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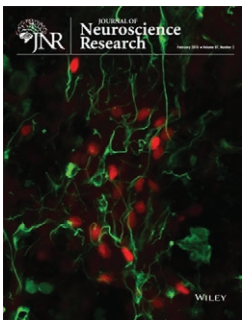
MINIREVIEW



Therapeutic spectrum of interferon-β in ischemic stroke

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Abstract

Ischemic stroke is devastating and a major cause of morbidity and mortality worldwide. To date, only clot retrieval devices and/or intravenous tissue plasminogen activators (tPA) have been approved by the US-FDA for the treatment of acute ischemic stroke. Therefore, there is an urgent need to develop an effective treatment for stroke that can have limited shortcomings and broad spectrum of applications. Interferon-beta (IFN-β), an endogenous cytokine and a key anti-inflammatory agent, contributes toward obviating deleterious stroke outcomes. Therefore, exploring the role of IFN-β may be a promising alternative approach for stroke intervention in the future. In the present review, we have discussed about IFN-β along with its different mechanistic roles in ischemic stroke. Furthermore, therapeutic approaches targeting the inflammatory cascade with IFN-β therapy that may be helpful in improving stroke outcome are also discussed.

KEYWORDS

Anti-inflammatory, cytokines, IFN-β, stroke

1 | STROKE

Stroke is a global health concern that leads to permanent disability in approximately 30% of survivors (Weinstein, Koerner, & Möller, 2010). It has devastating complications arising from either a sudden loss of blood supply to the brain (ischemic stroke) or rupturing of blood vessels in the brain (hemorrhagic stroke) (Deb, Sharma, & Hassan, 2010). Stroke leads to the induction of inflammatory cascade via migration of activated microglia to the ischemic core, worsening its outcomes (Perera et al., 2006). The narrow therapeutic window and insufficiency to recover or protect the dying neurons are certain limitations of current treatment strategies for stroke, so there is an urgent need for an alternative approach (Fann et al., 2013; Kaur et al., 2018). The limitation to improve the aggravated inflammatory condition by currently used thrombolytic agents necessitates newer treatment options for stroke (Carroll, 2009). Interferon-β is known to have immunomodulatory and anti-inflammatory properties and can be explored for improving conditions after stroke (Dhib-Jalbut & Marks, 2010). IFN-β plays a role as an anti-inflammatory agent through several immune cascades. IFN-β significantly helps in obviating neuro-inflammatory conditions of the central nervous system and improves the pathogenesis of many neurological conditions. A report suggested its role in decreasing neuronal cell death and increasing functional recovery attenuating inflammation after stroke onset (Kuo et al., 2016).

2 | INTERFERON

Interferons (IFNs) are signaling proteins belonging to a family of cytokines (Nallar & Kalvakolanu, 2014). IFNs are actively engaged in altering the cellular immune system against the viral infections

of host cells (Fritsch & Weichhart, 2016). IFNs generally act against extracellular biomolecules via the stimulation of Toll-like receptors (TLRs) and amplify the antigen presentation to specific T cells. They act by both paracrine and autocrine modes for the regulation of acquired and innate immunity via stimulation of intercellular and intracellular networks providing resistance to certain viral infections and maintenance of normal cell survival and tumor cell death (Le, Genin, Baines, & Hiscott, 2000).

2.1 | Types of interferons and their signaling pathways

Interferons have been classified according to their structural homology and receptor types as type I, II, and III. Type I IFNs include alpha (α), beta (β), delta (δ), epsilon (Ɛ), kappa (κ), and omega (ω). Type-II IFNs include gamma (γ) and type-III, also known as IFN-lambda (λ), have interferon-like activities (Kopitar-Jerala, 2017; Wack, Terczyńska-Dyla, & Hartmann, 2015). Type-I IFNs α and β act by binding to interferon alpha-receptors (IFNARs). The IFNAR is a heterodimeric transmembrane receptor consisting of two subunits that is, IFNAR1 and IFNAR2 (Sheppard et al., 2003). The binding of IFNs α and β with the IFNAR leads to the activation of receptor-associated protein tyrosine kinases. Janus kinase 1 and tyrosine kinase 2 in turn phosphorylate the signal transducer and activator of transcription 1 (STAT1) and 2 (STAT2). Activation of STAT 1 and 2 is followed by dimerization and translocation into the nucleus and, by combining with IFN-regulatory factor 9, forms a trimolecular complex called IFN-stimulated gene factor 3 (ISGF3). This ISGF3 further binds to DNA sequences, which are known as IFN-stimulated response elements, and directly activates the transcription of ISGs. The signal decays within a period of hours and the STATs are exported back to the cytoplasm for the next signaling process (Figure 1). Other key regulators of the IFN signaling cascade are the negative regulators which cover different mechanisms that suppress type I IFN-mediated expressions such as suppressor of cytokines signaling (SOCS) and ubiquitin carboxy-terminal hydrolase 18 (USP 18) (Kopitar-Jerala, 2017; Schreiber & Piehler, 2015) (Table 1).

2.1.1 | Role of interferons

Type I IFNs (IFN-α and IFN-β) exhibit a wide breadth of biological activities (antiviral, anti-inflammatory, and anti-proliferative) (Kuo et al., 2016). The latter occurs via cytotoxic stimulation of numerous cells of the immune system such as natural killer cells, monocytes, T cells, macrophages, and dendritic cells. IFNs can also upregulate the cell surface expression of major histocompatibility complex (MHC) antigens and

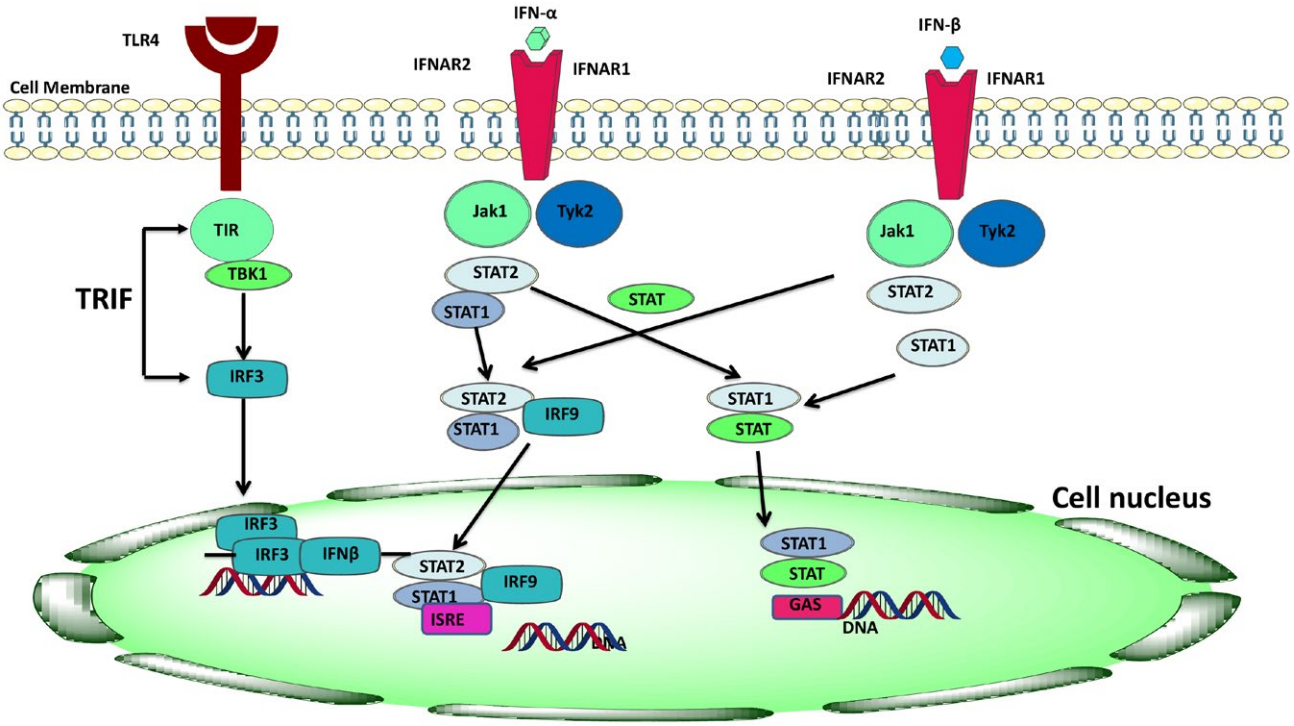

FIGURE 1 Interferon signaling pathway. Binding of IFNs (α and β) with IFNAR (Interferon-α/β receptor): Activation of receptor-associated protein tyrosine kinase. (a) Janus kinase-1. (b) Tyrosine kinase-2. (c) Signaling pathway through TRIF. These two protein tyrosine kinases start phosphorylation of signal transducer and activator of transcription1 STAT1 & STAT2. Activation of STAT1 & STAT2. Dimerization and translocation of STAT1 & STAT2 to the nucleus. Formation of trimolecular complex together with IFN-regulatory factor-9 (IRF-9) that is, IFN-stimulated gene factor-3 (ISGF3). Binding of ISGF-3 with DNA sequence called as IFN-stimulated response elements. These IFN-stimulated response elements activate transcription of ISGs directly and regulate signaling of IFNs. Within hours signal decays and STATs return to cytoplasm for next signaling pathway. TLR 4 mediated IFN-β activation through TRIF-dependent pathway via Interferon regulatory factor 3 (IRF-3) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Types of human IFN and IFN-like proteins

Ligand types	Names	Receptor chain 1	Receptor chain 2
IFN (Type-I)	IFN-α	IFN-α R1/IFNAR1	IFN-α R2/IFNAR2
	IFN-β		
	IFN-k		
	IFN-ε		
	IFN-ω		
	IFN-v		
IFN (Type-II)	IFN-γ	IFN-γ R1	IFN-γ R2
IFN-like proteins	IL-28A	IL-28R1	IL-10R2
	IL-28B		
	IL-29		

tumor-associated surface antigens. It helps in the induction or activation of pro-apoptotic genes and proteins (Bak, Bax, TNF-related apoptosis-inducing ligand (TRAIL), and caspases) as well as the repression or reduction of anti-apoptotic genes such as inhibitor of apoptosis protein (IAP) and B-cell lymphoma 2 (Bcl-2), responsible for cell proliferation and differentiation and anti-angiogenic activity (Pestka, 2007).

IFNs have been recognized to be deeply implicated in the pathogenesis of several diseases, for example, collagen diseases such as rheumatoid arthritis (Conigliaro et al., 2010), systemic lupus erythematosus (SLE) (Gao, Anolik, & Looney, 2018), multiple sclerosis (Rudick & Goelz, 2011), insulin-dependent diabetes mellitus (Qaisar, Jurczyk, & Wang, 2018), pancreatic cancer (Booy, Hofland, & van Eijck, 2015), fulminant hepatitis (Borst et al., 2018), atherosclerosis (Moss & Ramji, 2017), and allergic diseases (Gonzales-van Horn & Farrar, 2015). IFNs are clinically used in the therapy against viral infections such as hepatitis B and C (Asselah & Marcellin, 2018; Jaeckel et al., 2001) and for different malignancies (Baron et al., 1991; Imanishi, 1994).

Interferon-β

Interferon-β (IFN-β), a broadly expressed cytokine, was approved by the US FDA in the past for the relapsing-remitting multiple sclerosis (RRMS) treatment for more than a decade (Kuo et al., 2016). IFN-β drives innate immunity, acting in response to pathogenic attack or injury via activation of both pro-and anti-inflammatory cytokines. Currently, research is being conducted to find a protective role of IFN-β in several diseases such as ischemic stroke, subarachnoid hemorrhage, colitis, colorectal cancer (Kotredes, Thomas, & Gamero, 2017; Kuo et al., 2016; Tiebosch et al., 2013) along with other conditions (Table 2) (68), such as anti-inflammatory (Kuo et al., 2016), antiviral (Kraus & Oschmann, 2006; Samuel, 2001), immuno modulatory (Kasper & Reder, 2014), anti-proliferative (Dierckx et al., 2017), anti-angiogenic (Friedman, 2008), and cell differentiation (Kraus & Oschmann, 2006) (see Table 2).

2.2 | Interferon-beta (IFN-β): Mechanistic roles and actions

Neurodegeneration is mostly triggered by numerous inflammatory mediators that can lead to neurological pathologies including ischemic stroke (Zipp & Aktas, 2006). Inflammation is initiated by the release of various inflammatory mediators; activation of intravascular leukocytes helps in the infiltration of immune cells in the CNS (Anrather & Iadecola, 2016; Kieseier, 2011). Immune cells migration across the blood–brain barrier (BBB) causes breakdown of the BBB due to the release of numerous cytotoxic agents like cytokines, matrix metalloproteinase, nitric oxide (NO), and reactive oxygen species (ROS), leading to demyelination and axonal injury which are common outcomes of neurodegeneration (Kuo et al., 2016). Although the damage caused to neurons is not reparable, immunomodulatory therapies have been reported to decrease inflammation (Markowitz, 2007). IFN-β, a polypeptide produced by fibroblasts, attaches to its specific receptor and initiates a complex transcriptional reaction producing a pharmacological response at the site of injury. Markowitz reported that IFN-β helps in suppressing antigen presentation, decreasing T cell proliferation, and altering cytokine and matrix metalloproteinase expression (Kieseier, 2011; Markowitz, 2007).

IFN-β helps in the elevation of concentration and expression of anti-inflammatory agents while it down-regulates the pro-inflammatory cytokine expression (Kuo et al., 2016). A systemic application of IFN-β may reduce the increased cell count of inflammatory cells across the BBB and help raise nerve growth factor (NGF) levels, ultimately resulting in a dramatic increase in the survival of neurons (Kieseier, 2011). IFN-β may also help in raising the $CD56^{bright}$ natural killer cell count: these cells produce anti-inflammatory mediators very efficiently and have the capacity to mitigate neuronal inflammation in the peripheral blood circulation. With various mechanistic approaches, IFN-β manifests to be clinically relevant by reducing lesions, decreasing the risk of sustained disability progression, and decreasing brain atrophy (Kieseier, 2011).

Cerebral ischemia is responsible for producing various immune cell mediators which can exacerbate ischemic brain injury. These various inflammatory mediators, under certain situations, may induce tolerance to cerebral ischemia. Mediators like proinflammatory cytokines for example, interleukin 1 (IL-1), tumor necrosis factor (TNF), and damage-associated molecular patterns (DAMPs) are responsible for the activation of intracellular signaling pathways which mediate stress responses (Anrather & Iadecola, 2016).

TABLE 2 Clinical trials of interferon beta-1b and interferon beta-1a

Sr. No	Phase	Status	Condition	Count	References
Interferon-β					
Interferon-β1b					
1.	I	Completed	Disseminated Sclerosis	I	https://www.drugbank.ca/
2.	I	Completed	Human Immuno-deficiency Virus Infections (HIV)/ Kaposis Sarcoma	I	https://www.drugbank.ca/
3.	I, II	Completed	Acute Respiratory Distress Syndrome (ARDS)/ Acute Lung Injury (ALI)	I	https://www.drugbank.ca/
4.	II	Completed	Disseminated Sclerosis	III	https://www.drugbank.ca/
5.	II	Completed	Disseminated Sclerosis/Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
6.	II	Completed	Heart Disease/Prophylaxis of Cardiomyopathy	I	https://www.drugbank.ca/
7.	II	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
8.	II	Completed	Disseminated Sclerosis	I	https://www.drugbank.ca/
9.	II, III	Not known	Disseminated Sclerosis/Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
10.	II, III	Recruiting	Middle East Respiratory Syndrome Coronavirus (MERS-Coronavirus)	I	https://www.drugbank.ca/
11.	II, III	Recruiting	Disseminated Sclerosis	I	https://www.drugbank.ca/
12.	III	Terminated	Disseminated Sclerosis	II	https://www.drugbank.ca/
13.	III	Completed	Human Immunodeficiency Virus Infections	I	https://www.drugbank.ca/
14.	III	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS	II	https://www.drugbank.ca/
15.	III	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
16.	III	Terminated	Disseminated Sclerosis	I	https://www.drugbank.ca/
17.	IV	Withdrawn	Disseminated Sclerosis	I	https://www.drugbank.ca/
18.	IV	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	IV	https://www.drugbank.ca/
19.	IV	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
20.	IV	Terminated	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
Interferon-β1a					
1.	0	Completed	Disseminated Sclerosis	I	https://www.drugbank.ca/
2.	I	Completed	Healthy volunteers	II	https://www.drugbank.ca/
3.	I	Completed	Cerebrovascular Accidents	I	https://www.drugbank.ca/
4.	I	Completed	Disseminated Sclerosis	I	https://www.drugbank.ca/
5.	I	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	II	https://www.drugbank.ca/

(Continues)

TABLE 2 (Continued)

Sr. No	Phase	Status	Condition	Count	References
6.	II	Completed	Disseminated Sclerosis	V	https://www.drugbank.ca/
7.	II	Completed	Asthma Bronchial	I	https://www.drugbank.ca/
8.	II	Completed	Alzheimer's Disease (AD)	I	https://www.drugbank.ca/
9.	II	Completed	Polyradiculoneuropathy, Chronic Inflammatory Demyelinating	I	https://www.drugbank.ca/
10.	II	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	III	https://www.drugbank.ca/
11.	II	Completed	Ulcerative Colitis (UC)	II	https://www.drugbank.ca/
12.	II	Terminated	Crohn's Disease (CD)	I	https://www.drugbank.ca/
13.	II	Withdrawn	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
14.	II, III	Active Not Recruiting	Disseminated Sclerosis	I	https://www.drugbank.ca/
15.	II, III	Recruiting	Disseminated Sclerosis/Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
16.	III	Completed	Disseminated Sclerosis	III	https://www.drugbank.ca/
17.	III	Completed	Chronic Hepatitis-C Infection	I	https://www.drugbank.ca/
18.	III	Completed	Clinically Isolated Syndrome (CIS)	I	https://www.drugbank.ca/
19.	III	Recruiting	Respiratory Distress Syndrome, Adult	I	https://www.drugbank.ca/
20.	III	Terminated	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
21.	III	Terminated	Disseminated Sclerosis	I	https://www.drugbank.ca/
22.	III	Withdrawn	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
23.	IV	Completed	Disseminated Sclerosis	V	https://www.drugbank.ca/
24.	IV	Completed	Relapsing-Remitting Multiple Sclerosis (RRMS)	XII	https://www.drugbank.ca/
25.	IV	Completed	Clinically Isolated Syndrome (CIS)/Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
26.	IV	Terminated	Relapsing-Remitting Multiple Sclerosis (RRMS)	I	https://www.drugbank.ca/
27.	IV	Terminated	Disseminated Sclerosis	I	https://www.drugbank.ca/
28.	IV	Withdrawn	Demyelinating Disorders/Disseminated Sclerosis/Neuritis/Optic Neuritis	I	https://www.drugbank.ca/
29.	IV	Withdrawn	Relapsing-Remitting Multiple Sclerosis (RRMS)	II	https://www.drugbank.ca/
30.	Unavailable	Withdrawn	Disseminated Sclerosis	I	https://www.drugbank.ca/

Immune cell therapies are highly explored in not only preclinical but also clinical settings for various acute injuries related with the CNS, including stroke (Bang, 2016; George & Steinberg, 2015). IFN-β is immunomodulatory and helps regulate the function of immune cells in ischemic stroke.

IFN-β modulates antigen presenting cells (APCs) to reduce antigen presentation and stimulation of T cells (Jiang et al., 1995). IFN-β directly affects T cells and inhibits adhesion of molecules like intercellular adhesion molecule (ICAM) and vascular adhesion molecule (VCAM) to the BBB and passage through the same (Dhib-Jalbut & Marks, 2010). B cells secrete inflammatory mediators that are responsible for stimulating plasma cells to produce immunoglobulins (IGs) in the cerebrospinal fluid (CSF) (Dalakas, 2008). B cell activating factor (BAFF), belonging to the TNF family, is upregulated in the blood (Krumbholz et al., 2008) and is crucial for maintaining B cells level at the inflammation site and can aggravate local inflammation by facilitating B cell survival (Krumbholz et al., 2005). IFN-β modulates B-cell function which can alter antigen presentation. Expression of MHC II on B cells is reduced post-therapy with the help of IFN-β through a decrease in CD80 expression that inhibits antigen presentation to CD8+T cells (Genç, Dona, & Reder, 1997; Jiang et al., 1995). IFN-β treatment results in the upregulation of CD86 expressing B cells and contributes to the reduction of type 1 T helper (Th1) cell secretion of inflammatory cytokines (Huang, Ito, Dangond, & Dhib-Jalbut, 2013). Levels of BAFF are also upregulated in blood leukocytes and serum with IFN-β therapy, showing elevated B cell function (Krumbholz et al., 2008). With the correct combination of stimuli, it can lead to increased B cell secretion of anti-inflammatory cytokines like IL-8 and IL-10, suggesting that IFN-β can increase CD4 and CD8 regulatory T cells along with regulatory B cells (Meinl, Krumbholz, & Hohlfeld, 2006).

3 | ISCHEMIC STROKE AND INTERFERON-β: CROSSTALK

3.1 | Ischemic cascade

Cell death following brain ischemia is mediated by a diverse group of etiologies such as severe focal hypoperfusion that eventually results into excitotoxicity and oxidative damage (Lakhan, Kirchgessner, & Hofer, 2009). These events are responsible for causing microvascular injury, BBB dysfunction, and elicit inflammation after ischemia. Events of such kind worsen the primary injury and may result in severe cerebral damage. The extent of permanent cerebral damage relies upon different factors such as ischemic duration, infarct volume, along with the auto-repairing capability of the brain (Dirnagl, Iadecola, & Moskowitz, 1999; Lakhan et al., 2009).

The responses after inflammatory cascade that worsen the cerebral injury post-ischemia is an interesting target for therapeutics, as inflammation increases over time and is strongly involved in the exacerbation of neuronal outcomes (Jin, Yang, & Li, 2010). It has been reported that post-ischemia, systemically applied IFN-β helps in attenuating brain infarct progression (Veldhuis et al., 2003).

During the sub-acute phase of ischemia, resident microglial cells (MGs) and peripheral inflammatory cells infiltrate into the surrounding and core region of the infarct area of the brain, leading to secondary neurodegeneration (Weinstein et al., 2010). The onset of ischemia is mainly linked with the extravasation of plasma-derived protein, bioactive phospholipids, BBB disruption, and prompt resident MG activation and infiltration into the ischemic site. These multifarious events lead to the activation of pro-inflammatory cytokines like chemokines (C-C motif) ligand 2 (CCL2), chemokine (C-C motif) ligand 3 (CCL3), TNF-α, IL-1b, and endogenous NO release at the injury site, culminating in neuronal death (Denes, Thornton, Rothwell, & Allan, 2010; Weinstein et al., 2010).

3.2 | Neuroprotective role of IFN-β in Ischemic stroke

CNS inflammation induced due to ischemic conditions plays an essential role in stroke pathophysiology and exacerbates infarct formation at the injury site (Amantea et al., 2015; Benakis, Garcia-Bonilla, Iadecola, & Anrather, 2015; Kawabori & Yenari, 2015). IFN-β markedly reduces infarct size by inhibition of the production of inflammatory cytokines such as IL-6, IL-23p19, IL-1b, and TNF-α; all of these cytokines are found to be increased in the ipsilateral part of the ischemic brain (Kuo et al., 2016) (Figure 2). Endogenous IFN-β signaling limits local inflammation, regulates peripheral immune cells, and, thereby, may contribute positively to stroke outcome (Inácio et al., 2015).

Rapidly activated MGs in response to ischemic injury are a major factor for the production of inflammatory mediators and increased phagocytosis. Activated MGs trigger innate immune responses followed by increased production of matrix metalloproteinase (MMPs), leading to BBB damage. These inflammatory mediators cause various cytotoxic effects due to the increased expression of inflammatory cytokines at the ischemic site (Benakis et al., 2015; Xia, Han, Huang, & Ying, 2010). Recent findings report that during cerebral ischemia, activated MGs exhibit a high level of ionized calcium-binding adapter molecule 1 (IBA1) expression, confirmed by confocal images showing round and amoeboid shaped morphology with very short processes and bigger soma in the cortex of the ipsilateral hemisphere (Kuo et al., 2016). IFN-β treatment helps in the suppression of IBA1 expression by reducing MG activation at the site of injury, there by showing ramified morphology with longitudinally branched and smaller soma. Kuo et al. found that IFN-β's inhibitory effect on activation of MG is due to a reduction in the expression of pro-inflammatory cytokines interleukin 23p19 (IL-23p19), IL-1b, IL-6, and TNF-α at the site of infarct (Kuo et al., 2016) (Figure 2).

A study carried out by Cruz et al. reported that IFN-β requires IFN regulatory factor 2 binding protein 2 (IRF2BP2) to limit ischemic stroke injury. Mice lacking IRF2BP2-deficient microglia/macrophages lost the anti-inflammatory property of IFN-β, which failed to protect them from ischemic injuries (Cruz et al., 2017). Recent work has identified that TLRs and type 1 IFN signaling mediate neuroprotection in both ischemia/reperfusion and ischemic preconditioning

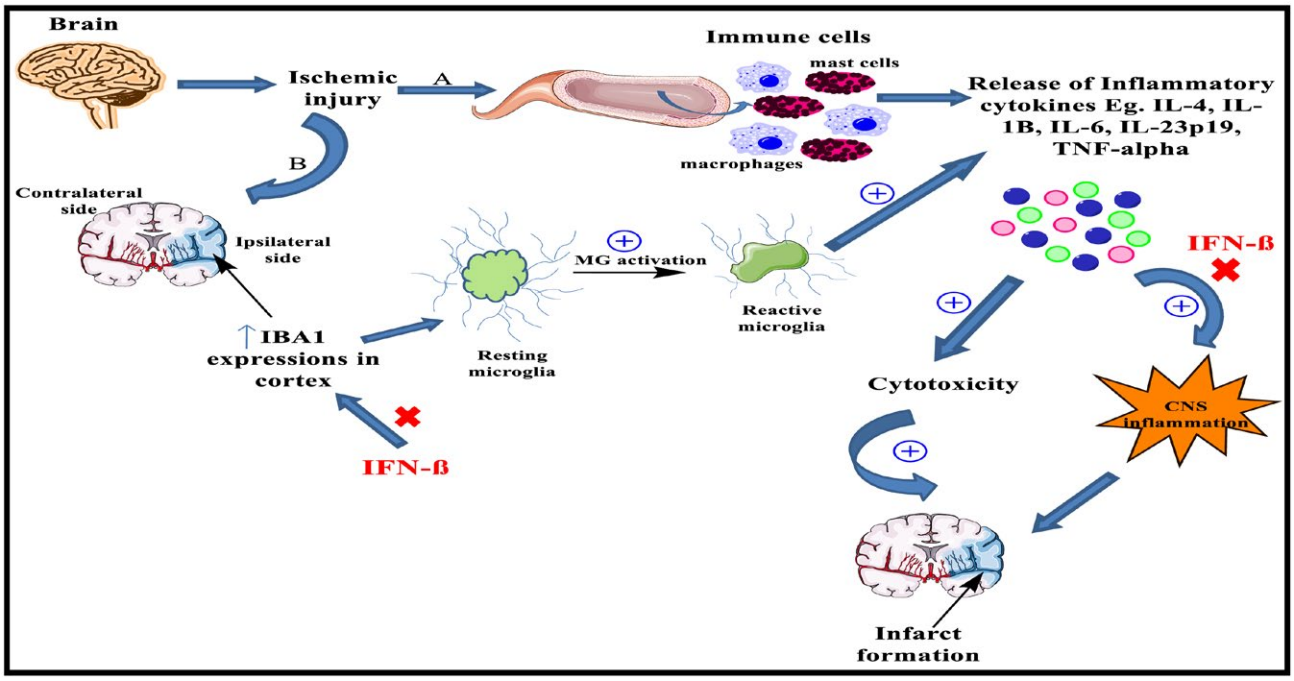

FIGURE 2 Mechanism of action of IFN-β. (a) After ischemic injury, immune cells like mast cells, macrophages, and neutrophils from the circulation release the inflammatory cytokines. These inflammatory cytokines include IL-6, IL-4, IL-1B, IL-23p9, and TNF-α. At ischemic injury site, there is over-expression of these inflammatory cytokines. These overexpressed inflammatory cytokines lead to CNS inflammation. Increased CNS inflammation results in infarct formation in the brain. IFN-β helps in suppressing overexpressed inflammatory cytokines and ultimately helps in reducing the brain infarct in ischemic brain. (b) After an ischemic injury on the ipsilateral side of the hemisphere, there are increased expressions of IBA1 (specifically expressed in microglial cells (MGs), helps in MG regulation) in the cortex. Increased IBA1 results in the transformation of resting MGs to reactive MGs. Reactive MGs influence release of inflammatory cytokines, for example, IL-6, IL-4, IL-1B, IL-23p9, and TNF-α leads to cytotoxicity which in turn results in infarct formation in the brain at the injury site. IFN-β inhibits upregulated IBA1 expression in the cortex of ipsilateral side and reduces the MG activation in the ischemic brain [Colour figure can be viewed at wileyonlinelibrary.com]

(IPC) (McDonough et al., 2017). It has been reported that in a mouse model of ischemic injury type 1, IFN signaling is essential for IPC-directed neuroprotection in white matter (Hamner et al., 2015) and gray matter (Stevens et al., 2011). McDonough et al. proposed that during ischemia/reperfusion injury MGs lead to the activation of endogenous neuroprotection pathways which are dependent on the IFN-stimulated genes (ISGs) response (McDonough & Weinstein, 2016). Wang et al. (2017) reported that by promoting expression of TIR-domain containing adapter-inducing interferon-β (TRIF) with the compound Dexmedetomidine improved stroke recovery, supporting the beneficial effect of interferon-beta in ischemic stroke (Wang et al., 2017).

Experimental preconditioning models are robust and primarily focus on neuroprotective actions (Gesuete et al., 2012). Gesuete et al., uncovered the protective preconditioning effect of polyinosinic polycytidylic acid (poly-ICLC) against cerebral ischemic injury. They found that treatment with poly-ICLC in in vitro and in vivo ischemia models induced IFN-β mRNA expression and type I IFN signaling in brain microvascular endothelial cells, which attenuated BBB dysfunction and was required for neuroprotection against ischemic injury (Gesuete et al., 2012).

During ischemic injury, chemokine induction enhances the peripheral immune cell recruitment to the ischemic brain. Chemokines, including monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), CCL2, and CCL3 are essential in the recruitment of monocytes/macrophage, while Chemokine (C-X-C motif) ligand 3 (CXCL3) is essential for neutrophil recruitment (Kuo et al., 2016). These are induced to greater levels in the ischemic brain (Hori et al., 2012; Wolinski & Glabinski, 2013; Zaremba, Ilkowski, & Losy, 2006). Minami et al. reported that the chemokine MCP-1/CCL2 binding to its respective receptor CCR2 expressed on the brain endothelial surface, leads to dynamic reorganization of the actin cytoskeleton and structural alteration of tight junctions (TJs). This causes a gradual morphological change which was characterized with an upregulated vascular permeability (Stamatovic, Keep, Kunkel, & Andjelkovic, 2003). The upregulated or increased vascular permeability leads to the formation of brain edema and is found to be a major reason for death with severe infarction (Ayata & Ropper, 2002; Minami, Katayama, & Satoh, 2006) (Figure 3).

Matrix metallopeptidase-9 (MMP-9), released throughout the course of ischemic injury, increases BBB permeability via degradation of extracellular matrix (ECM), TJs in brain endothelium facilitate the inflammatory immune cell infiltration into the CNS (Chaturvedi & Kaczmarek, 2014; Lakhan et al., 2009). Scientists have reported the significant effect of IFN-β on the production of MMP-9 and chemokines in MG, a major producer of inflammatory cytokines implicated

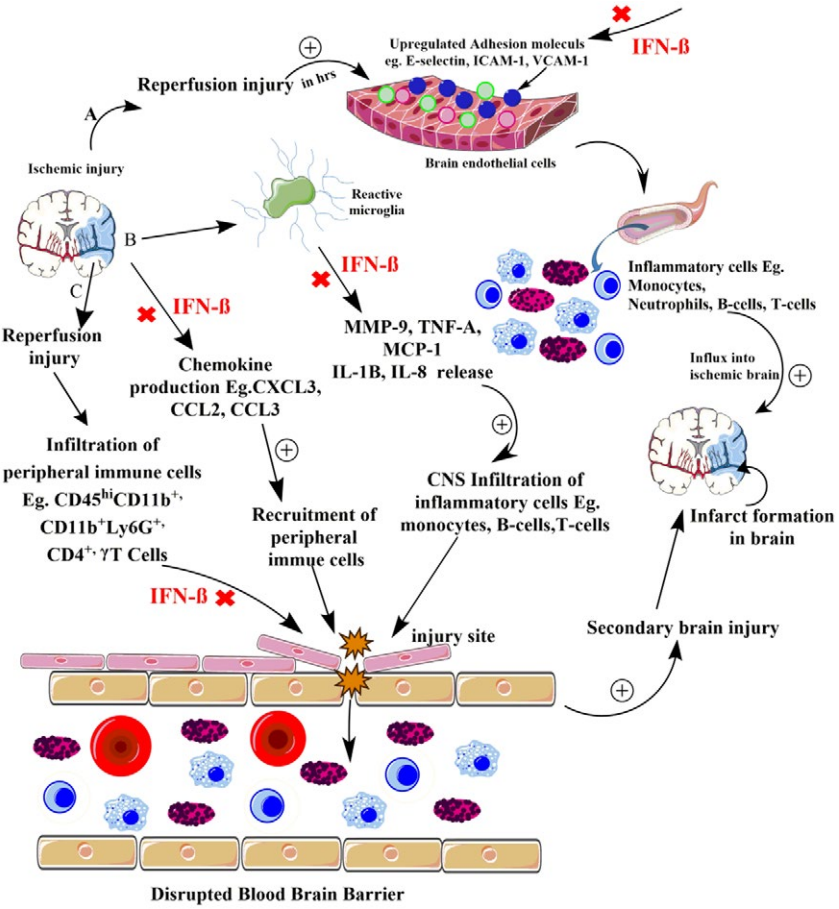

FIGURE 3 Mechanism of action of IFN-β. (a) Ischemic injury followed by reperfusion. Within hours of ischemia, upregulation of adhesion molecules expression (e.g., ICAM-1, VCAM-1, and E-selectin,) on the brain endothelial surface. These upregulated adhesion molecules increase the influx of inflammatory cells (e.g., monocytes, neutrophils, B cells, and T cells) to the ischemic brain, causing Infarct formation. IFN-β reduces the upregulated adhesion molecule expression (e.g., ICAM-1, VCAM-1, and E-selectin) and helps in reducing the infarct formation by decreasing inflammatory cell influx into the brain. (b) After ischemic injury, resting microglial cells are activated and increase the release of matrix metalloproteinase 9 (MMP-9), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukin 1B (IL-1B), IL-8 which facilitate inflammatory cellinfiltration (monocytes, neutrophils, B cells, and T cells) at the injury site in the brain. Increased infiltration of inflammatory cells compromises the blood–brain barrier (BBB) integrity and leads to secondary brain injury, responsible for increased infarct area in the brain. IFN-β impairs the ischemia-induced chemokine (C-C motif) ligand 3 (CCL3), Chemokine (C-X-C motif) ligand 3 (CXCL3), and MMP-9 expressions and helps to reduce brain infarct. (c) Ischemic injury is followed with reperfusion. Reperfusion increases the peripheral immune cell infiltration (CD45hiCD11b+, CD11b+Ly6G+, CD4+, γδ T Cells) at brain injury and leads to BBB compromise; it leads to BBB disruption and secondary brain injury, results in infarct formation in the brain. IFN-β lowers the number of infiltrating cells that is, CD45hiCD11b+, CD11b+Ly6G+, CD4+, γδ T Cells in ipsilateral side of the brain and shows a protective role in ischemic stroke by decreasing BBB disruption [Colour figure can be viewed at wileyonlinelibrary.com]

as a mediator of neuroinflammation (Kuo et al., 2016). It was found that in the ischemic brain, there is a dramatic increase in the expression of CCL3, CXCL3, and MMP-9 in the ipsilateral part but not in the contralateral part of the brain. IFN-β treatment helps in reducing the expression of CCL3, CXCL3, and MMP. Kuo et al., have carried out a study to find IFN-β's inhibitory effect lipopolysaccharide (LPS)-induced primary MGs. Their results showed that IFN-β decreased the expression of CCL3, CXCL3, and MMP-9 in LPS-activated MGs in a significant manner (Kuo et al., 2016) (Figure 3).

Cerebral ischemic injury followed by reperfusion is mainly responsible for infiltration of peripheral immune cells consisting of T cells, neutrophils, and monocytes/macrophages, resulting in secondary brain injury eventually responsible for increasing the degree of brain infarction (Benakis et al., 2015; Wang, Tang, & Yenari, 2007). Scientists have also reported that throughout the course of ischemic injury, there is a significant rise in various cell counts including CD11b+Ly6G+ neutrophils and CD45hiCD11b+ monocytes/macrophages in the ipsilateral part of the ischemic brain. In addition, they found that IFN-β treatment significantly helps in lowering the levels of these cells (Kuo et al., 2016) (Figure 3).

As per previous reports, both CD4+T cells and γδ T cells also playa pathogenic role in ischemic stroke (Gelderblom, Arunachalam, & Magnus, 2014; Shichita et al., 2009). There is arise in the numbers of CD4+T cells and γδT cells in the ischemic brain and this leads to

the BBB breakdown and increased infarct size associated with induction of MMP3 and MMP9. IFN-β treatment reduces both CD4+T cell and γδT cell numbers and decreases the infarct size. IFN-β treatment suppresses the infiltration of various peripheral immune cells like neutrophils, macrophages/monocytes, and CD4+T cells and γδT cells, providing a protective role in ischemic stroke (Kuo et al., 2016) (Figure 3).

During ischemia, inflammatory processes lead to migration of peripheral blood leukocytes into brain parenchyma, regulated by the adhesion molecules. Adhesion molecules including E-selectin, P-selectin, ICAM-1, and VCAM-1 are expressed on the activated brain endothelial cell surface and are upregulated after ischemia. They are responsible for facilitating the influx of inflammatory cells and conferring BBB breakdown. Reports suggest that within hours of reperfusion in the middle cerebral artery occlusion/reperfusion (MCAO/R) model in rats, adhesion molecules were found to be upregulated in brain endothelial cells (Kuo et al., 2016; Lindsberg, Carpe, Paetau, Karjalainen-Lindsberg, & Kaste, 1996; Zhang, Chopp, Zhang, Jiang, & Powers, 1998). Kuo et al. studied that 24-hr post-ischemia, there is a significant rise in ICAM-1 and E-selectin in the ischemic part of the brain. Further treatment with IFN-β helps in reducing upregulated ICAM-1 and E-selectin in the ipsilateral hemispheres of animals induced with ischemic stroke. Also, there is an increase in VCAM-1 expression in ischemic stroke, but IFN-β treatment has not shown any effect on its expression (Kuo et al., 2016). They also studied IFN-β effect on endothelial cell lines bEnd.3. Activation of bEnd.3 cell lines with TNF-α upregulates ICAM-1 and E-selectin at both levels that is, at the genetic level and protein level. They found that IFN-β treatment helps to obviate TNF-α-induced P-selectin, ICAM-1, and E-selectin upregulation but failed inattenuating VCAM-1 expression which is induced due to TNF-α on the surface of the cell (Kuo et al., 2016; Suárez, Wang, Manes, & Pober, 2010) (Figure 3). However, the beneficial effect of IFN-β to counteract ischemic stroke injury remains controversial. It was reported by Maier et al. that IFN-β failed to protect ischemic injury in a model of transient focal stroke (Maier, Yu, Nishi, Lathrop, & Chan, 2006).

3.2.1 | Limitations of IFN-β therapy in ischemic stroke

Since the discovery of IFNs, IFN has progressed from a poorly understood antiviral substance to being FDA-approved for the treatment of five disorders (Baron et al., 1991). We have discussed the various mechanisms of IFN-β and its therapeutic potential. However, certain side effects limit the use of IFN-β (Pestka, 2007). Although IFN-β is usually safe and well tolerated, it causes certain adverse effects. IFNs not only cause local adverse events but systemic adverse reactions as well (Kolb-Mäurer, Goebeler, & Mäurer, 2015). After treatment with IFN-β, patients have exhibited fatigue, myalgia, headache, malaise, and joint pain (Pestka, 2007). Depression has been reported in patients with no prior psychiatric history following IFN-β therapy (Fragoso et al., 2010). Reduced doses of IFN-β have elicited severe depression and altered tolerability, resulting in discontinuation of treatment (Asnis & De La Garza II, 2005). Few studies have demonstrated that endogenous molecules like melatonin, a potent antioxidant and a regulator of circadian rhythm, maybe helpful in mitigating the depressive symptoms associated with IFN-β (Hansen, Danielsen, Hageman, Rosenberg, & Gögenur, 2014). Also, it has been reported that therapy of IFN-β in combination with L-methyl folate or S-adenosyl methionine has varying degrees of outcomes in monotherapy or augmentation therapy for depression (Franscina Pinto & Andrade, 2016). However, till date, no studies have been examined in therapeutic treatment of the IFN-β-related depressive disorder and should, therefore, be appraised as a possibility in future studies. Thus, IFN-β therapy may serve as a substantial therapy for the treatment of acute ischemic stroke if the side effects of IFN-β can be reduced and prevented.

4 | CONCLUSION

Inflammation and immunity are an essential and fundamental parts of the pathogenesis initiated by ischemic and reperfusion injury. Inflammatory cascade is responsible for initiation of early molecular events caused due to blood vessel occlusion and culminates in brain invasion by various inflammatory cells. CNS inflammation, cytotoxicity, BBB disruption, and peripheral immune cell infiltration at the injury site play important roles in secondary brain injury and lead to increased brain infarct. IFN-β may play protective and multiphasic roles after ischemic stroke. This review focused on the neuroprotective role of IFN-β in ischemic stroke. As there is a growing body of evidence indicating that inflammatory mediators are predominantly deleterious in the primary phase after ischemic stroke, IFN-β may be a promising treatment option against ischemic stroke and may be salutary for future adjuvant therapy. With these preclinical findings, IFN-β has entered the clinical level as a therapeutic agent for ischemic stroke. However, some more substantial findings are required to be carried out in the future for better understanding of ischemic stroke in relation with CNS inflammation, cytotoxicity, BBB dysfunction, and the therapeutic potential of IFN-β in ischemic stroke.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Conceptualization, M.W., H.K., D.S. and P.B.; *Methodology*, M.W., H.K., D.S. and P.B.; *Writing – Original Draft*, H.K., D.S., J.S., K.P., K.V., K.K., A.B., D.Y., K.D., P.B.; *Visualization*, M.W., H.K., D.S., D.Y., K.D., A.B. and P.B.; *Writing – Review & Editing*, M.W., H.K., D.S., J.S., A.B., K.K., K.D. and P.B.

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REFERENCES

Amantea, D., Micieli, G., Tassorelli, C., Cuartero, M. I., Ballesteros, I., Certo, M., … Bagetta, G. (2015). Rational modulation of the innate immune system for neuroprotection in ischemic stroke. *Frontiers in Neuroscience*, *9*, 147. https://doi.org/10.3389/fnins.2015.00147

Anrather, J., & Iadecola, C. (2016). Inflammation and stroke: An overview. *Neurotherapeutics*, *13*(4), 661–670. https://doi.org/10.1007/s13311-016-0483-x

Asnis, G. M., & De La Garza II, R. (2005). Interferon-induced depression: Strategies in treatment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(5), 808–818. https://doi.org/10.1016/j.pnpbp.2005.03.006

Asselah, T., Marcellin, P., & Schinazi, R. F. (2018). Chronic HBV infection: Interferon therapy and long-term outcomes. *Hepatitis B virus and liver disease* (pp. 181–191). Singapore: Springer. https://doi:10.1111/liv.13673

Ayata, C., & Ropper, A. H. (2002). Ischaemic brain oedema. *Journal of Clinical Neuroscience*, *9*(2), 113–124. https://doi.org/10.1054/jocn.2001.1031

Bang, O. Y. (2016). Clinical trials of adult stem cell therapy in patients with ischemic stroke. *Journal of Clinical Neurology*, *12*(1), 14–20. https://doi.org/10.3988/jcn.2016.12.1.14

Baron, S., Tyring, S. K., Fleischmann, W. R., Coppenhaver, D. H., Niesel, D. W., Klimpel, G. R., … Hughes, T. K. (1991). The interferons: Mechanisms of action and clinical applications. *JAMA*, *266*(10), 1375–1383. https://doi.org/10.1001/jama.1991.03470100067035

Benakis, C., Garcia-Bonilla, L., Iadecola, C., & Anrather, J. (2015). The role of microglia and myeloid immune cells in acute cerebral ischemia. *Frontiers in Cellular Neuroscience*, *8*, 461. https://doi.org/10.3389/fncel.2014.00461

Booy, S., Hofland, L., & van Eijck, C. (2015). Potentials of interferon therapy in the treatment of pancreatic cancer. *Journal of Interferon & Cytokine Research*, *35*(5), 327–339. https://doi.org/10.1089/jir.2014.0157

Borst, K., Frenz, T., Spanier, J., Tegtmeyer, P.-K., Chhatbar, C., Skerra, J., … Köster, M. (2018). Type I interferon receptor signaling delays Kupffer cell replenishment during acute fulminant viral hepatitis. *Journal of Hepatology*, *68*(4), 682–690. https://doi.org/10.1016/j.jhep.2017.11.029

Carroll, W. (2009). Clinical trials of multiple sclerosis therapies: Improvements to demonstrate long-term patient benefit. *Multiple Sclerosis Journal*, *15*(8), 951–958. https://doi.org/10.1177/1352458509105426

Chaturvedi, M., & Kaczmarek, L. (2014). Mmp-9 inhibition: A therapeutic strategy in ischemic stroke. *Molecular Neurobiology*, *49*(1), 563–573. https://doi.org/10.1007/s12035-013-8538-z

Conigliaro, P., Perricone, C., Benson, R. A., Garside, P., Brewer, J. M., Perricone, R., & Valesini, G. (2010). The type I IFN system in rheumatoid arthritis. *Autoimmunity*, *43*(3), 220–225. https://doi.org/10.3109/08916930903510914

Cruz, S. A., Hari, A., Qin, Z., Couture, P., Huang, H., Lagace, D. C., … Chen, H.-H. (2017). Loss of IRF2BP2 in microglia increases inflammation and functional deficits after focal ischemic brain injury. *Frontiers in Cellular Neuroscience*, *11*, 201. https://doi.org/10.3389/fncel.2017.00201

Dalakas, M. C. (2008). B cells as therapeutic targets in autoimmune neurological disorders. *Nature Reviews Neurology*, *4*(10), 557. https://doi.org/10.1038/ncpneuro0901

Deb, P., Sharma, S., & Hassan, K. (2010). Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. *Pathophysiology*, *17*(3), 197–218. https://doi.org/10.1016/j.pathophys.2009.12.001

Denes, A., Thornton, P., Rothwell, N., & Allan, S. (2010). Inflammation and brain injury: Acute cerebral ischaemia, peripheral and central inflammation. *Brain, Behavior, and Immunity*, *24*(5), 708–723. https://doi.org/10.1016/j.bbi.2009.09.010

Dhib-Jalbut, S., & Marks, S. (2010). Interferon-β mechanisms of action in multiple sclerosis. *Neurology*, *74*(1 Suppl. 1), S17–S24. https://doi:10.1212/WNL.0b013e3181c97d99

Dierckx, T., Khouri, R., Menezes, S., Decanine, D., Farre, L., Bittencourt, A., … Van Weyenbergh, J. (2017). IFN-β induces greater antiproliferative and proapoptotic effects and increased p53 signaling compared with IFN-α in PBMCs of adult T-cell Leukemia/Lymphoma patients. *Blood Cancer Journal*, *7*(1), e519. https://doi.org/10.1038/bcj.2016.126

Dirnagl, U., Iadecola, C., & Moskowitz, M. A. (1999). Pathobiology of ischaemic stroke: An integrated view. *Trends in Neurosciences*, *22*(9), 391–397. https://doi.org/10.1016/S0166-2236(99)01401-0

Fann, D.-Y.-W., Lee, S.-Y., Manzanero, S., Chunduri, P., Sobey, C. G., & Arumugam, T. V. (2013). Pathogenesis of acute stroke and the role of inflammasomes. *Ageing Research Reviews*, *12*(4), 941–966. https://doi.org/10.1016/j.arr.2013.09.004

Fragoso, Y. D., Frota, E. R. C., Lopes, J. S., Noal, J. S., Giacomo, M. C., Gomes, S., … Finkelsztejn, A. (2010). Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. *Clinical Neuropharmacology*, *33*(6), 312–316. https://doi.org/10.1097/WNF.0b013e3181f8d513

Franscina Pinto, E., & Andrade, C. (2016). Interferon-related depression: A primer on mechanisms, treatment, and prevention of a common clinical problem. *Current Neuropharmacology*, *14*(7), 743–748. https://doi.org/10.2174/1570159X14666160106155129

Friedman, R. M. (2008). Clinical uses of interferons. *British Journal of Clinical Pharmacology*, *65*(2), 158–162. https://doi.org/10.1111/j.1365-2125.2007.03055.x

Fritsch, S. D., & Weichhart, T. (2016). Effects of interferons and viruses on metabolism. *Frontiers in Immunology*, *7*, 630. https://doi.org/10.3389/fimmu.2016.00630

Gao, L., Anolik, J., & Looney, R. (2018). PS7: 130 Interferon beta blockade rescues human bm-msc osteoblastogenesis defects in systemic lupus erythematosus: Archives of disease in childhood. http://dx.doi.org/10.1136/lupus-2018-abstract.173

Gelderblom, M., Arunachalam, P., & Magnus, T. (2014). γδ T cells as early sensors of tissue damage and mediators of secondary neurodegeneration. *Frontiers in Cellular Neuroscience*, *8*, 1–5, 368. https://dx.doi.org/10.1136/lupus-2018-abstract.173

Genç, K., Dona, D. L., & Reder, A. T. (1997). Increased CD80 (+) B cells in active multiple sclerosis and reversal by interferon beta-1b therapy. *The Journal of Clinical Investigation*, *99*(11), 2664–2671. https://doi.org/10.1172/JCI119455

George, P. M., & Steinberg, G. K. (2015). Novel stroke therapeutics: Unraveling stroke pathophysiology and its impact on clinical treatments. *Neuron*, *87*(2), 297–309. https://doi.org/10.1016/j.neuron.2015.05.041

Gesuete, R., Packard, A. E., Vartanian, K. B., Conrad, V. K., Stevens, S. L., Bahjat, F. R., … Stenzel-Poore, M. P. (2012). Poly-ICLC preconditioning

protects the blood–brain barrier against ischemic injury in vitro through type I interferon signaling. *Journal of Neurochemistry*, *123*, 75–85. https://doi:10.1111/j.1471-4159.2012.07946.x.

Gonzales-van Horn, S. R., & Farrar, J. D. (2015). Interferon at the crossroads of allergy and viral infections. *Journal of Leukocyte Biology*, *98*(2), 185–194. https://doi.org/10.1189/jlb.3RU0315-099R

Hamner, M. A., Ye, Z., Lee, R. V., Colman, J. R., Le, T., Gong, D. C., … Weinstein, J. R. (2015). Ischemic preconditioning in white matter: Magnitude and mechanism. *Journal of Neuroscience*, *35*(47), 15599–15611. https://doi.org/10.1523/JNEUROSCI.2544-15.2015

Hansen, M. V., Danielsen, A. K., Hageman, I., Rosenberg, J., & Gögenur, I. (2014). The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: A systematic review and meta-analysis. *European Neuropsychopharmacology*, *24*(11), 1719–1728. https://doi.org/10.1016/j.euroneuro.2014.08.008

Hori, M., Nakamachi, T., Rakwal, R., Shibato, J., Nakamura, K., Wada, Y., … Shioda, S. (2012). Unraveling the ischemic brain transcriptome in a permanent middle cerebral artery occlusion mouse model by DNA microarray analysis. *Disease Models & Mechanisms*, *5*(2), 270–283. https://doi.org/10.1242/dmm.008276

Huang, H., Ito, K., Dangond, F., & Dhib-Jalbut, S. (2013). Effect of interferon beta-1a on B7.1 and B7.2 B-cell expression and its impact on T-cell proliferation. *Journal of Neuroimmunology*, *258*(1), 27–31. https://doi.org/10.1016/j.jneuroim.2013.02.010

Imanishi, J. (1994). Interferon-alpha, beta, gamma. *Gan to kagaku ryoho. Cancer & Chemotherapy*, *21*(16), 2853–2858.

Inácio, A. R., Liu, Y., Clausen, B. H., Svensson, M., Kucharz, K., Yang, Y., … Issazadeh-Navikas, S. (2015). Endogenous IFN-β signaling exerts anti-inflammatory actions in experimentally induced focal cerebral ischemia. *Journal of Neuroinflammation*, *12*(1), 211. https://doi.org/10.1186/s12974-015-0427-0

Jaeckel, E., Cornberg, M., Wedemeyer, H., Santantonio, T., Mayer, J., Zankel, M., … Manns, M. P. (2001). Treatment of acute hepatitis C with interferon alfa-2b. *New England Journal of Medicine*, *345*(20), 1452–1457. https://doi.org/10.1056/NEJMoa011232

Jiang, H., Milo, R., Swoveland, P., Johnson, K. P., Panitch, H., & Dhib-Jalbut, S. (1995). Interferon β-Ib reduces Interferon γ-induced antigen-presenting capacity of human glial and B cells. *Journal of Neuroimmunology*, *61*(1), 17–25. https://doi.org/10.1016/0165-5728(95)00072-A

Jin, R., Yang, G., & Li, G. (2010). Inflammatory mechanisms in ischemic stroke: Role of inflammatory cells. *Journal of Leukocyte Biology*, *87*(5), 779–789. https://doi.org/10.1189/jlb.1109766

Kasper, L. H., & Reder, A. T. (2014). Immunomodulatory activity of interferon-beta. *Annals of Clinical and Translational Neurology*, *1*(8), 622–631. https://doi.org/10.1002/acn3.84

Kaur, H., Sarmah, D., Saraf, J., Vats, K., Kalia, K., & Borah, A., … Bhattacharya, P. (2018). Noncoding RNAs in ischemic stroke: Time to translate. *Annals of the New York Academy of Sciences*, *1421*(1), 19–36. https://doi.org/10.1111/nyas.13612

Kawabori, M., Yenari, A., & M. (2015). Inflammatory responses in brain ischemia. *Current Medicinal Chemistry*, *22*(10), 1258–1277. https://doi.10.2174/0929867322666150209154036

Kieseier, B. C. (2011). The mechanism of action of interferon-β in relapsing multiple sclerosis. *CNS Drugs*, *25*(6), 491–502. https://doi.org/10.2165/11591110-000000000-00000

Kolb-Mäurer, A., Goebeler, M., & Mäurer, M. (2015). Cutaneous adverse events associated with interferon-β treatment of multiple sclerosis. *International Journal of Molecular Sciences*, *16*(7), 14951–14960. https://doi.org/10.3390/ijms160714951

Kopitar-Jerala, N. (2017). The role of interferons in inflammation and inflammasome activation. *Frontiers in Immunology*, *8*, 873. https://doi.org/10.3389/fimmu.2017.00873

Kotredes, K. P., Thomas, B., & Gamero, A. M. (2017). The protective role of type I interferons in the gastrointestinal tract. *Frontiers in Immunology*, *8*, 410. https://doi.org/10.3389/fimmu.2017.00410

Kraus, J., & Oschmann, P. (2006). The impact of interferon-β treatment on the blood–brain barrier. *Drug Discovery Today*, *11*(15–16), 755–762. https://doi.org/10.1016/j.drudis.2006.06.008

Krumbholz, M., Faber, H., Steinmeyer, F., Hoffmann, L.-A., Kümpfel, T., Pellkofer, H., … Hafner, C. (2008). Interferon-β increases BAFF levels in multiple sclerosis: Implications for B cell autoimmunity. *Brain*, *131*(6), 1455–1463. https://doi.org/10.1093/brain/awn077

Krumbholz, M., Theil, D., Derfuss, T., Rosenwald, A., Schrader, F., Monoranu, C.-M., … Aloisi, F. (2005). BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma. *Journal of Experimental Medicine*, *201*(2), 195–200. https://doi.org/10.1084/jem.20041674

Kuo, P. C., Scofield, B. A., Yu, I. C., Chang, F. L., Ganea, D., & Yen, J. H. (2016). Interferon-β modulates inflammatory response in cerebral ischemia. *Journal of the American Heart Association*, *5*(1), e002610. https://doi.org/10.1161/JAHA.115.002610

Lakhan, S. E., Kirchgessner, A., & Hofer, M. (2009). Inflammatory mechanisms in ischemic stroke: Therapeutic approaches. *Journal of Translational Medicine*, *7*(1), 97. https://doi.org/10.1186/1479-5876-7-97

Le, C. P., Genin, P., Baines, M., & Hiscott, J. (2000). Interferon activation and innate immunity. *Reviews in Immunogenetics*, *2*(3), 374–386.

Lindsberg, P. J., Carpe, O., Paetau, A., Karjalainen-Lindsberg, M.-L., & Kaste, M. (1996). Endothelial ICAM-1 expression associated with inflammatory cell response in human ischemic stroke. *Circulation*, *94*(5), 939–945. https://doi.org/10.1161/01.CIR.94.5.939

Maier, C. M., Yu, F., Nishi, T., Lathrop, S. J., & Chan, P. H. (2006). Interferon-β fails to protect in a model of transient focal stroke. *Stroke*, *37*(4), 1116–1119. https://doi:10.1161/01.STR.0000208214.46093.d5

Markowitz, C. E. (2007). Interferon-beta mechanism of action and dosing issues. *Neurology*, *68*(24 Suppl. 4), S8–S11. https://doi.org/10.1212/01.wnl.0000277703.74115.d2

McDonough, A., Lee, R. V., Noor, S., Lee, C., Le, T., Iorga, M., … Weinstein, J. R. (2017). Ischemia/reperfusion induces interferon stimulated gene expression in microglia. *Journal of Neuroscience*, *37*, 0725–0717. https://doi.org/10.1523/JNEUROSCI.0725-17.2017

McDonough, A., & Weinstein, J. R. (2016). Neuroimmune response in ischemic preconditioning. *Neurotherapeutics*, *13*(4), 748–761. https://doi.org/10.1007/s13311-016-0465-z

Meinl, E., Krumbholz, M., & Hohlfeld, R. (2006). B lineage cells in the inflammatory central nervous system environment: Migration, maintenance, local antibody production, and therapeutic modulation. *Annals of Neurology*, *59*(6), 880–892. https://doi.org/10.1002/ana.20890

Minami, M., Katayama, T., & Satoh, M. (2006). Brain cytokines and chemokines: Roles in ischemic injury and pain. *Journal of Pharmacological Sciences*, *100*(5), 461–470. https://doi.org/10.1254/jphs.CRJ06005X

Moss, J. W., & Ramji, D. P. (2017). Cytokines in atherosclerosis. *Cytokine effector functions in tissues* (pp. 109–118). United Kingdom: Elsevier. https://doi.org/10.1016/B978-0-12-804214-4.00005-1

Nallar, S. C., & Kalvakolanu, D. V. (2014). Interferons, signal transduction pathways, and the central nervous system. *Journal of Interferon & Cytokine Research*, *34*(8), 559–576. https://doi.org/10.1089/jir.2014.0021

Perera, M. N., Ma, H. K., Arakawa, S., Howells, D. W., Markus, R., Rowe, C. C., & Donnan, G. A. (2006). Inflammation following stroke. *Journal of Clinical Neuroscience*, *13*(1), 1–8. https://doi.org/10.1016/j.jocn.2005.07.005

Pestka, S. (2007). The interferons: 50 years after their discovery, there is much more to learn. *Journal of Biological Chemistry*, *282*(28), 20047–20051. https://doi.org/10.1074/jbc.R700004200

Qaisar, N., Jurczyk, A., & Wang, J. P. (2018). Potential role of type I interferon in the pathogenic process leading to type 1 diabetes. *Current Opinion in Endocrinology, Diabetes and Obesity*, *25*(2), 94–100. https://doi.org/10.1097/MED.0000000000000399

Rudick, R. A., & Goelz, S. E. (2011). Beta-interferon for multiple sclerosis. *Experimental Cell Research*, *317*(9), 1301–1311. https://doi.org/10.1016/j.yexcr.2011.03.002

Samuel, C. E. (2001). Antiviral actions of interferons. *Clinical Microbiology Reviews*, *14*(4), 778–809. https://doi.org/10.1128/CMR.14.4.778-809.2001

Schreiber, G., & Piehler, J. (2015). The molecular basis for functional plasticity in type I interferon signaling. *Trends in Immunology*, *36*(3), 139–149. https://doi.org/10.1016/j.it.2015.01.002

Sheppard, P., Kindsvogel, W., Xu, W., Henderson, K., Schlutsmeyer, S., Whitmore, T. E., … Roraback, J. (2003). IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nature Immunology*, *4*(1), 63. https://doi.org/10.1038/ni873

Shichita, T., Sugiyama, Y., Ooboshi, H., Sugimori, H., Nakagawa, R., Takada, I., … Cua, D. J. (2009). Pivotal role of cerebral interleukin-17–producing γδT cells in the delayed phase of ischemic brain injury. *Nature Medicine*, *15*(8), 946. https://doi.org/10.1038/nm.1999

Stamatovic, S. M., Keep, R. F., Kunkel, S. L., & Andjelkovic, A. V. (2003). Potential role of MCP-1 in endothelial cell tight junctionopening': Signaling via Rho and Rho kinase. *Journal of Cell Science*, *116*(22), 4615–4628. https://doi.org/10.1242/jcs.00755

Stevens, S. L., Leung, P. Y., Vartanian, K. B., Gopalan, B., Yang, T., Simon, R. P., & Stenzel-Poore, M. P. (2011). Multiple preconditioning paradigms converge on interferon regulatory factor-dependent signaling to promote tolerance to ischemic brain injury. *Journal of Neuroscience*, *31*(23), 8456–8463. https://doi.org/10.1523/JNEUROSCI.0821-11.2011

Suárez, Y., Wang, C., Manes, T. D., & Pober, J. S. (2010). Cutting edge: TNF-induced microRNAs regulate TNF-induced expression of E-selectin and intercellular adhesion molecule-1 on human endothelial cells: Feedback control of inflammation. *The Journal of Immunology*, *184*(1), 21–25. https://doi.org/10.4049/jimmunol.0902369

Tiebosch, I. A., Dijkhuizen, R. M., Cobelens, P. M., Bouts, M. J., Zwartbol, R., van der Meide, P. H., & van den Bergh, W. M. (2013). Effect of interferon-β on neuroinflammation, brain injury and neurological outcome after experimental subarachnoid hemorrhage. *Neurocritical Care*, *18*(1), 96–105. https://doi.org/10.1007/s12028-012-9692-2

Veldhuis, W. B., Derksen, J. W., Floris, S., van der Meide, P. H., de Vries, H. E., Schepers, J., … Nicolay, K. (2003). Interferon-beta blocks infiltration of inflammatory cells and reduces infarct volume after ischemic stroke in the rat. *Journal of Cerebral Blood Flow & Metabolism*, *23*(9), 1029–1039. https://doi.org/10.1097/01.WCB.0000080703.47016.B6

Wack, A., Terczyńska-Dyla, E., & Hartmann, R. (2015). Guarding the frontiers: The biology of type III interferons. *Nature Immunology*, *16*(8), 802. https://doi.org/10.1038/ni.3212

Wang, S.-L., Duan, L., Xia, B., Liu, Z., Wang, Y., & Wang, G.-M. (2017). Dexmedetomidine preconditioning plays a neuroprotective role and suppresses TLR4/NF-κB pathways model of cerebral ischemia reperfusion. *Biomedicine & Pharmacotherapy*, *93*, 1337–1342. https://doi.org/10.1016/j.biopha.2017.06.051

Wang, Q., Tang, X. N., & Yenari, M. A. (2007). The inflammatory response in stroke. *Journal of Neuroimmunology*, *184*(1), 53–68. https://doi.org/10.1016/j.jneuroim.2006.11.014

Weinstein, J. R., Koerner, I. P., & Möller, T. (2010). Microglia in ischemic brain injury. *Future Neurology*, *5*(2), 227–246. https://doi.org/10.2217/fnl.10.1

Wolinski, P., & Glabinski, A. (2013). Chemokines and neurodegeneration in the early stage of experimental ischemic stroke. *Mediators of Inflammation*, *2013*, 1–9. https://doi.org/10.1155/2013/727189.

Xia, W., Han, J., Huang, G., & Ying, W. (2010). Inflammation in ischaemic brain injury: Current advances and future perspectives. *Clinical and Experimental Pharmacology and Physiology*, *37*(2), 253–258. https://doi.org/10.1111/j.1440-1681.2009.05279.x

Zaremba, J., Ilkowski, J., & Losy, J. (2006). Serial measurements of levels of the chemokines CCL2, CCL3 and CCL5 in serum of patients with acute ischaemic stroke. *Folia Neuropathologica*, *44*(4), 282–289.

Zhang, R., Chopp, M., Zhang, Z., Jiang, N., & Powers, C. (1998). The expression of P-and E-selectins in three models of middle cerebral artery occlusion. *Brain Research*, *785*(2), 207–214. https://doi.org/10.1016/S0006-8993(97)01343-7

Zipp, F., & Aktas, O. (2006). The brain as a target of inflammation: Common pathways link inflammatory and neurodegenerative diseases. *Trends in Neurosciences*, *29*(9), 518–527. https://doi.org/10.1016/j.tins.2006.07.006

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