Interferons, Signal Transduction Pathways, and the Central Nervous System

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The interferon (IFN) family of cytokines participates in the development of innate and acquired immune defenses against various pathogens and pathogenic stimuli. Discovered originally as a proteinaceous substance secreted from virus-infected cells that afforded immunity to neighboring cells from virus infection, these cytokines are now implicated in various human pathologies, including control of tumor development, cell differentiation, and autoimmunity. It is now believed that the IFN system (IFN genes and the genes induced by them, and the factors that regulate these processes) is a generalized alarm of cellular stress, including DNA damage. IFNs exert both beneficial and deleterious effects on the central nervous system (CNS). Our knowledge of the IFN-regulated processes in the CNS is far from being clear. In this article, we reviewed the current understanding of IFN signal transduction pathways and gene products that might have potential relevance to diseases of the CNS.

Introduction

CELLULAR STRESS ORIGINATING FROM diverse signals is integrated into various molecular pathways for restoring cellular homeostasis. In extreme cases, an improper execution of these pathways or their excessive activation can result in cell death. The first-line innate defense against an invading pathogen is the upregulation of interferons (IFNs). The IFN family of cytokines is essential for innate and acquired immunity against infectious pathogens and tumors (Kalvakolanu and others 2001; Borden and others 2007; Sen and Sarkar 2007; Vesely and others 2011). They are grouped into 3 types—I, II, and III—based on gene location and organization, structural and biochemical properties, and receptor usage [reviewed in (Pestka and others 2004)]. Members of all 3 IFN types, except type II, are produced by most mammalian cells in response to various pathogenic stimuli, which include viral and cellular nucleic acids, bacterial components, viral proteins, and foreign antigens. The aim of this review is to provide a bird's-eye view of IFN actions and signal transduction pathways. Since much of our current understanding of IFN signaling and actions came from nonneuronal cells, the reader is cautioned to take this review as a guiding map for understanding the processes in the central nervous system (CNS, a collective term for neurons in the brain and spinal cord with their supportive cells). We will provide examples for connections where genes and proteins that participate in IFN actions are altered in pathologies of the CNS in humans and animal models.

Since the breadth of coverage for this article is quite wide, we frequently refer to the historical work in certain areas of IFN action to recently published reviews that will provide a comprehensive picture of the state of the art.

Sensing Mechanisms That Activate IFN Synthesis

Normally, the levels of type I IFNs are undetectable or very low. The rapid synthesis of type I IFNs is favored by their intronless gene structure, and they need a very few number of transcription factors. The transcription factors are recruited to type I IFN promoters following their activation. The Toll-like receptor family members (TLRs) [reviewed in (Roach and others 2005)], Nod-like receptor family members (NLRs) [reviewed in (Franchi and others 2009)], and RIG-like receptor (RLR) family members [reviewed in (Yoneyama and others 2005)] function in pathogen recognition and instruct the production of cytokines necessary for effective innate immunity. The plasma membrane-resident TLRs 1, 2, and 4 recognize bacterial cell wall components; TLRs 3, 7, 8, and 9 recognize pathogen-derived nucleic acids (ds/ss DNA/RNA); TLR9 recognizes unmethylated CpG DNA; TLRs 5 and 11 recognize bacterial flagellin. TLR6 interacts with TLR2 to mediate responses to bacterial lipoproteins, while the function of TLR10 is not fully understood. Similarly, NLRs recognize signatures from intracellular bacteria. Among NLR family members, functions of NOD1 and 2 are the best understood. The RLR members

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appear to exhibit some preference in recognizing specific pathogen-derived nucleic acids.

In the TLR pathway, after the bacterial products are sensed, TRIF and/or MyD88 components are recruited to the activated receptor. A signaling cascade follows where receptor-associated kinases like IRAKs, TAK1, and TBK1 induce phosphorylation of key transcription factors (IRF3, IRF7, and NF- κ B) that are recruited to the promoter regions to induce transcription of type I IFN genes. A similar activation of NF- κ B occurs in the NOD pathway where kinases RIP2 and TAK1 are needed to degrade the inhibitory component I κ B α . In the RLR pathway, RIG1, MDA-5, and LGP2 detect viral RNA upon infection to activate mitochondrial antiviral-signaling protein (MAVS also known as VISA and cardif) by aggregation. This in turn activates IRF3, IRF7, NF- κ B, cJUN/ATF2, and CBP/p300 that initiate expression of type I IFNs (Kawai and Akira 2009). Transcription of IFN- β gene is dependent on NF- κ B, while those of IFN- α genes appear to occur independently of NF- κ B and rely only on IRFs.

Signal Transduction by IFNs

The type I IFNs are represented by at least 5 members: IFN- α (12–14 subtypes), IFN- β , IFN- ω , IFN- κ , and IFN- ϵ ; additionally, IFN- δ and IFN- τ have been described in ungulates [reviewed in (Chen and others 2004)]. In contrast to the induction of IFN- α or β by viral or bacterial pathogens, IFN- ϵ is constitutively produced by the epithelial lining of the female reproductive tract (Hardy and others 2004; Fung and others 2013). Type I IFNs, as ligands, bind to a heterodimeric cell surface transmembrane receptor composed of IFNAR1 and IFNAR2 subunits [see (de Weerd and others 2007) for a review]. The former binds the ligand, while the latter modifies it to a higher affinity state. Type I IFN receptor is constitutively expressed in all cells in the body, while type I IFN synthesis differs in orders of magnitude across cell types. The type II IFN is represented by a sole member, IFN- γ , which is primarily produced by antigen-activated T-cells and NK cells; macrophages secrete this cytokine in certain situations (Schroder and others 2004). The receptor for IFN- γ is composed the IFNGR1 and IFNGR2 polypeptides, which are expressed on all cell types. Again, IFNGR1 binds only the ligand, while IFGR2 provides signaling specificity. Since biologically active IFN- γ is a homodimer, the active signaling complex is a heterotetramer consisting of 2 copies of IFNGR1 and IFNGR2 (Bach and others 1997). Type III IFNs include λ 1, λ 2, and λ 3 that are expressed only in certain epithelial cells and bind to a distinct receptor (Kotenko and others 2003) formed by the ligand-binding subunit IFNLR1 (IL-28RA) and signal-transducing subunit IL-10R2. The latter is also employed by IL-10 family of cytokines for signal transduction. Similar signals can activate any IFN in a cell-specific and temporal manner, while a specific signal that selectively induces type III IFNs is yet to be described.

Despite the differences in their receptor usage, type I and type III IFNs induce similar target genes with indistinguishable kinetics. The ligand-engaged IFN receptors activate gene expression through the Janus tyrosine kinase (JAK)–signal transducer and activator of transcription (STAT) pathways [see (Stark and Darnell 2012) for a recent review]. The JAKs are nonreceptor protein tyrosine kinases,

comprising JAK1, 2, and 3 and TYK2, which associate with cytokine and/or growth factor receptors. In the IFN signal transduction pathway, at least 2 JAKs are required for a productive response. The type I and type III IFN receptors require TYK2 and JAK1 for signaling in human cells (Muller and others 1993a). Interestingly, in mouse cells lacking Tyk2 (Karaghiosoff and others 2000) or expressing soluble Ifnar2 (Hardy and others 2001), type I IFNs can still signal, although requires a higher dose than the wild-type cells, suggesting that they are not absolutely critical for signaling. IFNGR requires JAK1 and JAK2 for signal transduction (Bach and others 1997). It is generally agreed that upon engagement with their respective receptors, IFNs cause aggregation of the receptor polypeptides (Bach and others 1997), which leads to the cross activation of JAKs (bound to the intracellular portion of the receptor through box1 motifs) *via* tyrosyl phosphorylation.

Activated JAKs phosphorylate specific tyrosine residues on the receptor polypeptides, which serve as docking sites for the STAT proteins through their src-homology 2 (SH2) domains (Greenlund and others 1995). STATs are then phosphorylated at a specific tyrosyl residue (Y⁷⁰¹ on STAT1, Y⁶⁸⁵ on STAT2, and Y⁷⁰⁵ on STAT3) by JAKs (Muller and others 1993b). Once phosphorylated, STATs dissociate from the receptor, form dimers, and enter the nucleus (McBride and Reich 2003). In the type I and type III IFN-induced pathways, STAT1 and STAT2 are activated to form a heterodimer (Leung and others 1995), whereas in the type II IFN-induced pathway, STAT1 is activated to form a homodimer (Shuai and others 1993). In addition to the STAT1–STAT2 heterodimer, transcriptional activation by type I and type III IFN signaling pathways requires a non-STAT protein, IRF9 (also known as p48/ISGF3 γ) (Bluyssen and others 1996; Veals and others 1993). This protein belongs to the IFN-gene regulatory factor family of transcription factors. Even though the IRF9 protein has a DNA-binding domain, it weakly binds to DNA on its own and is incapable of activating IFN-induced transcription without associating with the STAT1–STAT2 complex (Bluyssen and others 1996; Veals and others 1993). The STAT1–STAT2–IRF9 complex, known as IFN-stimulated gene factor 3 (ISGF3), binds to the IFN-stimulated response element (ISRE) present in promoter regions of many genes. Similarly, STAT1 homodimers bind to the gamma-IFN-activated site (GAS) present in promoter regions of several genes (Stark and Darnell 2012). STAT activation in response to IFNs is terminated by the induction of JAK inhibitory proteins, the suppressor of cytokine signaling (SOCS) proteins (Alexander and Hilton 2004) whose genes are induced by STATs. Figure 1 shows the regulation of IFN- γ -induced JAK-STAT pathways. Indeed, deletion of *Socs1* leads to IFN- γ -dependent chronic inflammation, which reduces the postnatal survival of mice (Alexander and others 1999).

Apart from STAT1, IFN- α is known to activate STAT3. In some lymphoma cell lines, STAT3 was reported to act as an adaptor for the IFNAR1 chain (Pfeffer and others 1997) and activate the phosphatidylinositol 3 kinase (PI3K) pathway (Uddin and others 2000b). IFN- α also activates the p38MAP kinase pathway (Uddin and others 2000a; Li and others 2004), although the exact target is unclear. In addition, several other non-JAK-STAT signaling molecules are activated by IFN- α in human hematopoietic cell lines (Platanias 2005). Most notable of these is the activation of mammalian target of rapamycin (mTOR) and its downstream

FIG. 1. IFN-induced JAK-STAT signaling pathways. This diagram shows IFN- γ signaling. The IFNGR1 and IFNGR2 subunits, preassociated with JAK1 and JAK2, are away from each other in the unstimulated state. After ligand engagement, the receptor subunits are aggregated, leading to the juxta-positioning of JAK1 and JAK2, which cross activates them. JAKs then induce the tyrosyl phosphorylation of receptor. STAT1 is then recruited to the receptor, tyrosyl phosphorylated by the JAKs. The SH2 domain of STAT1 is essential for docking onto the receptor. STAT1 dimers are formed, which migrate to the nucleus, bind to GAS in the target gene enhancers, and stimulate their transcription. In addition, STAT1 induces the expression of *SOCS1* gene transcription, whose product binds to JAKs and blocks their persistent activity. In addition, STAT1 is dephosphorylated and exported out of the nucleus for terminating excessive transcription. Note: functional IFN- γ receptor is a heterotetramer consisting 2 each of the IFNGR1 and IFNGR2 subunits. The cartoon shows only 2 subunits for the sake of simplicity. IFN, interferon; JAK, Janus tyrosine kinase; STAT, signal transducer and activator of transcription. Color images available online at www.liebertpub.com/jir

factors such as the ribosomal S6 kinase and eIF4E-BP, which control the translation of ISG products (Kaur and others 2012). Type III IFNs also activate the JAK-STAT pathway. IL-10R2 is associated with TYK2, and IFNLR1 most likely binds JAK1. Upon ligand binding, the IFNLR1 subunit of the receptor is phosphorylated at Y³⁴³, Y⁴⁰⁶, and Y⁵¹⁷ residues. Of these, Y³⁴³ and Y⁵¹⁷ appear to be most critical, as a mutation of these residues not only causes a loss of IFN-induced antiviral response but also prevents STAT2 recruitment to the receptor (Dumoutier and others 2004). IFN- λ activates STAT3 and STAT5 in some cell types. However, the biological consequence of such activity is unclear at this stage. Unlike IFN- α/β , IFN- λ can activate STAT4 in some cell types. Type III IFNs also activate all 3 major MAP kinases, ERK1/2, JNK, and p38, and the PI3K signaling (Zhou and others 2007), although the exact targets are unknown. It is likely that some of these pathways are similar to those employed by IFN- α , which need to be settled. Type I, II, and III IFNs provide critical protection during early stages of viral, bacterial, or pathogen infection. Even though the cell-type-specific responses to these IFNs are different, there is evidence that an interaction between/among these components may be needed to mount innate immune responses that can be meaningfully translated to have proper acquired immunity (Muller and others 1994). IFN- γ induces other non-STAT signaling pathways (see a discussion on page 6), in addition to STAT1. Figure 2 shows the currently known IFN-stimulated pathways.

Currently, recombinant IFN- α 2, IFN- β , and IFN- γ are the only IFNs available as drugs indicated for controlling hepatitis B/C infection, MS, and chronic granulomatous disease, respectively. In addition, IFN- α 2 used for treating certain types of solid and hematological malignancies has met with some success (Ferrantini and others 2007). Some patients on high-dose or long-term administration of IFN- α 2 exhibiting neurological side effects (such as depression, anxiety, impaired cognition) were recognized very early in its therapeutic use (Mattson and others 1983). Fortunately, neurological functions returned to normalcy when IFN- α use was either reduced or stopped, implying no adverse cellular damage had taken place because of IFN signaling (Iivanainen and others 1985). Possible involvement of type I IFNs has been suggested in the development of autoimmune conditions (Guiducci and others 2009) (diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus [SLE, a type III hypersensitive reaction believed to be due to development of antibodies against self-antigens mostly of connective tissue origin], etc), and this is indicative of cellular destruction at play. Studies addressing IFN signaling have shown changes in biochemical markers such as enzymes and other cytokines during IFN excess either occurring naturally or during therapeutically administered IFN- α 2. Still these have not provided an answer as to whether the effect was directly on the nerves and the mechanisms involved. Since the intent of this review is to provide connection to CNS pathologies, we will restrict our description from the other systemic actions of IFNs and pathologies.

FIG. 2. IFN-induced signaling pathways. Currently known IFN signaling pathways are shown. In addition to the JAK-STAT pathways, IFNs activate non-STAT pathways, including the MAPK-driven pathways. ATF6, activating transcription factor 6 (an ER-resident stress-responsive transcription factor, eg, UPR); CRE/ATF, cAMP response element/ATF binding site; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; eIF-4E, eukaryotic translation initiation factor-4E; 4E-BP1, eIF-4E binding protein (an inhibitor); GAS, gamma-IFN-activated site; GATE, gamma-IFN-activated transcriptional element; ISG, IFN-stimulated gene; ISRE, IFN-stimulated response element; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEKK1, MAP ERK kinase kinase 1 (also known as MAP3K); MEK1, MAP ERK kinase 1; mTOR, mammalian target of rapamycin (a serine/threonine-specific protein kinase that regulates metabolic responses); RPS6, ribosomal protein S6; S6K, ribosomal protein S6 kinase. Color images available online at www.liebertpub.com/jir

IFNs and the CNS

In a healthy individual, the vast majority of myeloid lineage-derived cells present in the CNS are microglia that perform the roles of clearing cellular debris and antigen presentation. The systemic population of immune cells accesses the CNS only in very limited numbers. The blood-brain barrier (BBB) helps maintain this separation and also performs metabolite exchange to nourish the CNS. BBB arises from the intricate interactions and signaling among endothelial cells, perivascular astrocytes, pericytes, neurons, and the basement membrane called the neurovascular unit (Hawkins and Davis 2005), which is more stringently controlled compared with the BBB of the choroid plexus and other similar areas. The integrity and/or permeability of the BBB are compromised during inflammation, allowing systemic immune cells to infiltrate the CNS parenchyma (Persidsky and others 2006). Current understanding of IFN signaling in the CNS has mostly come from studies utilizing viral infections, genetic ablations, or overexpression strategies. Hence, as of date, it has not been possible to address physiological roles of IFN signaling independent of their immunity-related ones.

Genetic deficiency in IFN signal transduction factors (Table 1) can result in fatality of human newborns. Viral encephalitis (herpes, mumps, and others) appears to be the primary reason in such fatalities [see (Sancho-Shimizu and others 2011)]. As mentioned earlier, these components

(TBK1, TLR3, TRAF3, TRIF, and UNC93B1) relay signals to initiate and establish immune responses by inducing IFN gene induction to maintain homeostasis. Similarly, mice genetically engineered to lack IFNs or its signaling components (Table 1) are also extremely susceptible to most viral and/or bacterial infections. However, CNS functions are hardly affected at steady state. That said, natural excess of IFN production or signaling also causes disease conditions (Table 1).

Adenosine deaminases acting on RNA (ADARs), a class of dsRNA-editing enzymes that convert adenines to inosines by a hydrolytic deamination reaction, are important in cell function. Three genes have been described in mammals of which ADAR1 and ADARB1 (also referred to as ADAR2) have enzymatic activity. Deletion of *Adar1* is not compatible with mouse development (Wang and others 2000), while deletion of *Adar2* resulted in seizures and early death of mice (Higuchi and others 2000). An ADAR1 isoform (931 aa; referred as p110) is constitutively expressed, while the longer isoform (1226 aa; referred as p150) is induced by IFN (George and others 2005). In normal circumstances, noncoding Alu element-derived RNAs are edited in most cell types by ADAR1, while in the brain certain RNAs coding for ion channels, transporters, receptors, etc, are edited in a site-specific manner by ADAR1/2. A similar pathway is controlled by TREX1, an ER-associated DNA exonuclease that can translocate into the nucleus following oxidative stress, to degrade nucleic acids originating from endogenous

TABLE 1. DYSREGULATED INTERFERON SIGNALING IN MAMMALS MANIFEST AS DISTINCT PATHOLOGIES

Condition	Gene	Typical characteristics	Reference
Deficiency in IFN response and/or production	<i>STAT1</i>	Highly susceptible to mycobacterial and viral infections	Reviewed in (Jouanguy and others 2007; Boisson-Dupuis and others 2012; Hofer and Campbell 2013)
	<i>TYK2</i>	Impaired IFN- γ response	
	<i>TBK1</i>	Encephalitis caused by Herpes and other viruses	
	<i>TLR3</i>	Defective secretion of IFNs (α , β , and γ)	
	<i>TRAF3</i>		
	<i>TRIF</i>		
Excess IFN signaling	<i>UNC93B1</i>		
	<i>STAT1</i>	Impaired development of IL-17-producing T cells Extremely susceptible to <i>Candida albicans</i> infection	
Excess IFN production	<i>ADAR1</i>	Microcephaly	Reviewed in (Prinz and Knobeloch 2012)
	<i>RNASEH2</i>	Cerebral calcifications with atrophy	
	<i>SAMHD1</i>	Abnormal appearing white matter	
	<i>TREX1</i>	Seizures, poor appetite and improper sleep	
Absence of IFN signaling	<i>Ifnar1/2</i>	Highly susceptible to viral pathogens	Reviewed in (Bogdan 2000)
	<i>Ifnb1</i>		
	<i>Ifngr1/2</i>	Highly susceptible to intracellular bacteria	
	<i>Ifng</i>		
Absence of negative regulators	<i>Socs1</i>	Death before weaning (<3 weeks) Excessive T-cell apoptosis and inflammation	Naka and others (1998); Alexander and others (1999); Marine and others (1999)
	<i>Socs7</i>	Hydrocephalus caused by dilated ventricular system leading to death (within 15 weeks) Severe cutaneous disease with increased serum IgE and IgG levels	

IFN, interferon.

retroelements as well as invading pathogens (Stetson and others 2008). Loss of functional ADAR1 or TREX1 activates IFN-stimulatory nucleic acid response (ISNAR) that may explain why mice lacking these proteins die *in utero*. Two other proteins also control unwanted nucleic acid degradation: SAMHD1 (a deoxy triphosphohydrolase) (Rice and others 2009) and RNASEH2 complex (an RNase directed against RNA–DNA hybrids) (Crow and others 2006). Very little is known about these 2 proteins, and finding their nucleic acid targets will shed more light into the control mechanisms set in place. Loss of SAMHD1 or RNASEH2 activities elicits ISNAR (Crow and others 2006; Rice and others 2009). Additionally, whether these pathways operate independently of each other or there is some cross talk remains to be determined.

Excess IFN signaling caused by a genetic deficiency in natural feedback inhibitor comprising the SOCS family members results in either in prolonged signaling or early death (Table 1). An increased serum IgE level seen in *Socs7*-null mice is reminiscent of hyper-IgE syndrome caused by mutations in STAT3 (Holland and others 2007), and the mice also present with chronic dermatitis. Similarly, gain of STAT1 function can evoke an autoimmune-like response because of enhanced IFN- α/β -mediated immunity (Crow 2011). Interestingly, the same *STAT1* mutation is associated with chronic mucocutaneous candidiasis (Liu and others 2011; van de Veerdonk and others 2011) probably by

inhibiting the development of IL-17-producing T cells at the epithelial–mucosal interface. However, this gain of STAT1 function appears not to be detrimental in the nervous system.

In healthy animals or humans, levels of IFNs in peripheral tissues are generally very low (Taniguchi and Takaoka 2001), and in the CNS they are below detection limits (Pashenkov and others 2001). IFN production in the CNS (Trottier and others 2007) and peripheral nervous system (PNS, a collective term for nerves and their ganglia outside the brain and spinal cord) after viral infections appears to be lower than that in peripheral tissues (Ida-Hosonuma and others 2005), agreeing to its neuroinhibitory nature (Mattson and others 1983) as mentioned previously. Since neurons prefer noncytolytic means of clearing viral infections, eg, herpes virus cleared through autophagy (Yordy and others 2012), low levels of IFN signaling components may be present in the CNS to avoid potential neurotoxic effects, and this has been supported by the limited repertoire and expression of IFN-induced genes in neurons (Wang and Campbell 2005) compared with other cell types (de Veer and others 2001). However, even this minor amount is sufficient to interfere with normal neuronal functions associated with voluntary tasks. In the mouse CNS, when an infection was detected, astrocytes and microglia (Kallfass and others 2012) were the major producers of IFNs, while neurons (Delhaye and others 2006) and oligodendrocytes

(Kapil and others 2012) produced very little of it. Similarly in humans, glial cells produced IFN- α and IFN- β in areas adjacent to lesions in patients with multiple sclerosis (MS, a slowly progressing demyelinating–remyelinating disease associated with on–off CNS inflammation leading to progressive neurodegeneration) and Alzheimer’s disease (Yamada and Yamanaka 1995). The nature of cell-type-dependent pathogen-specific responses to infections varies in peripheral tissues [reviewed in (Mogensen 2009)], and there is very limited information available on how such differential responses occur in the CNS. Many viruses, such as polio, measles, rabies, and chickenpox, exploit this weakness to establish chronic persistence in the PNS [reviewed in (McGavern and Kang 2011)], while some like the rabies travel to the CNS to cause fatal outcomes when not treated in a timely manner. In rare cases, fatal encephalitis caused by measles virus is known. Various mechanisms have been invoked by viruses to gain access into the CNS—increasing permeability of endothelial cells, immune-cell-mediated entry via the choroid plexus, and axonal transport in peripheral nerves are the most favored routes [reviewed in (McGavern and Kang 2011)]. Probably, it is easier for viruses to neutralize IFN signaling in the CNS by employing their own proteases [see (Sorgeloos and others 2013)], ubiquitin ligases (Harle and others 2002; Sobol and Mossman 2006), antagonists (Andrejeva and others 2004; Rieder and others 2011), or sequestration factors (Brzozka and others 2006; Vidy and others 2007) as neurons express IFN signaling components at a much lower level than their surrounding glial cells (Kallfass and others 2012). In spite of such limitations within the CNS, a high level of IFN- α in the cerebrospinal fluid (CSF, a clear secretion by the choroid plexus providing protection to the brain) has been reported in cases of viral infections of newborn and children (Dussaix and others 1985). In patients with meningoencephalitis, HIV-associated syndromes, etc. neurocognitive impairments are associated with high IFN- α levels in the CSF (Bocket and others 1992; Masliah and others 2004). Whether IFN- α in the CSF is synthesized by CNS-resident cells in such situations is not known. Because of the chronic nature of such infections, whether there is progressive nerve damage in all these patients is also not known. Additionally, *de novo* environmental agents contracted can lead to aggravated neuropathy, making it very difficult to score time-dependent changes because of a single factor.

Experiments using genetically engineered mice for IFN signaling components have produced a mixed opinion on inflammation in the CNS. Whereas some studies have supported the paradigm that IFN signaling is detrimental, others have shown its protective effects (Table 2). The detrimental effect of IFN signaling has some support from human postmortem samples although the contribution from other cytokines cannot be excluded in the advanced stages of the disease. Studies using genetically engineered mice have shown a complex interplay of IFN signaling and the protective role of IFN- γ signaling in the CNS (Table 2). Earlier, it was shown that a transgenic mouse line expressing a myelin basic protein-specific monoclonal TCR (Wensky and others 2005) developed inflammation in the spinal cord when the gene for IFN- γ was intact, while brain was the primary inflammatory site when the gene for IFN- γ was deleted; this has been supported by other studies (Lees and others 2008; Lee and others 2012). Therefore, IFN- γ being

protective in the brain can be detrimental to other nervous tissues in situations like experimental autoimmune/allergic encephalomyelitis (EAE, a condition induced by injecting myelin components in Freund’s adjuvant to mount lymphocytic responses in the CNS). However, transgenic overexpression of IFN- γ induces hypomyelination leading to gliosis in the CNS (Corbin and others 1996; LaFerla and others 2000) even in the absence of other external agents like virus or EAE.

IFN-Induced Non-STAT Pathways That Might Have Relevance to CNS Diseases

Although STAT1 is critical for the initial IFN-induced responses, several studies have shown that IFN- γ induces several genes in a STAT1-independent manner. It is also known that IFNs, particularly IFN- γ , continue to induce the expression of a number of cellular genes and their biological responses even after the cessation of the JAK-STAT pathways (Boehm and others 1997), and even in *Stat1*^{−/−} cells (Gil and others 2001; Ramana and others 2001). Gene regulatory pathways mediated by transcription factors IRF1 and IRF8 are examples for some of the STAT-independent IFN-induced regulation (Taniguchi and others 2001; Tamura and Ozato 2002). Earlier, we have shown that transcription factor C/EBP- β participates in an IFN- γ response pathway that involves its binding to a novel IFN- γ -responsive element, GATE, identified in the *Irf9* promoter (Weihua and others 1997; Roy and others 2000). GATE-driven transcription, although IFN dependent, does not involve a direct binding of STATs to the *Irf9* promoter and occurs through C/EBP- β in a kinetically delayed manner, in the apparent absence of activated STAT1 and JAK1 (Weihua and others 1997; Roy and others 2000).

The C/EBPs are a group of structurally similar but functionally distinct transcription factors that belong to a superfamily constituted by other transcription factors: CREB, Fos, Jun/AP-1, ATF, and Maf/Nrf. The C/EBP subfamily includes C/EBP- α , C/EBP- β , C/EBP- γ , C/EBP- δ , C/EBP- ϵ , and C/EBP- ζ (Lekstrom-Himes and Xanthopoulos 1998; Kalvakolanu 2003). These proteins participate in a number of biological responses, including energy metabolism (Croniger and others 1997), fat storage, tissue differentiation (Darlington and others 1998; Seagroves and others 1998), hematopoiesis (Poli 1998), immune response (Akira and Kishimoto 1997), antibacterial defense (Tanaka and others 1995), and female fertility (Sterneck and others 1997). Among these proteins, C/EBP- β uniquely responds to a variety of extracellular and intracellular signals to mediate a number of responses (Lekstrom-Himes and Xanthopoulos 1998; Kalvakolanu 2003). In a subsequent study, we demonstrated that a number of cellular IFN- γ -stimulated genes were dependent on C/EBP- β (Gade and others 2008). Most notable among these is the calcium and calmodulin-stimulated enzyme and death-associated protein kinase 1 (DAPK1) (Deiss and others 1995). IFN- γ activates the mitogen-activated protein kinases ERK1/ERK2 using upstream enzymes MEKK1 and MEK1/2 (Roy and others 2002) and phosphorylates Thr¹⁸⁹ residue of C/EBP- β , which then binds to a unique CRE/ATF motif in the *DAPK1* gene promoter and induces transcription (Gade and others 2008). More recently, we have shown that *DAPK1* expression from this motif also requires the ER-associated stress-responsive transcription factor, ATF6

TABLE 2. STUDIES PERFORMED TO ADDRESS INTERFERON SIGNALING WITHIN THE CENTRAL NERVOUS SYSTEM

<i>Transgene expressed</i>	<i>Gene deleted</i>	<i>Characteristics compared to its control</i>	<i>Reference</i>
Moderate level of <i>Ifnα</i> in astrocytes	None	Clinical disease with fatal seizures resulting in early death	Campbell and others (1999)
Low level of <i>Ifnα</i> in astrocytes	None	Loss of cholinergic neurons, gliosis, calcification affecting basal ganglia and cerebellum No clinical disease	
<i>Ifnγ</i> in oligodendrocytes	None	Hypomyelination and abnormal cerebellar development Shivering/shaking is similar to natural mouse models of hypomyelination (shivery/jimpy/quaking).	Corbin and others (1996)
<i>Ifnγ</i> in astrocytes	None	Hypomyelination, cerebellar and hippocampal dysplasia, and ataxia Death before reaching sexual maturity	LaFerla and others (2000)
None	<i>Ifnγ</i>	Highly susceptible to EAE leading to death	Ferber and others (1996); Krakowski and Owens (1996); Tran and others (2000)
None	<i>Ifngr</i>	Highly susceptible to EAE	Willenborg and others (1996, 1999)
None	<i>Ifngr</i> ^{CNS} <i>Ifngr</i> ^{Peri}	Frequent and severe atypical EAE Atypical EAE	Lee and others (2012) ^a
Low level of <i>Ifnα</i> in astrocytes	<i>Stat1</i>	Early onset of more severe neurological disease with a short lifespan (<8 weeks)	Wang and others (2002); Hofer and others (2010)
	<i>Irf9</i>	Early onset of severe neurological disease with short lifespan (<15 weeks) Progressive weight loss leading to a moribund state Inflammatory ocular disease likely, contributing to cataracts	Hofer and others (2010)
	<i>Irf9</i>	Early onset of even more severe accelerated neurological disease with a short lifespan (<5 weeks)	
Low level of <i>Ifnα</i> in astrocytes	<i>Ifngr1</i> <i>Stat2</i>	Severe inflammation with a short lifespan (<4 weeks) Cerebellar dysplasia and medulloblastoma were seen.	Wang and others (2003)

^aExperiments performed using a severe combined immuno-deficiency (SCID) mouse strain.
EAE, experimental autoimmune/allergic encephalomyelitis.

(Gade and others 2012). This protein is critical for alleviating ER stress caused by the unfolded protein response (UPR) (Ron and Walter 2007) (Fig. 2). We reported that IFN- γ treatment causes nuclear migration of ATF6. ATF6 is produced as an 85-kDa protein and inserted into the ER membranes (Adachi and others 2008). The N-terminal portion of this protein contains the essential transcription function. The C-terminus of ATF6 hangs in to ER lumen and serves as a stress sensor. After IFN- γ treatment, this protein first migrated to the Golgi, where it underwent endoproteolysis to free the transcriptionally active N-terminus. ATF6, thus activated, joined ERK1/ERK2-activated C/EBP- β to drive *DAPK1* expression (Gade and others 2012). Initially, *DAPK1* was isolated as an IFN- γ -inducible death-associated gene, whose overexpression caused cell death by promoting membrane blebbing (Deiss and others 1995; Bialik and Kimchi 2006). Later this enzyme was also found to regulate autophagy (Inbal and others 2002). *DAPK1* phosphorylates Beclin-1 (also known as autophagy associated gene 6) (Zalckvar and others 2009). Indeed, our recent studies revealed that both C/EBP- β and ATF6 were required

for driving autophagy (Gade and others 2012), consistent with the idea that these 2 proteins are major regulators of *DAPK1*. *In vitro*, *DAPK1* phosphorylates myosin heavy chain polypeptide. *In situ*, *DAPK1* associates with actin filaments (Cohen and others 1997). Loss of *DAPK1* has been documented in a number of metastatic human tumors (Gozuacik and Kimchi 2006). *In vivo* studies with *Dapk1*^{-/-} null mice showed an interesting neuronal phenotype. N-methyl-D-aspartate (NMDA) receptors constitute a major subtype of glutamate receptors at extrasynaptic sites that link multiple intracellular catabolic processes responsible for irreversible neuronal death (Tu and others 2010). *DAPK1* associates with NMDA receptor during brain ischemia and causes neuronal death. Activation of *DAPK1* following ischemic insult phosphorylates the NMDA receptor NR2B subunit at Ser¹³⁰³ residue (Tu and others 2010), while deletion of *Dapk1* protected neurons from death caused by ischemia and excitotoxicity and also protected animals against stroke damage.

Interestingly, C/EBPs, in particular C/EBP- β and C/EBP- δ , play a central role in memory. For example, the β -adrenergic

receptors induce the nerve growth factor gene using C/EBP- δ (Colangelo and others 1998). In the mouse cerebral astrocytes, vasoactive intestinal peptide and noradrenaline induce the expression of C/EBP- β and C/EBP- δ for driving the expression of genes involved in glycogen metabolism (Cardinaux and Magistretti 1996). In mouse models, C/EBP- β appeared to be important for the consolidation of new hippocampal, but not the reactivated, memory (Taubenfeld and others 2001). Furthermore, expression of C/EBP- β and C/EBP- δ in the hippocampal neurons was confirmed, and their transcriptional activities were augmented by cAMP, Ca²⁺, and CaM Kinases. It is proposed that these CaM kinases phosphorylate C/EBP- β and C/EBP- δ for promoting gene expression. In mouse primary cerebral cortical astrocyte cultures, cytokines such as IL-1, IL-6, LPS, IFN- γ , and TNF individually upregulated the expression of C/EBP- β and C/EBP- δ (Cardinaux and others 2000). These latter observations suggest that C/EBP proteins may participate in CNS signaling in response to many proinflammatory signals.

Whether IFN- γ -inducible expression of *DAPK1*, which C/EBP- β drives in other cell types, contributes to inflammatory pathologies in the CNS remains to be determined. As already mentioned above, DAPK1 is a Ca²⁺ and calmodulin-activated kinase that participates in both apoptosis and autophagy. Given that deletion of *Dapk1* protects mice from neuronal death induced by ischemia, it is likely that DAPK1 may have central roles in other pathologies. Whether *Dapk1*^{-/-} mice continue to have better memory retention as they age than their wild-type counterparts needs to be determined. Also, whether *Dapk1*^{-/-} mice are resistant to CNS inflammation induced by EAE remains an open question. Could there be a biochemical connection between the highly resistant phenotype of mice lacking *Fas* and *Tnfr1* genes to EAE (Hovelmeyer and others 2005) needs to be addressed.

Similarly, other cytokines (IL-3, IL-6, IL-12, and TNF- α) expressed as transgenes in astrocytes promote inflammation (Campbell 1998; Pagenstecher and others 2000) within the CNS (Table 2). In the mouse model of astrocyte-limited IFN- α overexpression, although dose-dependent functional neurological alterations were evident along with calcification in certain brain areas and progressive loss of cholinergic neurons, these mice showed mild clinical disease in a delayed manner (Campbell and others 1999). Absence of IFN- γ signaling aggravated both disease onset as well as severity in this model (Wang and others 2002; Hofer and others 2010). This is in contrast to overexpression of IFN- γ in the CNS that promoted hypomyelination and a neurological phenotype (see Table 2). Similarly, intracranial injection of HIV-positive human macrophages in severe combined immunodeficiency (SCID, an inability to mount acquired immune responses because of absence of functional T lymphocytes) mice (Tyor and others 1993) elicits behavioral abnormalities without neuronal cell loss (Cook-Easterwood and others 2007), along with increased IFN in the CNS (Sas and others 2007). Whether demyelination–remyelination occurs in this model is not known.

Neuropathies with Minor Immune Component Involvement

Spinal muscular atrophy (SMA) is a condition characterized by general muscle wasting, respiratory distress, and impaired mobility. The motor neurons in the anterior horn of

the spinal cord gradually die when there is a defect in the *SMN1* gene. The severity of the disease is determined by dosage compensation provided by the tightly linked paralog *SMN2*. SMN proteins are needed for the biogenesis of sno/scaRNPs and splicing of pre-mRNA. Even though all cells in the body need this machinery, a functional basis for motor neuron-specific toxicity due to SMN1's absence is yet to emerge. The level of sno/scaRNPs is dependent on a cell's transcriptional activity and the best characterized function of sno and scaRNPs is in the processing and maturation of ribosomal and spliceosomal RNAs, respectively. Fibrillarin (a 2' ribose methylase) and dyskerin (DKC1, a pseudouridylyase) are important enzymatic components in the biogenesis of sno/scaRNPs. Antibodies targeting fibrillarin are found in scleroderma patients (Chen and others 2002; Herrera-Esparza and others 2002). Mutations in *DKC1* have been described in cases of dyskeratosis congenita (Knight and others 1999b) and its severe variant, Hoyeraal–Hreidarsson syndrome (Knight and others 1999a). Even though they present with wide clinical features, mental retardation caused by cerebellar hypoplasia and bone marrow failure leading to immunodeficiency are common in these patients. IFNs may influence these processes. Our earlier studies identified novel roles played by cellular genes, genes associated with retinoid-interferon induced mortality (GRIMs), that affected retinoic acid/IFN- β -induced growth suppression (Kalvakolanu 2004). We reported the isolation of a novel IFN-inducible *GRIM-1* (also known as *SHQ1*) using a genetic screen (Hofmann and others 2010). GRIM-1 attenuates sno/scaRNA levels by delocalizing DKC1 (Nallar and others 2011). SUMOylation imparts stability to the DKC1 protein (Brault and others 2013), while IFN β treatment suppressed DKC1 levels (Nallar and others 2011). IFN- β/γ or IRF-1 induced SMN protein levels and restored SMN2 levels (in fibroblasts from SMA patients) comparable to control fibroblasts, and this suggested that IFN- β has a potential therapeutic benefit in SMA patients (Baron-Delage and others 2000). However, IFN- β induces GRIM-1 levels much higher, and this is directly connected to the reduced and delocalized DKC1 protein, thus making the cell vulnerable to apoptosis. However, this experiment needs to be done in a specific cell type from SMA patients to draw meaningful conclusions. These may ultimately guide decisions to use IFNs as therapeutics in these patients.

Leigh syndrome is a condition characterized by hypotonia, dystonia, ataxia, progressive loss of voluntary eye movements, and respiratory distress (Agapitos and others 1997). Demyelinating lesions in the basal ganglia, brain stem, and cerebellum caused by genetic defects in the biogenesis of mitochondrial oxidative phosphorylation (OXPHOS) complex IV (cytochrome c oxidase) is believed to cause this disease (Pecina and others 2003). Histological signs of neuronal damage, gliosis, necrosis, and capillary proliferation are also seen. In general, defective OXPHOS and/or genetic loss of OXPHOS components elicit apoptosis; mice engineered to lack a single OXPHOS gene die *in utero* or shortly after birth (Huang and others 2004; Piruat and others 2004; Kruse and others 2008). However, OXPHOS capacity is kept to a minimum in tumors and downregulated OXPHOS gene products are evident in most cancers [reviewed in (Chandra and Singh 2011)]. IFNs regulate a number of mitochondrial gene products, including those involved in oxidative phosphorylation. IFN- β can downregulate mitochondrially coded

gene products corresponding to cytochrome b, cytochrome oxidase subunit I, and NADH dehydrogenase ND5 subunit (Shan and others 1990) while inducing a few nuclear gene products of OXPHOS (Huang and others 2007). Our earlier studies to find mediators of retinoic acid/IFN- β -induced growth suppression identified a nuclear genome-encoded *GRIM-19* (also known as *NDUFA13*) (Angell and others 2000) as one key member that regulates OXPHOS. In most cells, the majority of GRIM-19 protein is present in mitochondrial complex I (NADH dehydrogenase). The *GRIM-19* gene maps to a chromosomal locus frequently lost in prostate cancer and is downregulated in numerous human cancers (Kalvakolanu and others 2010), and a few point mutations were recently reported (Nallar and others 2013). In rat cerebrum, very high Grim-19 levels were found during ischemia-induced neuronal cell death (Mehravian and others 2007). OXPHOS complexes inter-regulate their stability [reviewed in (Lenaz and Genova 2010)]. Even though loss of GRIM-19 expression is observed in many different human and mouse cancers (Alchanati and others 2006; Kalvakolanu and others 2010), we addressed this question using a skin-specific deletion of *Grim-19* gene and found that such mice were highly prone to chemical carcinogenesis (Kalakonda and others 2013). Analysis of mitochondrial functions in *Grim-19*-deficient cells showed a clear loss of oxygen consumption, owing to a defective assembly of OXPHOS complexes. In this model, complexes I, II, IV, and V appear to be maintained in a suboptimal manner in the absence of Grim-19. Demyelination caused by selective loss of oligodendrocytes as seen in LS patients' defective in OXPHOS remains to be addressed. This cell selective toxicity is reminiscent of JC virus activation in humans. Interestingly, many pathogenic stimuli induce *GRIM-19* expression and some pathogens have arsenals to block GRIM-19's apoptotic function [reviewed in (Kalvakolanu and others 2010)]. Recently, the involvement of GRIM-19 in innate immune responses was shown by increased susceptibility of *Grim-19* heterozygous male mice to urinary tract infections caused by *Staphylococcus saprophyticus* (Chen and others 2012). In summary, a number of noncanonical IFN-responsive genes (those not directly involved in antiviral responses and/or immune modulation) are emerging. Their relevance to CNS pathologies in IFN-dependent and independent actions needs to be examined.

Conclusions and Future Perspectives

The foregoing discussion projects a potential relevance of IFN and IFN-inducible genes in CNS diseases. A very basic, yet fundamental, question to ask is—can the presence of a virus in the body, not necessarily in the CNS, make the BBB more permeable to immune cells in systemic circulation? If not, did the virus enter the CNS during the incubation period to induce CNS-limited IFN synthesis to alter BBB permeability? Why there are numerous *IFNA* genes and can their individual physiological functions be dissected? During cellular stress, translation of cellular mRNAs proceeds in a cap-independent manner. For this to occur, a *cis* structural feature called the internal ribosome entry site (IRES) is required. Almost all viral-encoded nucleic acid messages are dependent on IRES for their translation [reviewed in (Komar and Hatzoglou 2011)]. Ribosomal RNA modifications guided by snoRNAs were shown to be important for cap-independent translation of a few cellular mRNAs [re-

viewed in (Ruggero 2013)]. To our knowledge, all *IFN* and most ISG mRNAs lack IRES-like features that would permit their translation when PKR-like inhibitory signatures are prevalent in the cell either because of an infection or because of a direct IFN signaling through the receptor. Is it possible that some of the *IFN* mRNAs perform IRES-like task *in trans*?

Animal models of dys/hypomyelination have shown that myelination confers a benefit by decreasing the energy demands of axons to maintain homeostasis and reduces oxidative stress. The pathophysiological consequence of this dysregulated energy state is unfavorable to neurons, leading to permanent loss of nerve fibers. Neurons need a constant high supply of energy to cope with its metabolic demands. For this, neurons rely heavily on mitochondrial OXPHOS that provides the necessary flux of ATP to maintain and regulate $\text{Na}^+/\text{K}^+/\text{Ca}^{++}$ pumps/channels, antero/retrograde transport of cell cargo, and neurotransmission components. Loss of neuronal functions, as seen in MS, has been attributed to degeneration of axons that have lost their myelin coats. The protective effect of reactive oxygen species scavengers in preventing experimentally induced optic nerve degeneration needs to be tested as an alternative option in MS therapeutic interventions. Most of the demyelination/mitochondrial-linked pathologies are fatal and act in a quick fashion; ie, suffering is kept to a short time. Whereas most forms of MS appear to be the mildest form of CNS demyelination, should refocus our attention whether to treat or not given its obvious end point as relapse-free survival cannot be predicted with confidence in a disease that extends well into decades.

Aicardi–Goutières syndrome (a fatal, rapidly progressing encephalopathy seen in infants characterized by excess IFN production caused because of an accumulation of nucleic acids that are normally degraded in cells), SLE, and Sjögren's syndrome (an autoimmune condition that destroys lacrimal and salivary glands first and can progress to target other organs in a delayed manner) are examples for natural IFN- α production at a higher level that results in development of autoimmune responses. In mouse models, accumulation of endogenous retroviral-derived ssDNA products elicits ISNAR (Morita and others 2004), whether this leads to autoimmune conditions is not known across mouse strains. So could there be a viral trigger that aggravates MS disease symptoms in humans? Are resident memory T cells (Wakim and others 2010) to be blamed in these pathologies as they stay put for long periods? The “shiverer” and related mouse models offer a unique opportunity to study the influence of MHC alleles in eliciting the autoimmune component that may be relevant to MS. Even though IFN- β is more potent than IFN- α , minimal side effects observed during its use are rather surprising. MS is clinically unpredictable mostly because of its slow and long course. In a recent meta-analysis, the therapeutic benefit of IFN- β in relapsing-remitting MS patients appeared to be modest, and no association with a reduction in progression of disability was apparent (Ebers and others 2010; Shirani and others 2012) even though other studies suggested beneficial effect of IFN- β (Goodin and others 2011; Goodin and others 2012). Some patients who are diagnosed as presenting fulminant MS are valuable subjects to decipher the protective role of IFN- β in maintaining myelination and preserving neuronal functions in the CNS. A recent study found that

TABLE 3. GENES IMPLICATED IN NERVOUS SYSTEM DISEASES: INSIGHTS FROM MOUSE GENETIC STUDIES

<i>Clinical diagnosis</i>	<i>Human gene implicated</i>	<i>Mouse genotype</i>	<i>Phenotype in mouse line (compared to control)</i>	<i>Reference</i>
SMA	<i>SMN1</i>	<i>Smn1</i> ^{-/-}	Pathological changes similar to human SMA	Hsieh-Li and others (2000)
Amyotrophic lateral sclerosis	<i>SOD1</i>	<i>SMN2</i> <i>Sod1</i> ^{-/-}	High vulnerability of motor neuron loss following axonal injury Accelerated age-related muscle atrophy Shorter life span	Reaume and others (1996)
	<i>ADARB1</i>	<i>Adarb1</i> ^{-/-}	No developmental defects Highly seizure prone and early death	Higuchi and others (2000); Hideyama and others (2012)
Adrenoleukodystrophy	<i>ABCD1</i>	<i>Abcd1</i> ^{-/-}	Normal No demyelinating lesions in the CNS	Lu and others (1997)
Metachromatic adrenoleukodystrophy	<i>ARSA</i>	<i>Arsa</i> ^{-/-}	Normal appearing white matter Late-onset of gliosis Impaired neuromotor coordination	Hess and others (1996)
Krabbe disease	<i>GALC</i>	<i>Galc</i> ^{H186C (KI)}	Spontaneous tremulousness Accumulation of psychosine	Luzi and others (2001)
Pelizaeus–Merzbacher disease	<i>PLP1</i>	<i>Plp1</i> ^{-/-}	Normal Compacted myelin sheath is unaffected	Klugmann and others (1997); Sporkel and others (2002)
	<i>GJC2</i>	<i>Gjc2</i> ^{-/-}	Normal No gross demyelination in the CNS	Menichella and others (2003)
		<i>Gjc2</i> ^{-/-} <i>Gjb2</i> ^{-/-}	Death by 6 weeks Worsening tremors Thin or absent myelin sheaths, enlarged periaxonal collars, oligodendrocyte cell death, and axonal loss	
Charcot–Marie Tooth disease	<i>GJB2</i>	<i>Gjb2</i> ^{-/-}	Normal No gross demyelination of peripheral nerves	Nelles and others (1996)
Canavan disease	<i>ASPA</i>	<i>Aspa</i> ^{-/-}	Pathological changes similar to human disease Increased levels of NAA in brain and body fluids, severe mental retardation, and early death	Matalon and others (2000)
Alexander's disease	<i>GFAP</i>	<i>Gfap</i> ^{-/-}	Normal No gross histological or neurological changes Enhanced long-term potentiation in CA1 region Late onset of hydrocephalus, loss of vasculature in white matter, and CNS dysmyelination	Pekny and others (1995); Liedtke and others (1996); McCall and others (1996)
		<i>Mbp</i> ^{Golli -/-}	No gross defects in CNS myelination Delayed myelination with hypomyelination in certain brain areas	Jacobs and others (2005)
		<i>Mog</i> ^{-/-}	Normal No gross histological or neurological changes Resistant to EAE	Delarasse and others (2003)
		<i>Mag</i> ^{-/-}	Normal Slightly delayed myelination Subtle intention tremor seen Organization of the periaxonal cytoplasmic collar is partially impaired	Li and others (1994); Montag and others (1994); Fujita and others (1998)

CNS, central nervous system; NAA, N-acetyl aspartate (excess of this metabolite causes neurodegeneration, while low levels are associated with depression); SMA, spinal muscular atrophy.

chronic exposure of neuronal cultures to IFN- β inhibited brain-derived neurotrophic factor-stimulated neurite outgrowth and survival (Dedoni and others 2012). Given that there were no adverse clinical side effects associated with IFN- β administration, a mouse model of low IFN- β expression in the CNS should help us delineate its therapeutic benefit in demyelinating conditions.

Yet certain other neurological conditions do not have a significant immune contribution like Leber's hereditary optic neuropathy, a mitochondrially inherited condition caused by mutations in select genes coding for protein components of OXPHOS complex I (Wallace and others 1988). The retinal ganglion cells and their axons are the only cells that are destroyed leading to loss of central vision. Movement disorders seen in a few severe cases of this disease bear striking resemblance to changes observed in periventricular white matter of MS patients (Nikoskelainen and others 1995). Degeneration of specific motor neurons cripples voluntary muscle action leading to muscle atrophy. Depending on which neurons (upper or lower) have degenerated, clinically they are classified as primary lateral sclerosis (upper only), primary muscular atrophy (lower only), or the worst amyotrophic lateral sclerosis (upper and lower) at initial diagnosis. However with time, both nerve tracts eventually degenerate. When only select nerve fibers that enter or leave the brain stem degenerate, they are called pseudobulbar or progressive bulbar palsy, respectively. No definitive genetic causes have been found yet, although *SOD1* is a prime candidate in the familial form of amyotrophic lateral sclerosis (Bruijn and others 1998). Interestingly, other brain areas are not affected at presentation and cell types affected seem to be very restricted.

Alterations in lipid metabolism are also not tolerated by certain cell types that result in disease states like leukodystrophies [see (Compston and others 1997)]; regional loss of white matter in the CNS because of degeneration of oligodendrocytes and even astrocytes are affected in some forms. Genetic factors implicated in human leukodystrophies are summarized in Table 3. Genetic manipulation of mouse genes has highlighted the importance of a few but not others in these pathologies (Table 3). Even though inflammation is seen in these cases, presence of antibodies against proteins of nerve or oligodendrocyte origin has not been reported. To our knowledge, alterations in other cytokines are not reported in these mouse models. In light of what has been observed with mouse models as applicable to human nervous system diseases, we suggest a potential crosstalk among the biochemical, structural, and stress response components in the CNS and PNS.

Thus, it is apparent that either an excess or a lack of IFNs manifest as distinct pathologies; ie, specific cell types/tissues are effected much more than others. The CNS particularly becomes more vulnerable to virus-induced cytopathic effects when protections from IFNs are missing. However, none of the genetic knockouts of IFN signal transduction factors as such has shown neuronal dysfunction. This becomes intriguing that circadian rhythm, opioid receptor system, thermoregulation, etc, are hardly affected in IFNs' absence, while an excess of IFN- α in the CSF or administered IFN- α 2 [see (Reyes-Vazquez and others 2012)] was reported to alter these functions even in healthy subjects. Hence, how this system functions and responds in a physiological presence of an individual IFN- α remains to be addressed in the coming years. In summary, correct IFN levels and/or signaling are

needed to maintain hematopoietic and peripheral tissue integrity and functionality. Since these molecules quite often have pleiotropic functions, it is important to watch closely as therapeutically administered cytokines can promote unforeseen side effects. Inflammation in the CNS can be evoked by diverse stimuli like external agents, aberrant cellular factors, absence of certain plasma membrane protein components, anti-immune responses toward certain protein, and altered fatty acid metabolism. Therapeutic research strategies should be able to address this potentially increasing list of causes that we hope does not expand fast in the coming years.

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