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Review

Interferon in the CNS

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Key Words
Interferon • brain • CNS • homeostasis • virus in brain • developing brain • brain inflammation • blood-brain-barrier • cognitive and psychological functions and degeneration

Abstract
While the role of interferon during systemic disease is well known and its immune modulating functions and its role in antiviral activity were extensively studied, the role of IFN-I in the brain is less clear. Here we summarize the most important literature on IFN in homeostasis of the CNS and induction of an IFN response during viral infection in the brain. Furthermore, we present work on the roles of IFN in the developing brain as well as during inflammation in the brain. Lastly, we aim to enlighten the functions of IFN on the blood-brain barrier as well as circulation and in cognitive and psychological functions and degeneration. In short, CNS astrocytes produce IFN-β, which is of high relevance for homeostasis in the brain. IFN-β regulates phagocytic removal of myelin debris by microglia. IFN-I limits the permeability of the blood-brain barrier. Disruption of the blood-brain barrier facilitates entrance of peripheral lymphocytes and inflammation. Viral infections during vulnerable phases of embryonic development cause severe fetal pathology and debilitating impairments to human infants. The roles of IFN in these scenarios are diverse and include deficits due to overproduction of IFN during the developmental stage of the brain as seems to be the case in pseudo-TORCH2.

Introduction

Interferons: Interferons are cytokines, which play an essential role in the anti-pathogenic control and immune modulation. Interferons are separated in three groups, type I, type II and type III interferons. Type III interferon (IFN-λ, IL-28/29), is an essential component of the innate immune response. It plays an important role in the antiviral, antifungal and antiprotozoal defenses in the mucosa [1, 2]. Genome wide association screens revealed an important role of IFN-λ in the control of hepatitis C virus [3]. Type II interferon is defined of Interferon gamma (IFN-γ), a cytokine, which acts mainly on specialized immune cells (i.e. macrophages). Type I interferons (IFN-I: α, β, δ, ε, ζ, κ, ν, τ, ω) are a group of different IFN-α genes and the IFN-β gene. Although they all bind to the same receptor, IFN-α receptor chain 1 (IFNAR1), the induced signal can be very different depending on the kinetic and affinity of the different Interferon-α subtypes [4]. The major function of IFN-I is the direct antiviral

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activity against a broad range of viruses [5]. Beside this, IFN-I is an important activator of the innate and adaptive immune system. However, IFN-I can also induce inhibitory signals (i.e. IL-10 and PD-1L) and thereby dampen the immune activation [6].

Interferon induction: Upon viral infections, usually a type I interferon (IFN-I) response is induced. Pattern recognition receptors (PRRs) located at the cell surface, in the cytoplasm and in the endosomes recognize foreign nucleic acids and non-nucleic-acid pathogen-associated molecular patterns (PAMPs). Most important inducers of IFN-I are Toll like receptors 3, 4, 7, 8, and 9, and the cytosolic PRR, MDA-5, Cardif and cGAS [7-9]. A complex network of downstream signaling molecules including the transcription factors of the IFN regulatory factor (IRF) family leads to transcription of IFN-α and IFN-β. They bind to the cytosolic IFNAR receptor and cause transcription of IFN-stimulated genes (ISG), thereby limiting viral life cycle in infected cells and causing an anti-viral state in bystander cells [10].

Antiviral activity: Almost all nucleated cells can respond to IFN-I. Upon IFN-I signaling several antivirally active genes are induced. One of the first active ISGs is the myxovirus resistance (Mx) protein, targeting incoming capsids prior to replication in case of Mx1 or preventing nuclear entry of HIV-1 in case of Mx2, both ultimately causing nucleocapsid degradation [11]. Active at the stage of viral translation, 2, 5-oligoadenylate synthetase (OAS) activates RNase L, which degrades viral RNA [12, 13]. Proteinkinase R (PKR) phosphorylates eukaryotic initiation factor 2 (eIF2α) which limits translation of cellular and viral proteins [14]. Replication of retro- and some DNA viruses can be blocked by sterile alpha motif and HD-domain containing protein 1 (SAMHD1), which decreases the cell dNTP pool. The last step in the viral life cycle is escape from the cell. The ISG Tetherin traps virions of many enveloped viruses by anchoring them to the host cell.

Systemic autoimmunity: Beside its importance in the control of pathogens, IFN-I plays various roles during autoimmune diseases. In systemic lupus erythematosus (SLE) elevated levels of IFN-I are well recognized and are thought to contribute to pathogenesis [15]. Since long a role of interferon was described in type I diabetes [16]. In animal models onset of diabetes could be inhibited by blocking interferon gamma [17]. Also type I interferon can accelerate onset of type I diabetes [18-20]. Such hyperactivation of the immune response can be induced by strong activation of pattern recognition receptors [21]. In fact, a mutation in IFIH1 (Interferon Induced With Helicase C Domain 1) coding for MDA5, a sensor of viral nucleic acids and important inducer of type I interferon, is associated with increased onset of type I diabetes [22, 23] or SLE [24].

Interferons in central nervous system (CNS) homeostasis: First evidence for constitutively expressed type I IFN in the healthy brain was provided by Goldmann *et al.* [25] in a mouse model, showing that *Usp18* deficient microglia failed to downregulate IFN induced genes, resulting in a hyperactive IFN-I state. Low level IFN-β production enhances activation of microglia and phagocytosis of myelin debris and apoptotic cells in the CNS, thereby diminishing inflammation. Endogenous production of IFN-β by microglia was also shown in a myelin oligodendrocyte glycoprotein - experimental autoimmune encephalomyelitis (MOG-EAE) model were microglia was apparent in inflamed lesions associated with myelin debris [26]. On the other hand, complete absence of IFN-β was accompanied with neurodegeneration [27]. These data implicate that fine-tuning of IFN signaling is important not only during infection but also for brain homeostasis.

Interferon induction and viruses in the brain

Microglia are resident macrophages in the CNS and play an important role in physiological and immunological processes in the brain. Furthermore, they are the main producers of IFN-I in the CNS following HSV-1 infection [28]. Astrocytes respond to a variety of neurotropic viruses; i.e. Rabies virus, vesicular stomatitis virus and Theiler's murine encephalomyelitis virus, with IFN-β production [29]. In fact, astrocytes were shown to express TLR3, which leads to production of IFN-I via phosphorylation of IRF3 [30]. In line, infection of the brain

with a Rabies virus leads to fast induction of IFN-I [31]. In an animal model of simian and human immunodeficiency viruses (SIV and HIV respectively) infection, IFN-α production can be detected in the brain [32]. In a mouse model of La Crosse virus (LACV) infection, where IFN-β producing cells could be visualized, it was seen that both, microglia and astrocytes were able to produce IFN-β [33]. Studies on human cerebral organoids (COs), containing a variety of developing neurons revealed that LACV is capable of infecting neurons, which increases apoptosis in the cell cultures [34]. Responses in cells varied, depending on developmental stage, revealing that committed neurons, expressing lower levels of IFN-stimulated genes (ISGs) underwent apoptosis at a higher rate. Therefore, neuronal maturation increases the susceptibility of neurons to LACV-induced apoptosis, due to lower responsiveness to virus-induced IFN [34].

Upon brain infection of the lentiviruses, human and feline immunodeficiency viruses (HIV-1 and FIV, respectively), neuronal injury, inflammation, and neurobehavioral abnormalities can occur [35]. In a separate study, it was shown that interferon-induced genes act on the human brain microvascular endothelial cells. This might at least partially explain blood-brain barrier dysfunctions during HIV infection [36]. Transcriptomic network analyses showed a preponderance of genes involved in IFN-I signaling, which was verified by increased expression of the IFN-I-associated genes, Mx1 and CD317, in brains from HIV-infected patients [35]. *In vivo* studies of animals infected with the FIV strains, FIV(ch) or FIV(ncsu), revealed that FIV(ch)-infected animals displayed deficits in memory and motor speed compared with the FIV(ncsu)- and mock-infected groups [35].

Also reovirus infection can induce IFN-I in the brain [37]. Following intracranial (i.c.) inoculation with either serotype 3 (T3) or serotype 1 (T1) reovirus, increased expression of IFN-α, IFN-β, and myxovirus-resistance protein 1 (Mx1; a prototypical IFN-stimulated gene) in mouse brain tissue [37]. Lack of this IFN-I response accelerated lethality of mice, suggesting a protective role of IFN-I in the brain [37]. In line, the coronavirus mouse hepatitis virus (MHV) induced IFN-β in the brain, which was important for control of the infection [38]. MDA5 sensing of ssRNA was required for recognition of MHV and induction of IFN-I in microglia [38].

Interferon accumulation in the developing brain

Dependent on the stage of pregnancy certain infections, known as TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) and other viral infections, like parvovirus B19, Varicella and Zika virus severely affect the fetus. Beside a number of other symptoms, CNS abnormalities like microcephaly, hydrocephalus, and cerebral calcification are common.

Zika virus has recently received attention, as it causes severe fetal pathology and debilitating impairments to human infants, including fetal death, brain lesions, *in utero* growth restriction, and microcephaly [39, 40]. A recent study used porcine animal models and found in animals with no birth defects high IFN-α blood plasma levels one month after birth, while affected offspring showed dramatic IFN-α shutdown during social stress [41]. They therefore concluded that fetal Zika virus infection altered type I IFN response and molecular brain pathology, which persists after birth in offspring in the absence of congenital Zika syndrome [41].

Neural crest cell (NCC) migration is mandatory for normal cerebral cortex development and mutations in the DCX (double cortex X-linked) gene, results in abnormal neuronal migration resulting in microcephaly and developmental delay [42]. Recently Pallocca *et al.* [43] have shown in a migration inhibition of neural crest (MINC) assay, that prolonged exposure to IFN-β affects migration of NCC at low pM concentrations. Thus, congenital exposure to IFN-β during a vulnerable stage of development contributes to a variety of CNS abnormalities as described in TORCH infection. A genetic disease described as Pseudo-TORCH 2 (PTORCH2) underscores this assumption. PTORCH2 is characterized by homozygous truncating mutations in the USP18 gene in one family [44] or compound heterozygous

mutations observed in another family [45] leading to complete absence of the USP18 protein and impaired regulation of IFN-I expression. Patients presented with a variety of neurological symptoms including microcephaly, calcification, thrombocytopenia and others. Similarly, USP18 deficient mice show neuropathological symptoms and hydrocephalus [46]. Aicardi-Goutières syndrome (AGS 1-7) is a group of inflammatory diseases with a variety of severe neurological symptoms, elevated IFN-α activity in the cerebrospinal fluid (CSF) and blood and increased IFN-stimulated gene (ISG) signatures in peripheral blood, in the absence of infection [47]. Therefore, these diseases are also known as interferonopathies. Mutations in genes encoding proteins involved in nucleotide sensing or nucleotide metabolism are related to one of the seven AGS phenotypes: TREX1 (AGS1), RNASEH2A (AGS2), RNASEH2B (AGS3), RNASEH2C (AGS4), SAMHD1 (AGS5), ADAR1 (AGS6) and IFIH1 (AGS7). Impaired nucleotide metabolism which may interfere with self- and non-self-nucleic acid discrimination together with enhanced proinflammatory IFN-I and ISGs may explain why certain autoimmune diseases occur in patients with AGS, as for instance systemic lupus erythematosus (SLE) in AGS1, AGS6 and AGS7 or Diabetes type 1 (T1D) in AGS1 and AGS3. Additionally, certain mutations in IFIH1 predispose to SLE or T1D [48].

Interferons in modulating inflammation in the brain

Recent findings have revealed distinct roles for IFN-I and IFN-γ in the recruitment of immune cells to the CNS and highlighted the importance of this process for brain maintenance and protection and/or repair [49]. Interferon therapy is one treatment option for multiple sclerosis. The benefits of IFN-β therapy were demonstrated in several studies. In a three-year, open-label study, IFN-β-1a significantly slowed the progression of whole-brain and gray matter atrophy, and of T1-hypointense LV accumulation, when compared with the control group [50]. While the precise molecular mechanism of IFN-I therapy in MS patients remains to be shown, several studies suggest, that it might be related to modification of the blood-brain barrier [51]. IFN-β therapy was further shown to act via JAK-STAT pathway [52], and phosphorylation was proposed as a marker of disease activity since it is upregulated in peripheral blood mononuclear cells (PBMC) during active phases of the disease [53]. Additionally, IFN-ß therapy non-responders showed a greater activation in the JAK-STAT signaling pathway with elevated IFNAR1 and pSTAT1 levels in monocytes [53].

In another autoimmune disease, namely systemic lupus erythematosus (SLE), IFN-I is believed to be a hallmark of disease and high levels of IFNs as well as IFN-stimulated genes (ISGs) persist chronically in patients [54]. Upregulation of ISGs is often due to IFN-γ, which is upregulated in some SLE patient groups [55, 56]. However, the IFN signature in SLE patients is quite complex and IFN-α is the most abundant in SLE patients [54], while also the IFN-Is IFN-β and IFN-ω are elevated in SLE patients blood [57]. Interestingly, it was suggested that neurotoxic lymphocytes are activated by IFN-α and thereby could mediate CNS damage in an IFN-I dependent manner [54, 58].

Role of interferon on blood-brain barrier and circulation

The blood-brain barrier protects the CNS from pathogens [59]. It is the gatekeeper for molecules and cells passaging and consists of the highly specialized brain microvascular endothelial cells, which are connected via tight and adherens junctions, associated with pericytes and surrounded by endfeet of astrocytes [60]. Changes in the blood-brain barrier are hallmarks of several diseases, including the pathogenesis of multiple sclerosis (MS). Beside the immunomodulatory function of IFN-β there is increasing evidence that IFN-β directly effects the blood-brain barrier in several species including humans [51]. Also IFN-III can protect the brain from infection. A recent study using West Nile virus infection showed, while IFN-III did not act directly antiviral, it decreased the blood-brain barrier permeability.

Therefore, IFN-III protected the brain from viral spread and improved survival of mice [61]. On the other hand, the type II IFN, IFN-γ is secreted by Natural Killer (NK) and activated T cells and is a major signal for the recruitment and activation of leukocytes to sites of infection. It therefore enhances leukocyte trafficking, in a CXCL10 mediated manner, and thereby indirectly disrupts the blood-brain barrier as occurs in Rabies virus infection [62]. However, also direct effects of IFN-γ on vascular endothelia dysregulating barrier functions have been reported *in vitro* [63]. Disruption of the blood-brain barrier seems to facilitate entrance for circulating pathogens into the CNS, however, it can be required for cellular immunity and complete pathogen clearance from the CNS [64].

Interestingly IFN-I were shown to modulate the choroid plexus during aging [65]. By using multiorgan genome-wide analysis of aged mice, Baruch *et al.* found that the choroid plexus shows an IFN-I-dependent gene expression profile that was also found in aged human brains. Blocking IFN-I signaling within the aged brain partially restored cognitive function and hippocampal neurogenesis and reestablished IFN-II-dependent choroid plexus activity [65]. In line, preconditioning with poly(I:C) protects against cerebral ischemic damage [66]. Poly(I:C) treatment, which induced IFN-β in astrocytes and microglia, maintained the paracellular and transcellular transport across the endothelium and attenuated the drop in transendothelial electric resistance [66]. In line with this study, TLR-activation led to induction of interferon regulatory factor (IRF)-mediated transcription in the brain, which correlated with ischemic resistance. Using mice deficient in IRF3 or IRF7 the authors could prove the importance of IFN induced genes in this process [67].

Role of IFN-I in cognitive and psychological functions and degeneration

Sickness behavior and cognitive dysfunction occur frequently in virus-infected individuals. In a recent study, Blank *et al.* found that behavioral alterations were specifically dependent on brain endothelial and epithelial IFN-α receptor chain 1 (IFNAR1) [68]. Mechanistically the endothelia-derived chemokine ligand CXCL10 mediated behavioral changes through impairment of synaptic plasticity [68]. In line with these findings IFN-I treatment can induced depression as a side effect. This is seen in patients, which are treated with IFN-I as hepatitis C virus (HCV) therapy. In a recent study 15 genes that are associated with the development of severe depression, were upregulated during the standard therapy of HCV with IFN-α and ribavirin [69]. The onset of depression correlated with serum levels of brain-derived neurotrophic factor [70]. These findings suggest that the effect of IFN-α-induced immune activation on depression may be explained in part by alterations in neuroprotective capacity [70]. In line with these data additional studies suggest that the degeneration of axons containing serotonin and noradrenaline is involved in the pathophysiology of depression [71]. An immune histochemical study showed that IFN-α induced decreases in the density of serotonergic axons in the ventral medial prefrontal cortex and amygdala and decreases in the density of noradrenergic axons in the dorsal medial prefrontal cortex, ventral medial prefrontal cortex, and dentate gyrus [71]. Also cognitive functions of the brain can be modulated by IFN-I. A mouse study, where HIV is inoculated into the brain of mice, shows that HIV induces IFN-α in brains of these mice, which correlated with working memory errors for mice with HIV infected macrophages [72].

Pro inflammatory cytokines like Interleukin-1 β (IL1) and tumor necrosis factor α (TNF-α) have been found to be important regulators of sleep [73, 74]. Chronic insomnia was further shown to be related to increased IL-6 levels as well as a shift from nighttime to daytime IL-6 and TNF-α secretion [75]. Furthermore, IFN-α treated HCV patients show reduced sleep continuity and depth and induced a sleep pattern consistent with insomnia [76]. Therefore, sleep disturbances can relate to altered levels of inflammatory mediators.

Conclusion

Under physiological conditions, CNS astrocytes produce IFN-β, which is of high relevance for homeostasis in the brain, by regulating phagocytic removal of myelin debris by microglia and integrity of the blood-brain barrier. Neurotropic viruses, including La Crosse virus (LACV), infect the brain and are battled against by innate immune responses of microglia and astrocytes, the production of IFN-α and/or –β, and followed by an adaptive immune response. Disruption of the blood-brain barrier seems to facilitate entrance of peripheral lymphocytes and is therefore often required for complete pathogen clearance from the CNS. However, inflammation in the brain can also cause neurological impairment and whenever neurological defects remain is dependent on the infecting virus itself as well as viral loads and presumably constitution, and lastly the genetic background of the host. Viral infections during vulnerable phases of embryonic development cause severe fetal pathology and debilitating impairments to human infants. The roles of IFN in these scenarios are diverse and include deficits due to overproduction of IFN during the developmental stage of the brain as seems to be the case in pseudo-TORCH2. Genetic mutations causing a chronic production of IFN-α in the cerebrospinal fluid cause sever neurological symptoms as in Aicardi-Goutières syndrome (AGS) and are characterized by a IFN-stimulated genes (ISGs) signature in the peripheral blood. Lastly, altered levels of IFNs are involved in autoimmune diseases as in systemic lupus erythematosus and furthermore can cause psychological and cognitive impairments.

Dissection of the various effects of IFN-I in the brain is still demanding. A broad range of phenotypes in interferon mediated or accompanied diseases is well and long term documented in humans compared to the experimental conditions in the inbred mice. However, in mice compared to the human, the immunological conditions directly in the brain can be approached experimentally, hopefully revealing mechanistic insights into associated pathologies.

Disclosure Statement

The authors declare no competing interests.

References

1 Peterson ST, Kennedy EA, Brigleb PH, Taylor GM, Urbanek K, Bricker TL, Lee S, Shin H, Dermody TS, Boon ACM, Baldridge MT: Disruption of Type III Interferon (IFN) Genes Ifnl2 and Ifnl3 Recapitulates Loss of the Type III IFN Receptor in the Mucosal Antiviral Response. J Virol 2019;93:pii:e01073-19.

2 Ye L, Schnepf D, Staeheli P: Interferon-lambda orchestrates innate and adaptive mucosal immune responses. Nat Rev Immunol 2019;19:614-625.

3 Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Muller T, Bahlo M, Stewart GJ, Booth DR, George J: IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009;41:1100-1104.

4 Sutter K, Dickow J, Dittmer U: Interferon alpha subtypes in HIV infection. Cytokine Growth Factor Rev 2018;40:13-18.

5 Lee AJ, Ashkar AA: The Dual Nature of Type I and Type II Interferons. Front Immunol 2018;9:2061.

6 Teijaro JR, Ng C, Lee AM, Sullivan BM, Sheehan KC, Welch M, Schreiber RD, de la Torre JC, Oldstone MB: Persistent LCMV infection is controlled by blockade of type I interferon signaling. Science 2013;340:207-211.

7 Dixit E, Kagan JC: Intracellular pathogen detection by RIG-I-like receptors. Adv Immunol 2013;117:99-125.

8 Gekara NO, Jiang H: The innate immune DNA sensor cGAS: A membrane, cytosolic, or nuclear protein? Sci Signal 2019;12:pii:eaax3521.

9 Schulze S, Stoss C, Lu M, Wang B, Laschinger M, Steiger K, Altmayr F, Friess H, Hartmann D, Holzmann B, Huser N: Cytosolic nucleic acid sensors of the innate immune system promote liver regeneration after partial hepatectomy. Sci Rep 2018;8:12271.
10 Vidya MK, Kumar VG, Sejian V, Bagath M, Krishnan G, Bhatta R: Toll-like receptors: Significance, ligands, signaling pathways, and functions in mammals. Int Rev Immunol 2018;37:20-36.
11 Haller O, Arnheiter H, Lindenmann J, Gresser I: Host gene influences sensitivity to interferon action selectively for influenza virus. Nature 1980;283:660-662.
12 Clemens MJ, Williams BR: Inhibition of cell-free protein synthesis by pppA2'p5'A2'p5'A: a novel oligonucleotide synthesized by interferon-treated L cell extracts. Cell 1978;13:565-572.
13 Silverman RH: Viral encounters with 2',5'-oligoadenylate synthetase and RNase L during the interferon antiviral response. J Virol 2007;81:12720-12729.
14 Roberts WK, Hovanessian A, Brown RE, Clemens MJ, Kerr IM: Interferon-mediated protein kinase and low-molecular-weight inhibitor of protein synthesis. Nature 1976;264:477-480.
15 Niewold TB: Interferon alpha as a primary pathogenic factor in human lupus. J Interferon Cytokine Res 2011;31:887-892.
16 Sarvetnick N, Liggitt D, Pitts SL, Hansen SE, Stewart TA: Insulin-dependent diabetes mellitus induced in transgenic mice by ectopic expression of class II MHC and interferon-gamma. Cell 1988;52:773-782.
17 Nicoletti F, Meroni PL, Landolfo S, Gariglio M, Guzzardi S, Barcellini W, Lunetta M, Mughini L, Zanussi C: Prevention of diabetes in BB/Wor rats treated with monoclonal antibodies to interferon-gamma. Lancet 1990;336:319.
18 Huang X, Hultgren B, Dybdal N, Stewart TA: Islet expression of interferon-alpha precedes diabetes in both the BB rat and streptozotocin-treated mice. Immunity 1994;1:469-478.
19 Stewart TA, Hultgren B, Huang X, Pitts-Meek S, Hully J, MacLachlan NJ: Induction of type I diabetes by interferon-alpha in transgenic mice. Science 1993;260:1942-1946.
20 Chedin P, Cahen-Varsaux J, Boyer N: Non-insulin-dependent diabetes mellitus developing during interferon-alpha therapy for chronic hepatitis C. Ann Intern Med 1996;125:521.
21 Lang KS, Recher M, Junt T, Navarini AA, Harris NL, Freigang S, Odermatt B, Conrad C, Ittner LM, Bauer S, Luther SA, Uematsu S, Akira S, Hengartner H, Zinkernagel RM: Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. Nat Med 2005;11:138-145.
22 Smyth DJ, Cooper JD, Bailey R, Field S, Burren O, Smink LJ, Guja C, Ionescu-Tirgoviste C, Widmer B, Dunger DB, Savage DA, Walker NM, Clayton DG, Todd JA: A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat Genet 2006;38:617-619.
23 Looney BM, Xia CQ, Concannon P, Ostrov DA, Clare-Salzler MJ: Effects of type 1 diabetes-associated IFIH1 polymorphisms on MDA5 function and expression. Curr Diab Rep 2015;15:96.
24 Miner JJ, Diamond MS: MDA5 and autoimmune disease. Nat Genet 2014;46:418-419.
25 Goldmann T, Zeller N, Raasch J, Kierdorf K, Frenzel K, Ketscher L, Basters A, Staszewski O, Brendecke SM, Spiess A, Tay TL, Kreutz C, Timmer J, Mancini GM, Blank T, Fritz G, Biber K, Lang R, Malo D, Merkler D, et al.: USP18 lack in microglia causes destructive interferonopathy of the mouse brain. EMBO J 2015;34:1612-1629.
26 Kocur M, Schneider R, Pulm AK, Bauer J, Kropp S, Gliem M, Ingwersen J, Goebels N, Alferink J, Prozorovski T, Aktas O, Scheu S: IFNbeta secreted by microglia mediates clearance of myelin debris in CNS autoimmunity. Acta Neuropathol Commun 2015;3:20.
27 Ejlerskov P, Hultberg JG, Wang J, Carlsson R, Ambjorn M, Kuss M, Liu Y, Porcu G, Kolkova K, Friis Rundsten C, Ruscher K, Pakkenberg B, Goldmann T, Loreth D, Prinz M, Rubinsztein DC, Issazadeh-Navikas S: Lack of Neuronal IFN-beta-IFNAR Causes Lewy Body- and Parkinson's Disease-like Dementia. Cell 2015;163:324-339.
28 Tsalenchuck Y, Steiner I, Panet A: Innate defense mechanisms against HSV-1 infection in the target tissues, skin and brain. J Neurovirol 2016;22:641-649.
29 Pfefferkorn C, Kallfass C, Lienenklaus S, Spanier J, Kalinke U, Rieder M, Conzelmann KK, Michiels T, Staeheli P: Abortively Infected Astrocytes Appear To Represent the Main Source of Interferon Beta in the Virus-Infected Brain. J Virol 2016;90:2031-2038.

30 Kim H, Yang E, Lee J, Kim SH, Shin JS, Park JY, Choi SJ, Kim SJ, Choi IH: Double-stranded RNA mediates interferon regulatory factor 3 activation and interleukin-6 production by engaging Toll-like receptor 3 in human brain astrocytes. Immunology 2008;124:480-488.
31 Johnson N, McKimmie CS, Mansfield KL, Wakeley PR, Brookes SM, Fazakerley JK, Fooks AR: Lyssavirus infection activates interferon gene expression in the brain. J Gen Virol 2006;87:2663-2667.
32 Zaritsky LA, Dery A, Leong WY, Gama L, Clements JE: Tissue-specific interferon alpha subtype response to SIV infection in brain, spleen, and lung. J Interferon Cytokine Res 2013;33:24-33.
33 Kallfass C, Ackerman A, Lienenklaus S, Weiss S, Heimrich B, Staeheli P: Visualizing production of beta interferon by astrocytes and microglia in brain of La Crosse virus-infected mice. J Virol 2012;86:11223-11230.
34 Winkler CW, Woods TA, Groveman BR, Carmody AB, Speranza EE, Martens CA, Best SM, Haigh CL, Peterson KE: Neuronal maturation reduces the type I IFN response to orthobunyavirus infection and leads to increased apoptosis of human neurons. J Neuroinflammation 2019;16:229.
35 Polyak MJ, Vivithanaporn P, Maingat FG, Walsh JG, Branton W, Cohen EA, Meeker R, Power C: Differential type 1 interferon-regulated gene expression in the brain during AIDS: interactions with viral diversity and neurovirulence. FASEB J 2013;27:2829-2844.
36 Chaudhuri A, Duan F, Morsey B, Persidsky Y, Kanmogne GD: HIV-1 activates proinflammatory and interferon-inducible genes in human brain microvascular endothelial cells: putative mechanisms of blood-brain barrier dysfunction. J Cereb Blood Flow Metab 2008;28:697-711.
37 Dionne KR, Galvin JM, Schittone SA, Clarke P, Tyler KL: Type I interferon signaling limits reoviral tropism within the brain and prevents lethal systemic infection. J Neurovirol 2011;17:314-326.
38 Roth-Cross JK, Bender SJ, Weiss SR: Murine coronavirus mouse hepatitis virus is recognized by MDA5 and induces type I interferon in brain macrophages/microglia. J Virol 2008;82:9829-9838.
39 Wheeler AC, Ventura CV, Ridenour T, Toth D, Nobrega LL, Silva de Souza Dantas LC, Rocha C, Bailey DB, Jr., Ventura LO: Skills attained by infants with congenital Zika syndrome: Pilot data from Brazil. PLoS One 2018;13:e0201495.
40 Brasil P, Pereira JP Jr., Moreira ME, Ribeiro Nogueira RM, Damasceno L, Wakimoto M, Rabello RS, Valderramos SG, Halai UA, Salles TS, Zin AA, Horovitz D, Daltro P, Boechat M, Raja Gabaglia C, Carvalho de Sequeira P, Pilotto JH, Medialdea-Carrera R, Cotrim da Cunha D, Abreu de Carvalho LM,et al.: Zika Virus Infection in Pregnant Women in Rio de Janeiro. N Engl J Med 2016;375:2321-2334.
41 Trus I, Udenze D, Cox B, Berube N, Nordquist RE, van der Staay FJ, Huang Y, Kobinger G, Safronetz D, Gerdts V, Karniychuk U: Subclinical in utero Zika virus infection is associated with interferon alpha sequelae and sex-specific molecular brain pathology in asymptomatic porcine offspring. PLoS Pathog 2019;15:e1008038.
42 Aigner L, Uyanik G, Couillard-Despres S, Ploetz S, Wolff G, Morris-Rosendahl D, Martin P, Eckel U, Spranger S, Otte J, Woerle H, Holthausen H, Apheshiotis N, Fluegel D, Winkler J: Somatic mosaicism and variable penetrance in doublecortin-associated migration disorders. Neurology 2003;60:329-332.
43 Pallocca G, Nyffeler J, Dolde X, Grinberg M, Gstraunthaler G, Waldmann T, Rahnenfuhrer J, Sachinidis A, Leist M: Impairment of human neural crest cell migration by prolonged exposure to interferon-beta. Arch Toxicol 2017;91:3385-3402.
44 Knoblauch H, Tennstedt C, Brueck W, Hammer H, Vulliamy T, Dokal I, Lehmann R, Hanefeld F, Tinschert S: Two brothers with findings resembling congenital intrauterine infection-like syndrome (pseudo-TORCH syndrome). Am J Med Genet A 2003;120A:261-265.
45 Meuwissen ME, Schot R, Buta S, Oudesluijs G, Tinschert S, Speer SD, Li Z, van Unen L, Heijsman D, Goldmann T, Lequin MH, Kros JM, Stam W, Hermann M, Willemsen R, Brouwer RW, Van IWF, Martin-Fernandez M, de Coo I, Dudink J, et al.: Human USP18 deficiency underlies type 1 interferonopathy leading to severe pseudo-TORCH syndrome. J Exp Med 2016;213:1163-1174.
46 Knobeloch KP, Utermohlen O, Kisser A, Prinz M, Horak I: Reexamination of the role of ubiquitin-like modifier ISG15 in the phenotype of UBP43-deficient mice. Mol Cell Biol 2005;25:11030-11034.
47 Crow YJ, Chase DS, Lowenstein Schmidt J, Szynkiewicz M, Forte GM, Gornall HL, Oojageer A, Anderson B, Pizzino A, Helman G, Abdel-Hamid MS, Abdel-Salam GM, Ackroyd S, Aeby A, Agosta G, Albin C, Allon-Shalev S, Arellano M, Ariaudo G, Aswani V, et al.: Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A 2015;167A:296-312.

48 Gorman JA, Hundhausen C, Errett JS, Stone AE, Allenspach EJ, Ge Y, Arkatkar T, Clough C, Dai X, Khim S, Pestal K, Liggitt D, Cerosaletti K, Stetson DB, James RG, Oukka M, Concannon P, Gale M, Jr., Buckner JH, Rawlings DJ: The A946T variant of the RNA sensor IFIH1 mediates an interferon program that limits viral infection but increases the risk for autoimmunity. Nat Immunol 2017;18:744-752.
49 Deczkowska A, Baruch K, Schwartz M: Type I/II Interferon Balance in the Regulation of Brain Physiology and Pathology. Trends Immunol 2016;37:181-192.
50 Zivadinov R, Locatelli L, Cookfair D, Srinivasaraghavan B, Bertolotto A, Ukmar M, Bratina A, Maggiore C, Bosco A, Grop A, Catalan M, Zorzon M: Interferon beta-1a slows progression of brain atrophy in relapsing-remitting multiple sclerosis predominantly by reducing gray matter atrophy. Mult Scler 2007;13:490-501.
51 Kraus J, Oschmann P: The impact of interferon-beta treatment on the blood-brain barrier. Drug Discov Today 2006;11:755-762.
52 Hurtado-Guerrero I, Pinto-Medel MJ, Urbaneja P, Rodriguez-Bada JL, Leon A, Guerrero M, Fernandez O, Leyva L, Oliver-Martos B: Activation of the JAK-STAT Signaling Pathway after In Vitro Stimulation with IFNss in Multiple Sclerosis Patients According to the Therapeutic Response to IFNss. PLoS One 2017;12:e0170031.
53 Frisullo G, Angelucci F, Caggiula M, Nociti V, Iorio R, Patanella AK, Sancricca C, Mirabella M, Tonali PA, Batocchi AP: pSTAT1, pSTAT3, and T-bet expression in peripheral blood mononuclear cells from relapsing-remitting multiple sclerosis patients correlates with disease activity. J Neurosci Res 2006;84:1027-1036.
54 Crow MK: Type I interferon in the pathogenesis of lupus. J Immunol 2014;192:5459-5468.
55 Crow MK, Kirou KA, Wohlgemuth J: Microarray analysis of interferon-regulated genes in SLE. Autoimmunity 2003;36:481-490.
56 Hall JC, Casciola-Rosen L, Berger AE, Kapsogeorgou EK, Cheadle C, Tzioufas AG, Baer AN, Rosen A: Precise probes of type II interferon activity define the origin of interferon signatures in target tissues in rheumatic diseases. Proc Natl Acad Sci U S A 2012;109:17609-17614.
57 Yao Y, Higgs BW, Morehouse C, de Los Reyes M, Trigona W, Brohawn P, White W, Zhang J, White B, Coyle AJ, Kiener PA, Jallal B: Development of Potential Pharmacodynamic and Diagnostic Markers for Anti-IFN-alpha Monoclonal Antibody Trials in Systemic Lupus Erythematosus. Hum Genomics Proteomics 2009;2009:pii:374312.
58 Pulliero A, Marengo B, Longobardi M, Fazzi E, Orcesi S, Olivieri I, Cereda C, Domenicotti C, Balottin U, Izzotti A: Inhibition of the de-myelinating properties of Aicardi-Goutieres syndrome lymphocytes by cathepsin D silencing. Biochem Biophys Res Commun 2013;430:957-962.
59 Daniels BP, Klein RS: Knocking on Closed Doors: Host Interferons Dynamically Regulate Blood-Brain Barrier Function during Viral Infections of the Central Nervous System. PLoS Pathog 2015;11:e1005096.
60 Abbott NJ, Ronnback L, Hansson E: Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci 2006;7:41-53.
61 Lazear HM, Daniels BP, Pinto AK, Huang AC, Vick SC, Doyle SE, Gale M, Jr., Klein RS, Diamond MS: Interferon-lambda restricts West Nile virus neuroinvasion by tightening the blood-brain barrier. Sci Transl Med 2015;7:284ra259.
62 Chai Q, He WQ, Zhou M, Lu H, Fu ZF: Enhancement of blood-brain barrier permeability and reduction of tight junction protein expression are modulated by chemokines/cytokines induced by rabies virus infection. J Virol 2014;88:4698-4710.
63 Daniels BP, Holman DW, Cruz-Orengo L, Jujjavarapu H, Durrant DM, Klein RS: Viral pathogen-associated molecular patterns regulate blood-brain barrier integrity via competing innate cytokine signals. MBio 2014;5:e01476-01414.
64 Daniels BP, Klein RS: Viral sensing at the blood-brain barrier: new roles for innate immunity at the CNS vasculature. Clin Pharmacol Ther 2015;97:372-379.
65 Baruch K, Deczkowska A, David E, Castellano JM, Miller O, Kertser A, Berkutzki T, Barnett-Itzhaki Z, Bezalel D, Wyss-Coray T, Amit I, Schwartz M: Aging. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. Science 2014;346:89-93.
66 Gesuete R, Packard AE, Vartanian KB, Conrad VK, Stevens SL, Bahjat FR, Yang T, Stenzel-Poore MP: Poly-ICLC preconditioning protects the blood-brain barrier against ischemic injury in vitro through type I interferon signaling. J Neurochem 2012;123:75-85.

67 Stevens SL, Leung PY, Vartanian KB, Gopalan B, Yang T, Simon RP, Stenzel-Poore MP: Multiple preconditioning paradigms converge on interferon regulatory factor-dependent signaling to promote tolerance to ischemic brain injury. J Neurosci 2011;31:8456-8463.
68 Blank T, Detje CN, Spiess A, Hagemeyer N, Brendecke SM, Wolfart J, Staszewski O, Zoller T, Papageorgiou I, Schneider J, Paricio-Montesinos R, Eisel UL, Manahan-Vaughan D, Jansen S, Lienenklaus S, Lu B, Imai Y, Muller M, Goelz SE, Baker DP, et al.: Brain Endothelial- and Epithelial-Specific Interferon Receptor Chain 1 Drives Virus-Induced Sickness Behavior and Cognitive Impairment. Immunity 2016;44:901-912.
69 Hoyo-Becerra C, Huebener A, Trippler M, Lutterbeck M, Liu ZJ, Truebner K, Bajanowski T, Gerken G, Hermann DM, Schlaak JF: Concomitant interferon alpha stimulation and TLR3 activation induces neuronal expression of depression-related genes that are elevated in the brain of suicidal persons. PLoS One 2013;8:e83149.
70 Kenis G, Prickaerts J, van Os J, Koek GH, Robaeys G, Steinbusch HW, Wichers M: Depressive symptoms following interferon-alpha therapy: mediated by immune-induced reductions in brain-derived neurotrophic factor? Int J Neuropsychopharmacol 2011;14:247-253.
71 Ishikawa J, Ishikawa A, Nakamura S: Interferon-alpha reduces the density of monoaminergic axons in the rat brain. Neuroreport 2007;18:137-140.
72 Sas AR, Bimonte-Nelson HA, Tyor WR: Cognitive dysfunction in HIV encephalitic SCID mice correlates with levels of Interferon-alpha in the brain. AIDS 2007;21:2151-2159.
73 Krueger JM, Rector DM, Churchill L: Sleep and Cytokines. Sleep Med Clin 2007;2:161-169.
74 Dolsen MR, Soehner AM, Harvey AG: Proinflammatory Cytokines, Mood, and Sleep in Interepisode Bipolar Disorder and Insomnia: A Pilot Study With Implications for Psychosocial Interventions. Psychosom Med 2018;80:87-94.
75 Burgos I, Richter L, Klein T, Fiebich B, Feige B, Lieb K, Voderholzer U, Riemann D: Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. Brain Behav Immun 2006;20:246-253.
76 Raison CL, Rye DB, Woolwine BJ, Vogt GJ, Bautista BM, Spivey JR, Miller AH: Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis C: association with fatigue, motor slowing, and increased evening cortisol. Biol Psychiatry 2010;68:942-949.