capable of diminishing the type I IFN response by inhibiting the IRF3 pathway, still triggers the small amount of type I IFN

production by infected neurons (47). Although IFN- $\beta$  is shown to downregulate both IFN $\gamma$ -producing Th1 cells and IL-17-producing Th17 cells, a paradoxical disease exacerbation was witnessed after IFN- $\beta$  administration in a Th17-induced EAE murine model (48, 49).

Of interest, a study in patients with glioblastoma multiform (GBM) showed that in some cases neurons adjacent to the tumor express the IFN- $\beta$  induced programmed death-ligand (PD-L)-1, which in turn induces caspase-dependent apoptosis of malignant cells in association with better survival. In accordance with these findings, the deletion of IFN- $\beta$  in neurons of mice with experimental glioblastoma also led to worst outcomes (32). Finally, in a mouse model of Gaucher disease, a genetic lysosomal storage disease caused by acid- $\beta$ -glucosidase (glucocerebrosidase) deficiency, it was shown that specific cortical neurons (along with microglia) demonstrated increased IFN- $\beta$  production (33) (Figure 1—Neurons).

## Type I IFN in the CNS: Association with clinical phenotypes

### Multiple sclerosis

Multiple sclerosis is the prototype CNS autoimmune demyelinating disease. Its pathophysiology has been extensively studied but many pathways remain to be elucidated. Although traditionally considered a predominantly T-cell-mediated inflammation, recent advances, including the high effectiveness of B-cell depletion therapies, have unraveled the importance of humoral immunity as well (50). Innate immunity has recently attracted research interest, especially in progressive forms of the disease with potential therapies expected in the future (51, 52). Regarding type I IFN, it has long been implicated in the pathophysiology of MS mainly because of its protective role, with IFN- $\beta$  being the oldest approved treatment for relapsing-remitting MS (RRMS) (53). There are currently four IFN- $\beta$  approved drugs for the treatment of relapsing forms of MS, three of which are administered subcutaneously (SC), IFN $\beta$ -1b, IFN- $\beta$ -1a, and most recently peginterferon  $\beta$ -1a, one intramuscularly: IFN- $\beta$ -1a (54). Treatment with IFN- $\beta$  confers a decrease of approximately 30% in the annualized relapse rate (ARR) (55). On the contrary, administration of IFN- $\gamma$  to patients with MS exacerbates the disease and results in increased numbers of relapses (56). Major advancements in the understanding of MS, and the efficacy of IFN- $\beta$  as a treatment for the disease, came from studying the EAE model (57). Importantly, EAE has greatly facilitated the understanding of the role that type I IFN plays in the CNS under the MS setting. Although the exact mechanisms through which IFN- $\beta$  exerts its beneficial role have not been fully elucidated, there are some experimental data pointing to this direction.

For example, it was shown that IFN- $\beta$  production within the CNS coincides with the peak of EAE (36) and seems to positively affect the clinical course of the disease, as also implied by the detrimental clinical effects of IFNAR gene ablation in EAE (58, 59). The beneficial IFN- $\beta$  effect on the CNS was further highlighted as IFN- $\beta$  producing microglia mediate the clearance of myelin debris *via* phagocytosis (36). This IFN- $\beta$ -mediated elimination of damaged myelin sheath residues leads to a late-stage suppression of proinflammatory mediators, possibly contributing to favorable results in terms of neuroinflammation control (60) (Figure 2).

Furthermore, with respect to neurons, IFN- $\beta$  potently induces nerve growth factor (NGF) production in IFN- $\beta$ -treated astrocyte cultures (72), and in endothelial cells interacting with IFN- $\beta$ -treated lymphocytes *in vivo* and *in vitro* (61). IFN- $\beta$  further induces brain-derived neurotrophic factor (BDNF) production in PBMCs from patients with RRMS after 6 months of IFN- $\beta$  treatment, who show clinical remission for at least 1 year of follow-up (62). However, in these settings, whether these factors act directly on neuronal cells to promote repair or proliferation, remains to be elucidated (61). Moreover, IFN- $\beta$  was shown to directly promote human neural progenitor cells (NPCs) proliferation and differentiation *in vitro*, in a dose-dependent manner (73) (Figure 2).

IFN- $\beta$  treatment in patients with MS also induces B-cell activation factor (BAFF) and drives B cells toward a regulatory phenotype (63). BAFF blockade with atacicept, in the setting of RRMS led to disease exacerbation, which further proves the unexpected protective effect of IFN- $\beta$ -induced BAFF induction (74). Surprisingly, the previously identified risk allele for both MS and SLE of TNFSF13B (GCTGT>A) is linked to increased numbers of circulating B cells and drastically increased levels of soluble BAFF, as well as increased antibody production (75). Furthermore, IFN- $\beta$  has been shown to inhibit T-cell proliferation (64), while it induces immune cell apoptosis (76). Recombinant IFN- $\beta$  administered to patients with RRMS is associated with increased proliferation of CD56<sup>bright</sup> natural killer (NK) cells, Foxp3<sup>+</sup> regulatory T cells (Treg), as well as FoxA1<sup>+</sup> Treg cells, favoring Th2 over Th1 responses (60, 61, 72) (Figure 2).

In addition, IFN- $\beta$  treatment in patients with MS leads to increased levels of soluble vascular cell adhesion molecule-1 (VCAM-1), which subsequently leads to a significant decrease in VLA-4 expression on lymphocytes, interfering with their capacity to bind endothelial cells thereby preventing their diapedesis through the BBB (68). Finally, IFN- $\beta$  further prevents the erosion of the BBB by reducing matrix metalloproteinase 9 (MMP-9) levels (69) or by increasing counter-acting tissue inhibitor of matrix metalloproteinase (TIMP-1) levels (63, 74) (Figure 2).

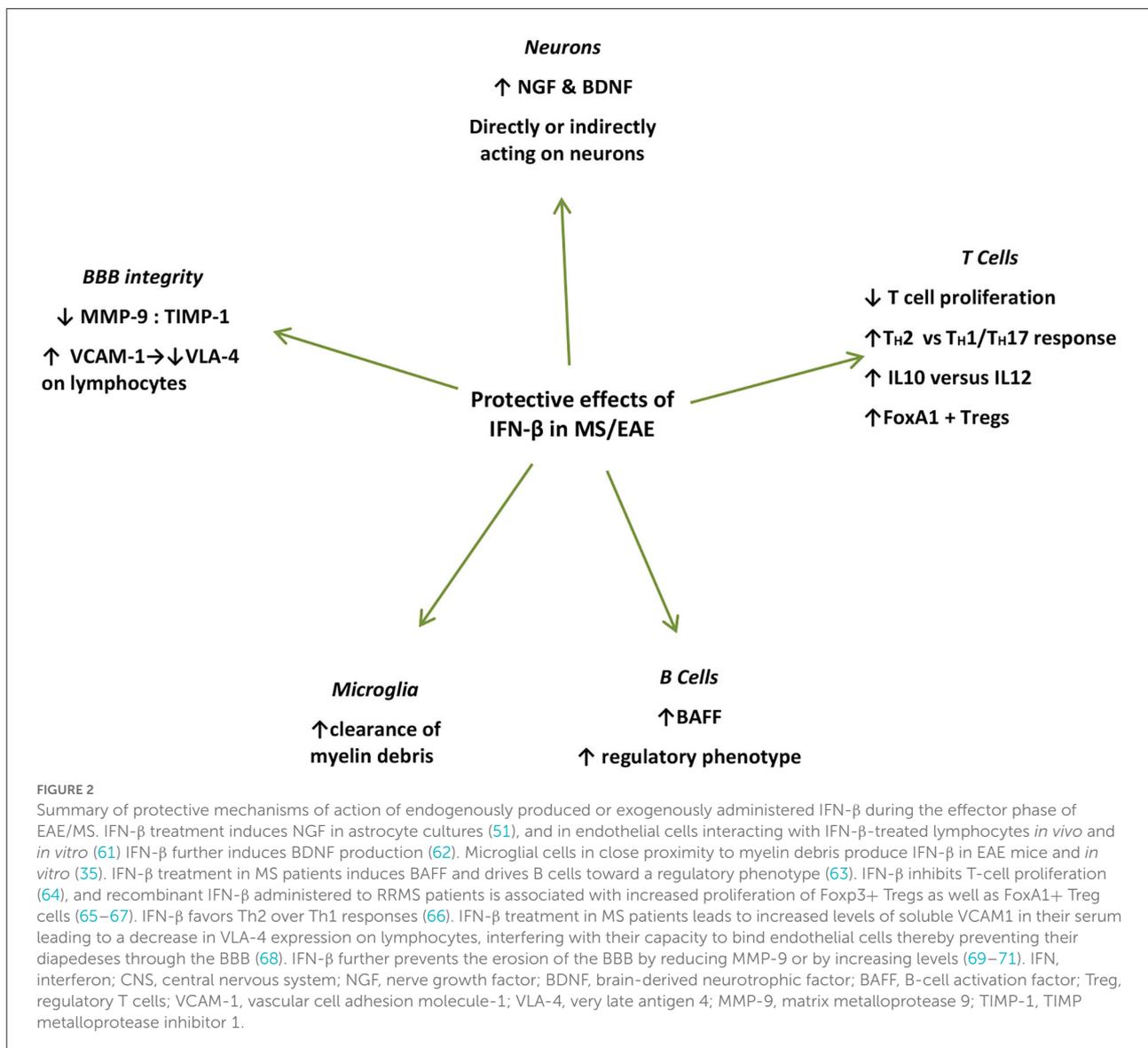
While the aforementioned evidence supports the therapeutic role of type I IFN in the context of neuroinflammation, conflicting data have also emerged to shine the light on

some less favorable aspects of this cytokine effect on CNS. For instance, pDCs, the professional type I IFN-producers in the periphery, promote the priming of encephalitogenic T cells during the induction phase of EAE, partially implicating IFN- $\alpha/\beta$  (77). Despite MS/EAE being traditionally perceived as mainly IFN $\gamma$ -mediated, deletion of a negative regulator of IFN- $\alpha/\beta$ , c, in myeloid cells of EAE mice, resulted in uncontrolled type I IFN signaling and white matter microglia activation due to prolonged STAT1 phosphorylation, leading to disease exacerbation (78). Importantly, IFN-I-induced STAT1 is key for priming cellular responses to type II IFN signals (79). Communication between type I and II IFN pathways is constant and their disequilibrium in terms of excessiveness or timing could be rendered as a key contributor to CNS autoimmunity in the context of EAE/MS (80). Interestingly, our group investigated the interferon signature in patients originally presented with MS-like CNS manifestation. A subset of these patients was shown to meet classification criteria for a systemic autoimmune disease (e.g., Sjogren's syndrome, SLE). These patients displayed higher expression of type I IFN-stimulated genes in peripheral blood, compared to the patients who received a final diagnosis of MS or cerebral small vessel disease and so this distinct group may be of potential therapeutic benefit from type I IFN blockade (81).

## Neuropsychiatric lupus erythematosus

SLE is a heterogeneous autoimmune disease with multisystemic presentations and a wide range of clinical and serological manifestations (82). NPSLE is a term used to collectively describe the symptoms of neurological and psychiatric nature present in 80% of patients with SLE (83). These symptoms affect the CNS and peripheral nervous system (PNS) and can range from localized or isolated to diffuse manifestations, while they can also vary in severity. The diagnosis of NPSLE can be challenging due to the lack of disease-specific clinical and laboratory criteria (84). Moreover, the pathogenesis of NPSLE has not been well characterized so far, mainly due to the heterogeneity in the clinical characteristics of patients with NPSLE. However, it is believed that BBB disruption may play a key role here, similarly to MS, whereby immune cells and autoantibodies eventually enter the CNS, possibly promoting neuroinflammation (85). On a genetic basis, a single-nucleotide polymorphism (rs11797) on the *TREX1* gene has been associated with NPSLE as it discriminates patients with NPSLE from patients with SLE without CNS involvement (86).

It is reported that 50–75% of adult patients with SLE have elevated production of type I IFN, giving rise to an increased IFN signature (87), while patients with active SLE benefit from the treatment with anifrolumab, a human monoclonal antibody against type I IFN receptor subunit 1, blocking the activation of



type I IFNs (88). However, NPSLE was an exclusion criterion for the clinical trials of anifrolumab (89), possibly due to the lack of evidence that associates NPSLE and the IFN signature. However, there are several studies and animal models of NPSLE that relate the IFN signature to NPSLE.

Among the first groups to hypothesize that type I IFN plays a role in NPSLE pathology was that of Shiozawa in 1992 who demonstrated that IFN- $\alpha$  in CSF of patients with NPSLE was higher compared to those with SLE alone. Moreover, IFN- $\alpha$  levels in the CSF from patients with NPSLE were found to be higher compared to serum IFN- $\alpha$ , suggesting that type I IFN synthesized in the brain may be implicated in the neuropsychiatric manifestations of SLE. Moreover, upon brain autopsy in one of the patients with NPSLE, neuron localization of IFN- $\alpha$  protein and mRNA was detected (90). In addition,

Santer *et al.* used a bioassay using pDCs to demonstrate that NPSLE CSF induced significantly higher IFN- $\alpha$  compared with CSF from patients with MS or other autoimmune disease controls (91). Recently, IFN- $\alpha$  was shown to have a moderate correlation ( $\rho = 0.33$ ;  $p = 0.05$ ) with NPSLE at the onset of neuropsychiatric manifestations (92). However, the exact implication of type I IFN in NPSLE pathophysiology remains to be elucidated.

Numerous animal models have been developed in an effort to study NPSLE and characterize its pathology; however, none is a true depiction of the disease due to its heterogeneous nature [reviewed in (93)]. The Pristane-induced lupus (PIL) model more closely resembles the human NPSLE manifestations. Upon pristane injection, mice develop lipogranulomas containing mononuclear cells and DCs

allowing the initiation of the inflammatory response. The model is characterized by a strong IFN signature, autoantibody production, glomerulonephritis, arthritis, and anemia. Among the neuropsychiatric manifestations in this model are learning and memory deficits as well as decreased locomotion (80, 81). The spontaneous NZB/NZW F1 mouse NPSLE model is characterized by splenomegaly, glomerulonephritis, haemolytic anemia, and lymphadenopathy, while learning and memory deficits are among its neuropsychiatric manifestations. Similarly to other models, NZB/NZW F1 mice are characterized by elevated production of IL-6, IFN- $\gamma$ , and TNF- $\alpha$ , as well as antinuclear antibodies and anti-dsDNA, while their IFN signature is weak (94). Finally, the spontaneous MRL/lpr model shares some similarities with the aforementioned models with the neuropsychiatric manifestations such as depression, anhedonia, apathy, and anxiety being more pronounced here (94). Of interest, the intraperitoneal injection of captopril, an angiotensin-converting enzyme (ACE) inhibitor, in MRL/lpr mice reduced the ISGs expression in the brain and the periphery as well as IFN- $\alpha$  levels in the plasma. Of interest, microglial activation in the brain was also dampened. After short-term oral captopril treatment, there was a decrease in the depressive-like behavior responses in MRL/lpr mice, highlighting the potential therapeutic benefits of ACE inhibitors in treating NPSLE (95).

## Type I interferonopathies with CNS involvement

Autoinflammatory diseases result from immune system dysfunction and mainly affect the innate immune system. This differentiates them from autoimmune diseases such as MS and NPSLE, which are traditionally attributed to a malfunctioning adaptive immune system. Clinically, most autoinflammatory diseases are characterized by symptoms of systemic inflammation. Most significantly, type I interferonopathies that fall under the umbrella of autoinflammatory diseases are characterized by the significant involvement of the CNS, in relation to type I IFN as it will be discussed later.

A strong link between autoinflammatory diseases and the CNS can be seen in type I interferonopathies. The prototypic mendelian disease that demonstrated the potential harm of interferon in humans was firstly described by J. Aicardi and F. Goutières in 1984. They reported a progressive familial encephalopathy in infancy (96), characterized by dysregulated type I IFN pathway and accompanied by IFN- $\alpha$ -producing astrocytes that have neurotoxic effects in the CNS, as subsequently highlighted by the Campbell group (97). Type I interferonopathies are triggered by host nucleic acids, due to the failure of the innate immune system to distinguish self

from non-self. Technological advancements have enabled the understanding of type I interferonopathies at least on a genetic basis, and it is now suggested that 38 Mendelian genotypes can be classified as type I interferonopathies (98). The genetic background of interferonopathies with neuroinflammatory manifestations has been greatly investigated. However, the way in which type I interferonopathies present neurological manifestations and whether type I IFNs are directly implicated in this process is greatly understudied. Apart from AGS, for the interferonopathies that were most recently described, there is very little evidence around the origin of type I IFN induction.

Collectively, the dysregulation of type I IFN that eventually leads to interferonopathies may be a consequence of variable mechanisms that are summarized here and are mainly found in the periphery. As seen in AGS, monogenic SLE, trichohepatoenteric syndrome, and X-linked reticulate pigmentary disorder, the accumulation of endogenous nucleic acids in the cytosol that trigger aberrant type I IFN production, result from loss-of-function mutations in genes encoding for enzymes targeting nucleic acid degradation. Furthermore, AGS and monogenic SLE are characterized by alterations in the intracytosolic nucleic acid sensor, which in turn leads to a lowered threshold for IFN production, a mechanism also observed in Singleton–Merten syndrome. Other interferonopathies such as STING-associated vasculopathy with onset in infancy are triggered by a gain of function mutation of positive IFN signaling regulators, leading to continuous activation of the IFN pathway (99).

Diagnostic testing for type I interferonopathies is a novel concept that has not yet reached standard clinical practice. However, the assessment of type I IFN signature has been shown to define a spectrum of inflammatory diseases, related to aberrant type I IFN signaling (100). In addition, IFN- $\alpha$  can be measured through digital enzyme-linked immunosorbent assay technology (98).

Generally, type I IFN is involved in microglial function by regulating the balance between physiological clearance of debris and aberrant phagocytosis. A dysregulation of this balance can lead to neurodegeneration (101). Fetal nervous tissues appear to be more prone to IFN insult, particularly during developmental processes such as neurogenesis and myelination (102). As a consequence, neurological involvement, such as psychomotor retardation and intracerebral calcifications, seen in some interferonopathies such as AGS are reported early on during the disease onset (100). Interestingly, a group of organisms causing congenital fetal infections (toxoplasma, rubella, CMV, and HSV), collectively termed TORCH, also cause intracranial calcifications in neonatal periods, reminiscent of the ones found in interferonopathies (103). We will discuss here the genetic background and immunopathology of interferonopathies with neurological involvement (summarized in Table 1).

TABLE 1 Genetic background and immunopathology of interferonopathies with neuroinflammatory manifestations.

Interferonopathy	Associated genes	Immunopathology	Clinical manifestations
Aicardi–Goutières syndrome	<i>TREX1 RNASEH2B RNASEH2C RNASEH2A SAMHD1 ADAR IFIH1 LSM11 RNU7-1 USP18 STAT2</i>	Dysregulated nucleic acid sensing resulting in immune activation and aberrant type I IFN production.	Encephalopathy, intracranial calcifications, cerebral atrophy (104).
ISG15 deficiency	<i>ISG15</i>	Deficiency in <i>ISG15</i> leads to upregulated type I IFN and downregulated type II IFN signaling.	Cerebral calcifications, susceptibility to mycobacterial infection (105).
DNase II deficiency	<i>DNASE2</i>	Lack of DNase endonuclease activity results in aberrant sensing of self-DNA resulting in aberrant type I IFN induction.	Anemia, glomerulonephritis, liver fibrosis, cerebral calcifications, white matter (106).
Spondyloenchondrodysplasia (SPENCD)	<i>ACP5</i>	Deficiency in <i>ACP5</i> results in upregulated type I IFN response	Bone lesions, autoimmune thrombocytopenia, SLE, vasculitis, cerebral calcifications, developmental delay (107)
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE).	<i>PSMB8</i>	Immuno-proteosomal dysfunction possibly leads to the accumulation of misfolded or damaged proteins resulting in type I IFN induction.	Recurrent fever, rashes, arthralgia, progressive lipodystrophy, cerebral calcifications (108)

## Aicardi–goutières syndrome

AGS is characterized by basal ganglia calcifications, CSF lymphocytosis, as well as increased levels of type I IFN in the CSF (109). There are seven AGS genetic subgroups (AGS1-7), based on the mutations found in the following genes: 3′-5′ DNA exonuclease-*TREX1*, *RNASEH2B*, *RNASEH2C*, and *RNASEH2A*, SAM and HD domain-containing deoxynucleoside triphosphate triphosphohydrolase *1-SAMHD1*, and adenosine deaminase acting on RNA *1-ADAR1*, as well as on the RNA sensor IFN-induced helicase C domain-containing protein *1-IFIH1* (101, 110). Mutations in *TREX1* and the genes encoding the RNASEH2 complex led to the hypothesis that these proteins are involved in nucleic acid ‘debris’ clearance and their dysfunction could result in the failure of such clearance thereby leading to an innate immune response that would physiologically be induced by viral nucleic acids (93, 111). Deficiency in *TREX1* results in the accumulation of intracellular ssDNA. As demonstrated by Stetson and colleagues, *Trex1*-null mice experience the activation of the TLR-independent cytosolic pathway by ssDNA, resulting in type I IFN production (112). However, the question still remains regarding the source of IFN in the CNS.

As mentioned, astrocytes and microglia are key producers of IFN- $\alpha$  within the CNS when responding to viral infection or synthetic poly I:C treatment. Post-mortem studies of patients with AGS revealed co-localization of the GFAP astrocyte marker and IFN- $\alpha$  along with the cytokine CXCL10 (113). What are more, investigations led by Campbell’s group utilizing a transgenic mouse model expressing IFN- $\alpha$  in astrocytes

specifically (GFAP-IFN), resulted in mice developing a clinical phenotype that overlapped with AGS individuals but lacked the genetic basis of AGS. Importantly, these transgenic mice developed encephalopathy, seizures, and calcium deposits in the basal ganglia, clinical characteristics matching AGS (97). In favor of this theory is the *in vitro* model of astrocytes exposed to poly I:C that exhibits an innate immune response with elevated cytokines such as IFN- $\alpha$  (114). Specifically, when treated with IFN- $\alpha$  for 3 weeks, these astrocytes showed reduced proliferation along with downregulation of genes and proteins crucial for white matter maintenance. In addition, withdrawal from IFN- $\alpha$  for 7 days did not rescue or revert the aforementioned effect (114). This evidence can collectively support the idea of IFN- $\alpha$ -producing astrocytes as a probable mediator in the pathogenesis of AGS.

In terms of clinical characteristics and in the context of early-onset AGS, delay in psychomotor development and liver anomalies are present since birth whereas in the context of later-onset AGS, after a small window of normal development, cognitive and developmental delay become evident (115). Neuroimaging greatly facilitates the diagnosis of AGS, in which brain atrophy, white matter hyperintensities (WMH), and intracranial calcifications are present (116). Extra-neurological symptoms are also prominent in patients with AGS with the skin being most commonly (35%) involved in the form of chilblain-like lesions localized in fingers and toes. In addition, thrombocytopenia, hepatosplenomegaly, psoriasis, and interstitial lung disease (ILD) can also manifest in the context of AGS (101). Taking into account that patients with

AGS have increased IFN- $\alpha$  in CSF and peripheral blood, Rice and colleagues proposed in 2013 that the interferon signature could facilitate the diagnosis of AGS, as a possible biomarker. Indeed, the upregulation in expressions of *IFI27*, *IFI44*, *IFIT1*, *ISG15*, *RSAD2*, and *SIGLEC1* was confirmed in the peripheral blood of patients with AGS (98, 99).

## ISG15 deficiency

*ISG15* deficiency is a moderately severe interferonopathy. *ISG15* is an intracellular IFN- $\alpha/\beta$  inducible ubiquitin-like modifier which covalently binds other proteins, a process called ISGylation. Through a loss-of-function mutation, *ISG* deficiency in humans leads to increased type I IFN signaling and decreased type II IFN signaling. Zhang and colleagues demonstrated that patients with *ISG15*-deficient displayed clinical signs of enhanced IFN- $\alpha/\beta$  immunity as seen in AGS and spondyloenchondrodysplasia (SPENCD) such as cerebral calcifications (nearly 100% of patients with *ISG15*) and sporadic reports of seizures. It was further shown by the same group that the absence of intracellular *ISG15* prevents the accumulation of USP18 thereby sustaining the effect of IFN- $\alpha/\beta$  inflammation (105, 117). *ISG15* also acts as an extracellular inducer of type II IFN and, therefore, its deficiency is subsequently associated with increased susceptibility to mycobacterial disease (117). It was later shown that myeloid cells (monocytes and DCs) were the primary responders to IFN-I-mediated inflammation in the peripheral blood of patients with *ISG15* deficiency (118). However, the role of CNS cells in mediating the type I IFN inflammation in the context of *ISG* deficiency remains to be elucidated.

## DNase II deficiency

Deoxyribonuclease (DNase) II is a lysosomal endonuclease that facilitates the degradation of extracellular DNA debris generated by homeostatic erythropoiesis and apoptosis (119). DNase II deficient mice accumulate a lethal amount of undigested DNA in the lysosomes of macrophages which chronically induces type I IFN production resulting in lethal perinatal anemia (106). DNase II deficiency is a distinct clinical entity of autoinflammation and elevated type I IFN signaling. Neurological manifestations include once more cerebral calcifications and WMH (117).

## Spondyloenchondrodysplasia

Spondyloenchondrodysplasia (SPENCD) is a rare autosomal recessive skeletal dysplasia that manifests itself through vertebral dysplasia and enchondroma-like radiolucent metaphyseal lesions of the long bones, while affected individuals are presented with short-trunked short stature (107). Among

other clinical manifestations, neurological involvement such as intracranial calcification and immune dysregulation manifesting through autoimmune diseases or immunodeficiency are also present (120). Loss-of-function mutations in the *ACP5* gene (117) which encodes tartrate-resistant acid phosphatase (TRAP) was identified as the genetic cause of SPENCD. As a consequence, the deficit in TRAP leads to elevated levels of phosphorylated osteopontin, which in turn results in dysregulated endochondral ossification but also increased type I IFN signature (120). However, very little is known regarding the induction of type I IFN signature in SPENCD and specifically the way it affects the CNS.

## Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is an autoinflammatory disorder characterized by recurrent fevers, purpuric annular plaques, acral pernio-like lesions, periorbital violaceous oedema, lipodystrophy, arthralgias, anemia, and elevated inflammatory markers (121). Similarly to other interferonopathies, cerebral calcifications and rarely aseptic meningitis have also been reported. In addition, the elevated type I IFN signature found in patients with CANDLE may be a key mediator of the inflammatory response and serve as a therapeutic target (108). CANDLE is now classified under the subcategory of interferonopathies called proteasome-related autoinflammation (PRAAS1) and is called PRAAS1 (117). The ubiquitin-proteasome system (UPS) is involved in various cellular functions such as misfolded protein clearance, MHC class I antigen processing, and others (122). Particularly, the loss-of-function mutation in proteasome 20S subunit beta 8 (PSMB8) (117), associated with PRAAS1, results in autoinflammation dominated by a prominent type I IFN gene signature due to impaired proteasome activity and perturbing protein homeostasis. However, the exact mechanism is not fully understood (108).

## Discussion

Since their discovery in 1957, interferons have been implicated in numerous pathophysiological conditions while they have also paved the way for many therapeutic interventions. Here, we summarized the implication of type I IFN in autoimmune and autoinflammatory diseases affecting the CNS. In the past decade, substantial evidence has aided our understanding of the way type I IFN signaling may protect the CNS against viral infection. More importantly, great progress has been made in elucidating how dysregulations in this pathway can lead to neurological diseases. A plethora of observations supports the protective effect of type I IFN in the context of

MS and its murine disease analog EAE. On the other hand, NPSLE and type I interferonopathies highlight the detrimental effects of type I IFN on several organ systems, including the CNS, for patients affected by these diseases. Taking everything into account, we conclude that a disproportionate enhancement in type I IFN signaling can lead to autoinflammatory CNS manifestations, whereas peripherally administered type I IFN- $\beta$  can be beneficial at least for a subset of patients with MS.

## Author contributions

CM and ME conceived, designed, and supervised the review. SR, AR, and DK drafted the manuscript. CM and SR edited the manuscript. All authors critically reviewed the manuscript and agreed to its published version.

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## Conflict of interest

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