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The talented interferon-gamma

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ABSTRACT

IFN-γ is an extraordinarily pleotropic cytokine. It can not only heighten both the innate and adaptive immune response against pathogens and tumors, but also has the ability to maintain immune homeostasis. Since the effects of IFN-γ are cell and tissue specific, it is important to consider the recent advances in IFN-γ signaling in the context of different diseases. To this end, we review the involvement of IFN-γ in the pathogenesis of several inflammatory diseases, its therapeutic potential as an anti-tumor agent and its effects upon stem cells.

Keywords: IFN-γ; Inflammation; Autoimmune; Cancer; Inflammatory Bowel Diseases; Neurodegenerative Diseases; Stem Cells

1. INTRODUCTION

Interferons (IFNs) were first described in 1957 by Issacs and Lindenmann as substances that restrict viral replication. In the 1970s, these substances were further characterized based on the inducing properties and cell type expression patterns. Interferon-γ (IFN-γ) was first named Immune IFN, then later Type II IFN. The major sources of IFN-γ are natural killer (NK) cells, T cells and NKT cells, and its receptor is expressed ubiquitously on almost all cell types. Binding of IFN-γ to its receptor triggers the Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway. STAT1 is phosphorylated, subsequently dimerizes and then translocates into the nucleus to initiate the transcription of target genes. IFN-γ can induce both pro- and anti-inflammatory responses, and its ability to induce these two responses is critical for a balanced immune response. In addition to its function in activating innate immune cells, IFN-γ signaling also plays a role in T cell development. IFN-γ signaling facilitates Th1 development by inducing T-bet expression and suppressing the expression of GATA3, a protein that drives Th2 differentiation. In addition, IFN-γ inhibits development of Th17 cells by inhibiting the effects of cytokines that promote Th17 cell development. This complex yet delicate signaling network allows IFN-γ to tailor the immune response either for defense against infection or towards maintaining the homeostasis of the host [1]. In this review, we will recapitulate the recent advances in the study of IFN-γ signaling in the context of disease and therapeutic potential.

2. ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory condition that contributes to the development of cardiovascular diseases (CAD). The process is initiated by retention of oxidized lipoproteins (LPs) in pre-lesional endothelium of the artery wall. Endothelial cells (EC) sense LPs through receptors include scavenger receptors and pattern recognition receptors. Triggered by LPs, ECs produce cell surface adhesion molecules, chemokines and inflammatory cytokines that recruit macrophages to extravasate into the arterial wall and phagocytose oxidized LPs. Lipid engorged macrophages evolve into foam cells, many of which become activated via scavenger or toll-like receptors and produce inflammatory chemokines and cytokines. The increased production of inflammatory chemokines and cytokines attracts other immune cells to the blood vessel wall, such as T cells, resulting in a cascading inflammatory response. As the condition progresses, the oxidized LPs and cell debris together with smooth muscle cells develop into atheroma, an advance lesion. This atheroma can further develop to form a fibrous plaque which is subject to rupture [2] (**Figure 1**). IFN-γ expressed by the incoming T cells activates macrophage phagocytosis capacity and up regulates the adhesion molecules on smooth muscle that not only maintain the inflammation state but also promote plaque formation.

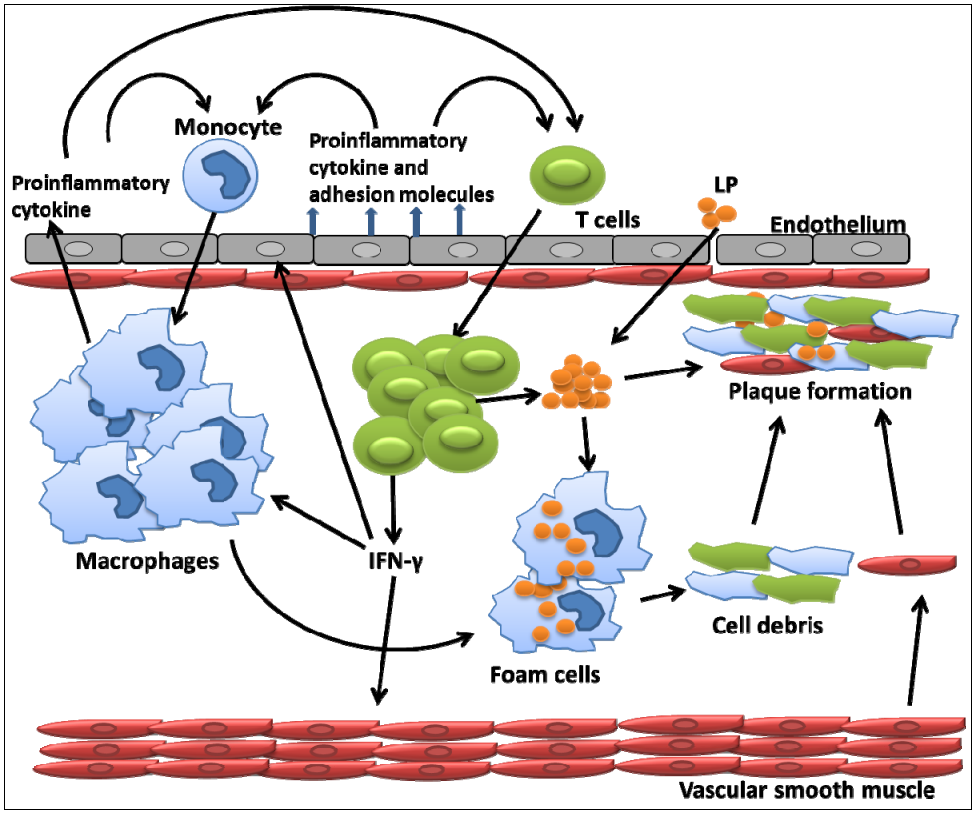

Figure 1. In response to lipoprotein retention in pre-lesional artery wall, endothelial cell permit monocyte infiltration. This infiltrated monocyte derived macrophages ingest lipid and transform into foam cells. This foam cell eventually died. Dying cells and other cellular debris along with cholesterol crystals form a necrotic core that eventually progress into atherosclerotic plaques.

ATP-binding cassette transporter A1 (ABCA1) is a key regulator that facilitates cholesterol efflux from macrophages and prevents the formation of pathological foam cells. IFN-γ has been shown to down regulate ABCA1 expression in Human THP-1 cells, a macrophage cell line, by suppressing ABCA1 expression regulation factor through the JAK/STAT pathway [3]. In addition, IFN-γ activates the ERK pathway that is required for the uptake of modified lipoprotein by theTHP-1 cells [4]. These data indicate that IFN-γ plays a very important role in the lipid accumulation in the artery wall by increasing lipoprotein uptake and inhibiting cholesterol efflux from marcophages. In addition to macrophages, IFN-γ also has effects on nonimmune cells, the coronary arteries and smooth muscle cells. IFN-γ sensitizes intact arteries and cultured vascular smooth muscle cells (VSMCs) to exogenous dsRNA as well as self-RNA. These IFN-γ primed VSMCs express higher levels of TNF-α and IP-10 when stimulated compared to non-treated samples. This study implies in the presence of viral infection and cell death, IFN-γ would further accelerate atherosclerosis by augmenting inflammatory responses in the microenviorment [5]. A recent report also showed that peripheral IFN-γ may contribute to coronary artery disease (CAD). In the peripheral blood of CAD patients, $CD8^+CD56^+$ T cells constitute 30% of the total $CD8^+$ T cell population compared to 21% in normal subjects. The presence of these cells has been linked to several autoimmune diseases. They produce higher levels of IFN-γ, and are resistant to apoptosis. The capacity of $CD8^+CD56^+$ T cells to express higher level IFN-γ may drive the disease progression by maintaining an inflammatory response in the periphery [6].

3. AUTOIMMUNE DISEASE

IFN-γ has been associated with promoting autoimmune diseases due to its proinflammatory properties. The most notable diseases associated with IFN-γ are systemic lupus erythematous (SLE), multiple sclerosis (MS) and Rheumatoid Arthritis (RA). The main characteristic of the complex autoimmune disease SLE is the generation of autoantibodies by activated B cells. The antibody-complement complex causes local and systemic inflammation that can lead to kidney failure. Although previous studies identified the importance of IFN-α in lupus pathogenesis, recent studies have implied IFN-γ as the primary culprit for this disease. There are reports linking

the single-nucleotide polymorphisms (SNP) of IFN-γ genes to lupus susceptibility. The allele with the greatest risk, SNP (rs2430561), is located in an NF-κB binding site and has elevated IFN-γ expression compared to a low-risk allele [7]. Also, peripheral blood T cells from SLE patients expressed significantly higher levels of IFN-γ when stimulated with anti-CD3/CD28 antibodies compared to those from normal controls [8]. Increased level of STAT1/pSTAT1 can be detected in both lymphocytes and monocytes from SLE patients, and expression levels of STAT1 correlate with disease activity [9]. These results align with the findings in our laboratory. We have observed rapid appearance of SLE-like symptoms in our AU-rich element deletion mice whose deletion results in a constant expression of low levels of IFN-γ (Hodge *et al*. manuscript in preparation). Furthermore, a recent report by Lee and colleges provides a probable mechanism of the IFN-γ contribution to lupus pathogenicity. At 7 weeks of age, IFN-γ can be detected in the serum in lupus-prone Roquin$^{san/san}$ mice used in this study. The detection of IFN-γ coincided with the onset of disease. They found excessive IFN-γ expression contributed to lupus pathology by promoting accumulation of T follicular helper cells, leading to abnormal germinal center formation and autoantibody production [10].

MS is an autoimmune disease caused by infiltration of autoreactive T lymphocytes into the central nervous system and result in damages to neurons and axons. Although MS pathogenesis involves IFN-γ secreting T cells, IFN-γ has been shown to be neuron protective and able to mitigate the severity of disease. In the MS animal model, experimental autoimmune encephalomyelitis (EAE), IFN-γ receptor knockout (IFN-$\gamma R^{-/-}$) in the CNS resulted in more severe neurological deficits as compared to IFN-$\gamma R^{-/-}$ in the periphery [11]. In another similar study, EAE was induced in transgenic mice expressing signaling defective dominant-negative IFN-γ receptors (GFAPγ R1Δ mice) on astrocytes. Inhibition of IFN-γ signaling did not prevent disease onset. In contrast, GFAPγR1Δ mice exhibited extensive demyelination at peak acute disease with increased mortality [12]. These data could explain the findings that treatment in MS patients with anti-IFN-γ antibodies did not ameliorate the symptoms, but actually aggravated the disease. Without the inhibition of IFN-γ, Th1 cells will commit to the Th17 lineage whose contributory role in EAE has been widely reported. Nevertheless, administration of IFN-γ is not an appropriate therapy for MS, since only CNS-restricted IFN-γ is neural protective. Exogenous IFN-γ in the periphery would only aggravate the inflammatory responses and lead to undesirable outcomes. In fact early clinical trials with IFN-γ in MS patients did show a worsening of the disease [13].

The role of IFN-γ in the pathogenesis of RA still remains controversial. RA is characterized by the accumulation of effector T cells that target joints resulting in damage to the cartilage and bone. In several studies, IFN-γ has been shown to be a disease limiting factor in an RA animal model, collagen-induced arthritis (CIA), IFN-γ administration ameliorated disease severity, while CIA disease progression was worse in IFN-$\gamma R^{-/-}$ [14]. IFN-γ was also found to inhibit IL-1β-induced cartilage-degrading matrix metalloproteinase production when cultured with RA synovial tissue specimens [15]. However, other reports implied the involvement of IFN-γ in RA pathogenesis. In RA patients, higher level of STAT1 can be found in the peripheral blood and there was a correlation of STAT1 levels to disease activity [16]. A study by Doodes *et al.* found neutralization of IFN-γ inhibits arthritis. IFN-$\gamma^{-/-}$ mice developed less severe proteoglycan-induced arthritis with delayed onset. The IL-17 level in these mice contributed to the disease development, since IFN-γ/IL-$17^{-/-}$ mice have disease in less severity in comparison. The results suggested that both IFN-γ and IL-17 have the potential to induce arthritis, though the strength of IFN-γ signaling dictates IL-17 contribution to disease onset [17]. While this study clearly addresses the importance of IFN-γ in RA pathogenesis, it also displays the discrepancy among disease models. In the CIA model, IL-17 expression is more detrimental with respect to disease progression; hence, disease severity is worse in IFN-$\gamma R^{-/-}$ mice. However in the Doodes' report [17], arthritis induced by proteoglycan was more severe in IL-$17^{-/-}$ mice. Also, the Saha *et al.* have shown that, in the CIA model, the symptoms improved when animals treated with anti-IFN-γ antibodies in the early phase of disease induction while symptoms worsen when the antibodies were given during the later stage of the disease [18]. These results indicate that even under the same disease context, any change in disease factors, such as antigen, gender, timing of treatment and age of subjects, would result in different immune environments, leading to differences in outcome.

4. CANCER

It is well-documented that IFN-γ can contribute to the containment of tumor progression and growth by increasing tumor antigen presentation to tumor specific T cells and increased susceptibility to NK cytotoxicity. In addition to promote immune response to the tumor, IFN-γ also can induce the expression of tumor suppressing factors. For example, Mig-1, the monokine attracting activated T and NK cells, is induced by IFN-γ and was recently shown to limit metastasis in a mammary tumor model. Furthermore, GBP-1, a major product of IFN-γ signaling, was shown to significantly inhibit the growth

of highly malignant TS/A mammary carcinoma cells in immune-competent Balb/c mice [19]. IFN-γ was also shown to inhibit growth and promote cell death in human hepatocyte carcinoma cells by inducing autophagy—through IRF-1 signaling pathway [20]. In the study by Schmitt *et al*., IFN-γ induced the expression of miR-29, an anti-tumor factor. MiR-29 family members target the expression of proteins involved in invasion, migration or proliferation of cells and silencing of these target proteins would significantly inhibit tumor growth. MiR-29 expression levels were inversely correlated with the proliferation rate of various melanoma cell lines [21]. In murine renal cell carcinoma cell line model (RCC), culturing the cells with IFN-γ induced expression of nitric oxide synthase (iNOS). The resulting high elevation of nitric oxide (NO) and citrulline, and a decrease in arginase activity lead to cell cycle arrest, and significantly inhibit RCC proliferation [22].

Despite the antiangiogenesis property of IFN-γ, there is ample evidence to indicate that it has a protumorigenic effect as well. A meta-analysis genetic study with over 1900 cancer cases indicated a correlation of IFN-γ + 874 T/A with a significantly increased risk of cervical cancer in the comparison of the AT versus TT genotype [23]. Transgenic expression of IFN-γ in the mouse stomach induced an extensive inflammatory response accompanied with increased cell proliferation. These data imply that IFN-γ may contribute to inflammation-associated gastric neoplasia [24]. Furthermore in an animal model of UVB-induced melanoma, IFN-γ was indicated as driving a protumorigenic microenvironment through the activation of melanocytes, an effect that was abolished by systemic administration of anti-IFN-γ antibodies [25]. In the tumor microenvironment, IFN-γ can also function to protect tumor cells from immune destruction. It has been shown that IFN-γ induced PD-L1 expression on acute myeloid leukemia and human oral squamous carcinoma. The interaction of PD-L1 expressed on the cancer cells and PD-1 expressed on T cells suppresses T cell activation and induces T cell apoptosis. As a result, the antitumor immunity of T cells is inhibited in the micro-environment, thus promoting tumor survival [26,27].

These studies suggest that anti- and protumorigenic-functions of IFN-γ are cell and tumor specific. Therefore, to be effective, the therapies and vaccines incorporating IFN-γ may need to be tailored in the context of the specific tumor type.

5. INFLAMMATORY BOWEL DISEASE (IBD)

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), is triggered by abnormal immune responses toward common gut microbiota. During the course of disease, epithelial cells are exposed to an array of proinflammatory cytokines which results in a disruption of epithelium homeostasis and compromises the mucosal barrier. Subsequently, the penetration of gut bacteria across the corrupted mucosal epithelium leads to infiltration of T cells [28]. Vigorous IFN-γ production by T cells can be detected in colonic mucosal tissue cultures and intestinal lamina propria mononuclear cells from IBD patients. Ample evidence has implicated IFN-γ signaling to the pathogenesis of this disease by both augmenting the inflammatory response and compromising the mucosal barrier.

Wnt-β-catenin signaling is one of the signaling pathways that maintain epithelium homeostasis by regulating intestinal epithelial cell (IECs) proliferation and survival. There is a strong association between aberrant Wnt-β-catenin signaling and IBD as well as intestinal cancer. Treatment of IECs with IFN-γ leads to activation of β-catenin signaling through phosphoinositide-3 kinase (PI3K) and AKT. IFN-γ induced AKT-β-catenin activation promotes IEC proliferation. However, this activation can also induce the expression of a Wnt inhibitor, Dkk. As a result, increased incidence of apoptosis and reduced IEC proliferation can be seen in a mouse colitis model and IEC cultured with extended IFN-γ treatment, as Dkk1 suppresses Wnt-β-catenin signaling [29]. In addition, IFN-γ induces GBP-1 expression which suppresses the expression of β-catenin, and in turn disrupts Wnt-β-catenin signaling [30]. The mucosal barrier in the intestine provides a physical hurdle that limits access of toxins and microbes to underlying tissues. During inflammation, epithelial cells express hypoxia-inducible factor (HIF)-1,resulting in induction of several genes that strengthen the mucosal barrier [31]. IFN-γ was shown to inhibit the expression of HIF-1β which in turns suppresses HIF-1 activity and expression in IECs both *in vitro* and *in vivo* [32]. This weakening of the mucosa enhances bacterial content leakage, thus attracting immune cells to the inflamed gut and hence further promoting the developing of disease.

Contrary to its role in promoting IBD, several reports have shown IFN-γ could be a negative regulator of disease severity by inhibiting Th17 generation. IL-23 has been shown to be colitogenic, as it promotes the generation of Th17 cells and suppresses Treg differentiation in the intestinal microenvironment [33]. Sheikh and colleagues used an IL-10$^{-/-}$ mice experimental colitis model and showed that IFN-γ inhibits IL-23 expression in macrophages isolated from lamina propria of IL-10$^{-/-}$ mice. Furthermore, IFN-γR1/IL-10$^{-/-}$ mice have severe colonic inflammation with increased IL-23 expression [34]. A study by Jin *et al.* also showed that IL-17 plays a critical role in IBD pathogenesis. IFN-$\gamma^{-/-}$ mice develop severe colitis upon 2,4,6-trinitrobenzene sulfonic acid

treatment , while IL-17$^{-/-}$ mice develop colitis to a lesser degree [35]. However, one needs to be cautious because these reports do not suggest IFN-γ as a treatment for IBD. While blocking the tissue destructive effects of IL-17 may ameliorate the severity of IBD, the presence of IFN-γ would induce profound inflammatory responses and results in IBD pathology as shown in numerous reports [35,36].

6. NEURODEGENERATIVE DISEASES

Injury or infection in the brain activates microglia and glial cells function as the first line of defense as well as astrocytes, another type of glial cell that plays a role in the repair process. When activated, these cells release an array of proinflammatory cytokines, including IL-1β, TNF-α, and IL-6, as well as ROS and NO, which are toxic to neurons and result in cell death [37]. When inflammation resolves, astrocytes start the repair process. However, in neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD) and MS, sustained inflammation is observed that ultimately causes the pathology associated with these diseases. The characteristic of PD is gradual and progressive loss of dopaminergic neurons in the *substantia nigra*. Microglial activation and T cell infiltration are commonly observed in postmortem PD brain tissue. Accumulation of proinflammatory cytokines can be detected in the brain and cerebrospinal fluid of PD patients. These observations suggest the involvement of inflammation in disease development, although the pathogenic mechanisms are still unclear. In AD, the two hallmark features of this disease are the extracellular Aβ plaques, a result of the cleavage of the amyloid precursor protein (APP), and intracellular neurofibrillary tangles (NFTs). NFTs are composed of the tau protein which is abnormally hyperphosphorylated and forms insoluble fibrils in AD patient that initiate the deposition within the cell. It has been widely believed that Aβ deposition play a major role in the pathogenesis of AD by activating microglia in an effort to clear Aβ. However, microglia in AD patients fail to phagocytose Aβ that results in Aβ plaque formation and profound inflammatory response.

IFN-γ has been known to activate microglia and astrocytes and induces iNOS expression in CNS [38]. Injection in the mouse cerebral ventricles with recombinant adeno-associated viruses (rAAV) expressing mIFN-γ results in accumulation of activated microglia and astrocytes in the CNS. Basophilic lesions in the basal ganglia caused by calcified deposits can be found in the brain of these mice. This pathology is described in PD as well as idiopathic basal ganglia calcification, also a neurodegenerative disease [39]. In chronic Parkinsonian monkeys, increased IFN-γ was found in the serum and CNS years after disease initiation. Also, constant IFN-γR signaling was detected in both microglial and astroglial cells in these animals. Moreover, there was a positive correlation between the levels of IFN-γ in CNS and the degree of dopaminergic neuronal degeneration in the diseased monkeys. In PD-induced mice, microglia and astroglia are activated before the death of dopaminergic cells, and the activation level of these cells was severely dampened in IFN-$\gamma^{-/-}$ mice [40]. These data imply that IFN-γ not only is critical in the initial glial cell activation in PD, but also is responsible for maintaining the perpetual activation status throughout the course of disease. In the AD mouse model, where APP is overexpressed, infiltration of IFN-γ expressing T cells can be detected in the CNS. Adoptively transferring Aβ specific Th1 cells into these mice increased Aβ deposition and microglial activation. Treatment with anti-IFN-γ antibodies ameliorated AD-like symptoms [41]. This study clearly shows the association of IFN-γ in accelerating the pathology of AD.

Despite the proinflammatory properties, IFN-γ has been shown to be also neuroprotective. Studies have shown that IFN-γ plays a major part in CNS reparation after injury. In the rat hippocampus following status epilepticus, neutralizing IFN-γ or its receptor aggravated the neuronal injury, while intracerebroventricular injection of IFN-γ attenuates the damage [42]. IFN-γ might also play a role in neuron injury repair, since more extensive neurodegeneration can be observed in IFN-$\gamma^{-/-}$ mice compared to WT mice after injury induction in the ventral horn of the spinal cord [43]. In the case of AD, IFN-γ has been shown to decrease Aβ plaque burden in the beginning stage of the disease. Microglial cells of APP transgenic mice upregulate MHCII and CD11c as well as a component of complement system after injection of rAAV expressing mIFN-γ in the brain. These IFN-γ primed mouse microglia cells are able to decrease Aβ aggregation through phagocytosis. However, the immune response against the Aβ aggregate is clearly inefficient to clear Aβ deposition since the Aβ deposit continues to accumulate with age in these animals. [44].

7. STEM CELL RESEARCH

Hematopoietic stem cells (HSCs) are in a constant state of differentiation and proliferation to maintain sufficient blood cells in the periphery. Recently, more and more research is focused on the impact of proinflammatory cytokines on hematopoiesis, since HSC output is altered in response to these signals during infection, injury or radiation/chemotherapy. In line with previous reports that IFN-γ suppresses hematopoiesis, a recent report by de Bruin *et al.* showed that IFN-γ inhibited STAT5 phosphorylation which is an important positive regulator

for HSC self-renewal. When infected with lymphocytic choriomeningitis virus, HSC recovery was more efficient in IFN-$\gamma^{-/-}$ mice than WT [45]. However, new studies have emerged that suggest the effects of IFN-γ on HSCs may not be all negative. IFN-γ has been shown to be able to increase proliferation and mobilize HSCs during chronic infection by *Mycobacterium avium* [46]. In a study by MacNamara and colleges, IFN-γ signaling altered myeloid progenitor function and phenotype in order to augment the production of granulocytes and monocytes during *Ehrlichia muris* infection [47]. These results indicate that IFN-γ regulates HSC in the states of homeostasis as well as infection. The discrepancy among reports could be a result of different microenvironments used for experiments, as the BM niche is proven to be important for HSC maintenance. Thus, the system used for HSC generation or maintenance may affect the results. Also, IFN-γ may only affect certain HSC/progenitors at specific stages of differentiation. Thus, different experimental settings may give rise to different results.

IFN-γ also has been indicated in inducing tissue regeneration and differentiation in stem cell transplantation studies. Stem cell transplantation provides a cell source that could replace dead or injured tissue. Factors that control stem cell proliferation and tissue differentiation would be beneficial for optimizing the efficacy of therapy. Results from *in vitro* screening of different neural stem/ progenitor cells (NSPCs) factors found that IFN-γ had the best capacity among tested treatments in promoting neuronal differentiation based on neural morphology and β-III tubulin expression [48]. However, not all neural stem cell/progenitors respond to IFN-γ in the same manner and can be used for transplantation therapy. In the report by Duque *et al.*, treatment of IFN-γ on oligodendrocyte-type 2 astrocyte progenitor cells (O-2A/ OPC) caused cell arrest and inhibited the generation of oligodendrocytes [49]. In addition to neural stem cell research, IFN-γ also has been showed to drive the differentiation of human mesenchymal stem cells (hMSC) into osteoblasts in an autocrine manner. Additional of exogenous IFN-γ in hMSC cell culture accelerated osteoblast differentiation and induced higher levels of Runx2 expression, a gene essential for osteoblast differentiation and function, [50]. As the interest in stem cell transplantation therapy continues to increase, we can expect to see an influx of studies on the impact of IFN-γ on stem cell development and maturation in the very near future.

8. CONCLUSION

Nearly five decades after the first discovery of IFN-γ, we are yet to fully understand the complexity of its function. What we can be sure about is that the effects of IFN-γ are cell and tissue specific. Researchers should pay additional attention to the samples and conditions used when studying IFN-γ. Different cells, tissues and mouse genetic backgrounds will give rise to different outcomes. In the content of disease, the stage of disease progression, age and gender during sampling will impact on the study readout. All these factors make it even more difficult to decipher the biological function of this complex gene and thus there will be a continuing effort to understand the role of IFN-γ on host cell biology.

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