Interferon gamma in autoimmunity: a complicated player on a complex stage

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Abstract

Early views of autoimmune disease cast IFN γ as a prototypic pro-inflammatory factor. It is now clear that IFN γ is capable of both pro- and anti-inflammatory activities with the functional outcome dependent on the physiological and pathological setting examined. Here, the major immune modulatory activities of IFN γ are reviewed and current evidence for the impact of IFN γ on pathology and regulation of several autoimmune diseases and disease models is summarized.

1. Introduction

The recognition of the profound influence cytokines secreted by immune cells have on the interaction between an organism and its environment has long informed and defined the study of immunology. Interferon gamma (IFN γ) was one of the first recognized cytokines, and is known to play well characterized roles in immune responses to microbial infection. However, despite decades of work and tens of thousands of published studies our understanding of the role(s) IFN γ plays in human autoimmune disease continues to evolve. Originally characterized as a prototypic pro-inflammatory factor, it is now clear that IFN γ is more accurately described as a modulator of inflammation, capable of both pro- and anti-inflammatory activities, with the functional outcome of cytokine activity dependent on biological context.

IFN γ is the only characterized Type II interferon, as defined by its interaction with the IFN γ receptor (IFN γ R). The IFN γ R consists of a complex of two receptor chains, designated IFN γ R1 and IFN γ R2 [1]. IFN γ R1 binds IFN γ with high affinity, allowing further stabilization of binding and productive signaling events through IFN γ interactions with both chains. Both chains have been shown to be involved in recruitment of canonical signaling components of the Janus kinase family with JAK1 and JAK2 bound to the IFN γ R1 and IFN γ R2 respectively [1]. Following activation of the JAKs, STAT1 molecules are recruited via their SH2 domains to form homodimers, allowing translocation to the nucleus and interaction with gamma-interferon activation sequence (GAS) elements. Following binding to GAS elements the expression of multiple additional transcription factors including members of the interferon regulatory factor family is enhanced. This GAS driven expression of transcription factors allows amplification of IFN γ 's effects via modulation of secondary transcription targets. It should be noted that in addition to the canonical signaling pathways outlined above multiple non-canonical signaling pathways are also activated and clearly play a role in diverse IFN γ R activities [2, 3].

One of the important transcription factors expressed due to IFN γ R signaling is T-bet, the master transcriptional regulator necessary for inducing and maintaining an interferon gamma producing, Th1, differentiation state in CD4⁺ helper T cells. The expression of T-bet thereby acts to amplify continued IFN γ production. This is only one of the feedback loops that IFN γ signaling itself induces that may modulate future IFN γ R signaling [4, 5]. Another, contrasting, example is the IFN γ R mediated expression of molecules from the suppressor of cytokine signaling (SOCS) family of proteins, notably SOCS1. The induction of SOCS1 acts as a critical negative regulatory element acting to control continued JAK/STAT signaling. Indeed, in the absence of SOCS1, mice demonstrate a lethal group of autoimmune pathologies associated with STAT1 signaling [6].

Modulation of IFN γ R expression and cellular localization are additional regulatory mechanisms thought to be vital to limiting IFN γ signaling [7-10]. While expression of IFN γ R1 is almost ubiquitous in mammalian cells, a more variable and dynamic expression of IFN γ R2 is thought to determine the extent of IFN γ induced signaling in given cell populations [7, 11-15]. As an example, T cell expression of IFN γ R2 has been shown to be affected by antigen driven activation, differentiation status, and prior exposure to IFN γ . The regulation of IFN γ R availability through these pathways appears critical to determining if signaling results in enhanced T cell activity or in cell death [11-13, 15, 16].

In addition to receptor regulation, both transcription [17, 18] and translation [19] of IFN γ also provide checkpoints for controlling IFN γ signaling. Further, recent reports suggested that Tmevpg1, a

long intergenic noncoding RNA, is involved in optimal IFN γ gene transcription [18, 20] highlighting new elements to be considered in examinations of IFN γ functional regulation [17].

2. Interferon gamma cellular expression and functions

The nearly ubiquitous distribution of interferon gamma receptor complexes (IFN γ R) and the overwhelming number of transcriptional targets modified upon IFN γ R activation have hindered simple descriptions of IFN γ R activity in disease and homeostasis. Overall, IFN γ has been implicated in many processes including, among others, inhibition of viral replication, resistance to multiple viral/bacterial/fungal pathogens, regulation of cell growth and death, tumor resistance/development, antigen presentation, and immune cell trafficking. As mentioned above, unrestrained IFN γ signaling can result in extensive tissue damage, providing ample reason for the numerous regulatory mechanisms that modify IFN γ activity [21]. Despite the complex and potentially hazardous responses induced by treatment, IFN γ has been examined as a therapeutic in patients with chronic granulomatous disease [22] and pulmonary tuberculosis [23] without severe adverse effects, suggesting that activation of IFN γ R signaling could potentially be utilized in other diseases.

IFN γ is produced by a limited number of cell types, largely restricted to specialized cells of the immune system. IFN γ is produced by multiple lymphocyte cell types with conventional producers including CD4 $^{+}$ and CD8 $^{+}$ $\alpha\beta$ T cells, $\gamma\delta$ T cells, NKT cells, and NK cells [24]. NK cells have recently been classified as a member of the Group 1 innate lymphoid cells (ILC1) as defined by phenotypically lymphoid or lymphoid-like cells that do not recombine antigen receptors and that produce IFN γ [25]. Multiple other ILC1s, separate from NK cells, have been also identified based on precursor cells, receptor usage, and tissue localization [25, 26]. In addition, several studies have also demonstrated the capacity of B cells to express IFN γ , although the functional importance of this expression to specific aspects of the immune response is still being determined [27]. Taken together these findings support IFN γ production as a common potential among lymphoid cells.

In addition, many reports have demonstrated that other leukocytes are also capable of producing IFN γ under some conditions. Notably, several groups showed that purified populations of macrophages can produce IFN γ [28, 29], although early reports are controversial due to potential contamination of the cells with known IFN γ producing NK and T cells [30]. More recent work that utilized more stringent techniques to avoid contaminating populations (e.g. T cell and NK deficient RAG2 and common gamma cytokine chain double deficient transgenic mice) have shown IFN γ production in monocytes/macrophages [31], dendritic cells [32], and neutrophils [33]. Further, evidence is now emerging that IFN γ production from these cells during inflammation can have profound physiological and pathological effects in some specific settings [33, 34]. However, at present the preponderance of evidence suggests that T cells and NK cells are the major sources of IFN γ production in most physiological and pathological settings as demonstrated both by loss of IFN γ production following depletion of these cell types and by relative levels of IFN γ production in mixed cell environments.

Functionally IFN γ is a pleiotropic cytokine, with current evidence suggesting that IFN γ signaling can significantly modulate expression of 2339 human genes [35], many of which are targets shared with Type I interferons. The vital importance of IFN γ to normal homeostasis and immunity is exemplified by the enhanced susceptibility to infections seen in patients with deficiencies in IFN γ signaling. These deficiencies result in susceptibility to infections from multiple pathogens particularly mycobacterial and fungal species [36-38]. Despite the many transcriptional targets shared with type I interferons, IFN γ has non-redundant roles in immunity as evidenced by incomplete recovery of IFN γ R deficient patients with disseminated mycobacterial infections following treatment with Type I interferon [39]. Some of the broadly applicable cellular effects of IFN γ signaling are briefly discussed below.

Anti-viral effects

As might be expected, IFN γ mediates strong anti-viral responses including transcriptional induction of the double-stranded RNA activated protein kinase (PKR), 20-50 oligoadenylate synthetase (2–5A synthetase), and dsRNA specific adenosine deaminase (dsRAD) [24]. In addition, production of oxidation products [40] and many of the other mechanisms discussed below have primary or secondary anti-viral effects.

Modulation of additional signaling pathways

IFN γ can enhance and/or limit the signaling capacity of a variety of signaling pathways. This modulation can occur by restriction of receptor expression and/or by modulation of downstream signaling component expression or function. The result is an extraordinarily complex set of interactions that are still being described [4]. However, several instances of signaling modulation seem particularly applicable to autoimmune inflammation. As one example, an increase in Type I interferon signaling occurs after IFN γ priming associated with increased levels of STAT1 and ISGF3 γ that allow enhanced primary signaling through the Type I interferon receptor [41, 42]. This interaction is of particular importance as Type I interferons are thought to play a role in a variety of autoimmune conditions [43].

Another example with profound implications for immunity is the modulation of Toll-like receptor (TLR) signaling pathways. IFN γ has been shown to enhance TLR signaling by increasing expression of TLRs, increasing expression of downstream signaling components, sensitizing NF- κ B to activation [44, 45], and by blocking inhibitory feedback mechanisms, including the production of IL-10 [46]. This enhancement of TLR signaling could act to amplify the adjuvant properties of TLR ligands, increasing the inflammatory response and associated tissue pathology.

As mentioned above, IFN γ can block the production of IL-10, a cytokine that is generally considered an anti-inflammatory cytokine, although like IFN γ is capable of opposing effects under some circumstances [47]. Overall IL-10 is an active immunosuppressive factor in multiple settings [48] and as such the inhibition of IL-10 is thought to be a major contributor to IFN γ 's pro-inflammatory effects.

Growth inhibition and cell death

IFN γ has been well characterized as a growth inhibitory and cell death inducing signal. However, an array of potential responses to IFN γ is clearly evident, with responses, sometimes in the same cell type, ranging from cell death to proliferation. Growth inhibition is induced through expression of the cell cycle regulator p21 [49] and reduced expression of c-myc [50]. In turn, modulation of apoptotic factor production/release allows IFN γ to modulate cell death [51].

In addition, the capacity of IFN γ to potentiate endoplasmic reticular stress has been characterized in multiple tissues [52-54]. This stress is perhaps not surprising given the vast array of genes whose expression is increased following IFN γ signaling [53], as well as the increases in reactive oxygen species and concomitant oxidation of proteins. In turn, ER stress has been implicated in sensitivity to cell death induction [55]. Indeed, several groups have suggested that ER stress induced cell death is involved in tissue destruction associated with the induction of autoimmune conditions including type 1 diabetes [54] and multiple sclerosis [53]. In contrast, the IFN γ mediated induction of the immunoproteasome has been shown to counterbalance ER stress [56] while IFN γ mediated induction of PERK could protect from future ER stress [57].

Along similar lines, IFN γ has been shown to induce autophagy in monocytic cells [58]. Given the array of responses impacted by autophagy induction this could result in either induction or protection from cell death.

Finally, IFN γ mediated inhibition of angiogenesis has been shown to be an important factor in tissue destruction and tumor control [59].

Modulation of cell trafficking

IFN γ can impact cell trafficking through multiple mechanisms acting in different cell types. In both myeloid and endothelial cells IFN γ signaling results in profound changes in expression of chemokines and adhesion molecules [60, 61]. IFN γ drives the expression of several chemokines

including CCL2, CCL3, CCL4, CCL5, CCL15, CCL20, CXCL9, CXCL10, and CXCL11 [35, 62]. These chemokines allow recruitment of circulating leukocytes through cognate interactions with chemokine receptors. In addition IFN γ can also induce CCR1, CCR3, and CCR5 in myeloid cells allowing recruitment of these cells to IFN γ primed inflammatory sites [63]. Interestingly, IFN γ signaling acts to block chemotaxis in monocytes through regulation of the actin cytoskeleton suggesting that in these cells the IFN γ signal may act as a retentive factor to hold effector monocytes at the site of cytokine release [64, 65].

The changes outlined above result in increased cell recruitment to sites of inflammation. However, there is also evidence that IFN γ can decrease the expression of several matrix metalloproteinases [66], thereby preventing modification of the extracellular matrix and potentially decreasing cell entry into some tissues.

3. Interferon gamma and immune function

While initial observations of direct anti-viral effects resulted in IFN γ 's name, perhaps the best recognized effects of interferon gamma are targeted to the admittedly broad group of cells that comprise the functional immune system. The impact of IFN γ signaling is evident in both innate and adaptive immune cells, and clearly impacts the continual and complex interactions between the groups. Brief outlines of some of the mechanisms IFN γ may induce in innate and adaptive immunity with potential impact on autoimmune disease are presented below.

Innate immune cells:

IFN γ was found to be the predominant factor involved in lymphoid cell induction of macrophage activation [67, 68], a vital effector component of the adaptive immune response [69]. IFN γ drives activation of multiple innate immune effector mechanisms including production of reactive oxygen species, secretion of generally pro-inflammatory cytokines such as TNF α and IL-12, and enhancement of antigen presentation.

Production of reactive oxygen species

The increased production of reactive oxygen species driven by IFN γ signaling occurs in monocytes, macrophages, and neutrophils via transcriptional up-regulation of the inducible nitric oxide synthase (iNOS or NOS2) [40], cofactors for iNOS [70], and components of the NADPH oxidase (gp91-phox, p67-phox, and p47-phox)[71]. IFN γ treatment results in rapid increase of iNOS message and protein that in turn results in production of nitric oxide and associated oxidant species.

Cytokine production

Cytokine production is a critical part of innate immune effector activity. IFN γ signaling acts to modulate expression of several cytokines. Modulation of cytokine production takes both positive and negative forms with increases in IL-12 expression to enhance continued IFN γ secretion from innate cells and to drive CD4 cell differentiation toward the Th1 phenotype in parallel with repression of IL-10 production to prevent negative regulation of ongoing inflammatory activity (described above in *Modulation of additional signaling pathways*).

IL-12 is one of the most critical cytokines IFN γ regulates. IL-12 is a vital component of IFN γ production in both innate and adaptive immune compartments. IL-12 signaling drives helper cell differentiation towards a Th1 phenotype and directly induces the production of IFN γ from NK cells. A recent study suggested that IFN γ signaling from NK cells controls the differentiation state of monocytes recruited to an inflammatory site. These recruited cells matured into inflammatory macrophages and dendritic cells capable of producing IL-12 [72]. The IL-12 produced then drove further NK IFN γ production perpetuating a positive feedback loop.

Antigen presentation

IFN γ can modulate multiple pathways that allow enhanced antigen presentation including directly increasing expression of MHC class I and II molecules and associated molecules including the MHC class II master regulator CIITA [73]. In addition, through amplification of downstream signaling components IFN γ can also enhance adjuvant induced APC maturation and concomitant immune

stimulatory antigen presentation [74, 75]. Other elements of the antigen processing machinery regulated by IFN γ include components of the immunoproteasome [76-79] and cytoskeletal elements that mediate trafficking of MHC/peptide complexes [64, 80]. In addition to enhancing antigen presentation among professional antigen presenting cells IFN γ can also allow production of MHC class II molecules in cells that do not express MHC class II antigen under steady state conditions, providing new targets for CD4 $^{+}$ T cell recognition and activation [81-83].

Metabolic pathways

One of the primary mechanisms involved in IFN γ mediated immune suppression is the induction of enzymes that limit availability of critical metabolic factors to the metabolically intense adaptive immune response. The best characterized of these enzymes is indoleamine-2,3-dioxygenase (IDO) a rate limiting step in tryptophan catabolism [84]. IFN γ signaling induces expression of IDO in dendritic cells resulting in reduction in locally available tryptophan and consequent reduction in T cell proliferation and effector function [85].

Another intriguing possible metabolic mechanism for IFN γ mediated regulation of innate/adaptive interactions is induction of arginase-1 (ARG1), an enzyme that is involved in arginine catabolism. Reduction in arginine availability is known to have immunosuppressive effects, particularly in the context of a tumor setting [86]. Originally, ARG1 and iNOS were thought to be reciprocally regulated, with IFN γ inducing iNOS [87, 88]. However, a more recent study has suggested that IFN γ increases ARG1 expression induced by a TLR signal [89] suggesting that context may again play a vital role in determining how IFN γ modulates ARG1 .

Adaptive immune cells:

IFN γ has profound effects on adaptive immunity including regulation of differentiation states, cell growth, and survival. Interestingly, innate capacity to produce IFN γ has been described in T and B lymphocyte subsets [27, 90] suggesting that cognate antigen driven and non-specific T and B cell activity may both be impacted by locally available IFN γ .

Cellular differentiation

IFN γ is the defining cytokine of the Th1 CD4 $^{+}$ helper T cell lineage and can impact differentiation patterns of effector T cells. Unlike innate or innate-like IFN γ producing cells conventional T cells require de novo expression of the transcription factor T-bet before making large amounts of IFN γ . As such, the T-bet inducing capacity of IFN γ acts to drive IFN γ production in newly activated Th1 T cells.

Several groups showed that IFN γ also decreases T cell differentiation to Th2 and Th17 lineages [91-93], resulting in a model that described mutual exclusivity of lineage development. While this exclusivity was once thought to be a major factor involved in the immunoregulatory aspects of IFN γ it is now clear that there is greater plasticity in T cell differentiation than was previously appreciated and that IFN γ production can occur concurrently with IL-17 production with pathogenic consequences [94-97]. Indeed, Th1 produced IFN γ has been suggested to modulate the effector function and/or tissue recruitment of established Th17 T cells, again suggesting that the timing of IFN γ production is critical to determining the ultimate outcome of IFN γ R signaling on the immune response [97].

Interestingly IFN γ signaling has been shown to stimulate the production and activity of acquired regulatory capacity in T cells [98-101]. Indeed, IFN γ signaling seems to both drive suppressive function and also to insure, through T-bet mediated expression of the same chemokine receptors that are typically found on TH1 cells, that the regulatory T cells occupy the same tissues as effector Th1 cells.

In addition to the effects of IFN γ on T cell differentiation and function it also impacts B cell function, particularly the isotypes of antibodies produced, by repressing IL-4 mediated switching to IgG1 and IgE isotypes and driving isotype switching to IgG2a and IgG3 isotypes [102-104].

Cell growth and survival

As mentioned above, the effect of IFN γ R signaling on T cell viability is another example of the complex capacities of IFN γ . Depending on a variety of factors, including the amount given, the T cell

determined by the context of the system examined [109-111].

4. Interferon gamma in select autoimmune settings

The potential for IFN γ to mediate autoimmune disease was evident from early transgenic models that showed induction of tissue specific [112, 113] and systemic [114, 115] autoimmunity following overexpression of IFN γ using cell specific promoters preferential for specific cell types. In addition, disease in a model of multi-organ autoimmunity resulting from deficiency in FoxP3⁺ regulatory T cells is clearly ameliorated when IFN γ signaling is deficient [116], suggesting that IFN γ may play a role in autoimmune pathogenesis in multiple tissues.

Multiple sclerosis (MS)

MS is a neuroinflammatory disease marked by an accumulation of inflammatory cells within the central nervous system (CNS) associated with demyelination via destruction of oligodendrocytes. Several pieces of evidence support a role for IFN γ in MS disease. Examination of lymphocytes from MS patient blood and CSF demonstrated increased production of IFN γ [117, 118]. In addition, MS lesions revealed increased expression of IFN γ [119, 120] and of IFN γ induced chemokines [121]. Further, in a small scale studies administration of IFN γ to patients with MS resulted in exacerbated disease [122] while administration of antibodies specific for IFN γ resulted in a minor delay in disability progression [123].

In addition to studies done in MS patients, many studies have utilized common inflammatory models of MS, including experimental autoimmune encephalomyelitis (EAE), to dissect the roles of IFN γ signaling in demyelinating disease. Interestingly, unlike several other tissues [112, 113, 115] overexpression of IFN γ within the mouse CNS did not result in fulminant adaptive autoimmunity to the CNS [124]. Instead the overexpression led to innate immune activation and target cell pathology,

suggesting that IFN γ mediated pathology is not sufficient to drive induction of autoimmunity within the CNS of animal models.

Additional work demonstrated that IFN γ was also not necessary for induction of EAE as EAE could be induced in the absence of IFN γ signaling. Further, induction in the absence or reduced numbers of IFN γ producing T cells can result in enhanced disease severity [125, 126] and/or differential selection of lesion localization [127-129]. Indeed, several groups have described a protective effect of IFN γ on demyelinating disease in autoimmune, toxic, and infectious inflammatory settings [127, 130-133]. However other studies have demonstrated a pathogenic impact of IFN γ in demyelinating disease [134, 135], while still others saw no effect of IFN γ deficiency on demyelination associated with an infection [136]. Further, there are clear indications that IFN γ can exacerbate neuroinflammatory disease and drive neuronal loss in other settings [137].

Intriguingly, groups have reported differences in IFN γ impact based on the timing of IFN γ activity ranging from modulation of antigen processing prior to effector differentiation [138] to strong pro-inflammatory effects of IFN γ during fulminant disease [134] to late pathological effects on regeneration of damaged tissue following resolution of acute inflammation [139-142]. Ultimately, it is clear that IFN γ signaling can have opposing effects on neuroinflammatory disease depending on the timing, disease model, and target tissue effected [127].

While we understand some of the ways that different CNS and immune cell types tend to respond to IFN γ [143], it is not clear at this point what precise mechanism is at work in the IFN γ mediated protection of some CNS tissues. More work will be needed to determine which cells are critical to pro- and anti-inflammatory effects and how dynamic changes in specific responses within defined cell types impact clinical outcomes.

Rheumatoid Arthritis (RA)

IFN γ appears to have differential roles in different models of RA [144]. In Collagen Induced Arthritis (CIA) systems IFN γ had divergent effects depending upon the method of disease induction and site of IFN γ activity. An early study in CIA disease induced by injection with collagen type II in Incomplete Freund's Adjuvant (IFA) supplemented with *Mycobacterium* species antigens (Complete Freund's Adjuvant (CFA)) found that administration of IFN γ to the site of auto-inflammation exacerbated disease [145] possibly by enhancing inflammatory cell recruitment to the site. If however IFN γ was administered outside the inflammatory site it had an ameliorating effect suggested to work through modulation of auto-antibody production [146]. This second effect was similar to the results observed in IFN γ R deficient systems that suggested IFN γ had a generally anti-inflammatory effect apparently by inhibiting signaling through IL-17 [147-150]. In another arthritis model, Adjuvant Induced Arthritis (induced by treatment with CFA alone), IFN γ was also generally found to have protective effect [151, 152].

In contrast another CIA system that utilized the collagen type II injection in IFA without the addition of mycobacterial antigens showed that IFN γ had an obligate pro-inflammatory effect [150]. These data demonstrate the importance of additional inflammatory inputs in determining IFN γ 's role in CIA pathogenesis. In addition the effects of IFN γ in these models were dependent on the timing of IFN γ activity relative to the disease challenge.

Type 1 Diabetes (T1D)

Type 1 diabetes is a condition induced by autoimmune destruction of insulin producing β -islet cells of the pancreas. It was one of the first diseases designated as a Th1 mediated autoimmune disease, as either transgenic overexpression of IFN γ within the β -islet [112] or adoptive transfer of IFN γ producing, but not IL-4 producing, T cell clones resulted in disease [153]. Further, treatment with anti-IFN γ antibodies was sufficient to ameliorate disease in the spontaneous NOD mouse model of T1D [154, 155]. However, in other studies deficiency in IFN γ R signaling was shown to have no appreciable effect on disease in the NOD system [156, 157]. Further, adoptive transfer of IFN γ /IL-10 producing pancreatic

antigen specific cells was sufficient to ameliorate diabetes induction by diabetogenic T cells [158]. Although the exact nature of the disconnect between all of these findings remains unsettled, a recent study suggested that specific subsets of diabetogenic T cells had differential requirements for IFN γ signaling during disease development.

Systemic lupus erythematosus (SLE)

SLE is a systemic chronic autoimmune condition marked by production of autoantibodies, renal damage, and variable systemic tissue involvement. Several animal models of SLE suggest that IFN γ signaling is vital to the pathogenesis of disease. In the NZB/W F1 model of spontaneous SLE administration of IFN γ exacerbates disease while reduction of IFN γ /IFN γ R signaling abrogates disease [159]. Similar findings were also reported in the MRL-Fas^{lpr} model of SLE [160]. Similarly, deficiency of IFN γ signaling in SLE models induced by exposure of mice to 2,6,10,14-tetramethylpentadecane [161] or mercury [162] ameliorates disease. In patients there is strong evidence for an “interferon signature”, several immune associated genes with increased expression over healthy controls, that is thought to be associated with Type I interferon signaling [43]. However, given the overlap in enhanced genes [35] and the impact Type II interferon signaling has on Type I receptor activity [4, 163] the possibility that IFN γ plays a substantial role in SLE remains open. A phase I trial of an anti-IFN γ antibody was estimated for completion in August 2014 (ClinicalTrials.gov (NCT00818948)).

Sjögren's syndrome (SjS)

SjS is a chronic autoimmune disease primarily marked by inflammatory infiltration and destruction of salivary, lacrimal, and meibomian glands with consequent dry mouth and eye symptoms, as well as variable manifestation of systemic issues [164]. There is strong evidence for the involvement of both Type I and Type II interferons in SjS pathogenesis [165, 166]. Further deficiency in IFN γ ameliorates disease in SjS mouse models [167-169]. Interestingly, deficiency in IL-4 expression also ameliorates disease in one model, with the defect occurring at a later stage of disease [170]. These findings suggest that IFN γ and IL4 producing cells must cooperatively act to drive SjS disease in this system.

Summary

IFN γ is a pleiotropic cytokine with complex roles in inflammation and homeostasis. As a consequence, IFN γ is a critical factor in several autoimmune disorders. Both direct and indirect activities of IFN γ can play a crucial role in determining disease outcome. While this review largely focused on immune cells, non-hematopoietic cell responses to IFN γ will also certainly impact disease processes, and in some models will determine if responses are pathogenic or controlled [127, 171].

This review discusses a variety of functional outcomes of IFN γ signaling associated with different physiological and pathological states. While each setting will have its own unique inflammatory environment some commonalities regarding the expected pro- and/or anti-inflammatory contributions of IFN γ have begun to emerge. While there is some evidence to suggest that IFN γ can act as an anti-inflammatory factor after inflammation has been initiated, the majority of studies that have demonstrated anti-inflammatory effects for IFN γ have done so in the context of disease initiation. In these studies the anti-inflammatory effects of IFN γ are thought to be related to modulation of the T cell differentiation program necessary to drive pathology or modulation of tissue activities, such as chemokine production, that in turn modulate immune cell recruitment. In contrast, in both studies of EAE and CIA introduction of IFN γ at the site of ongoing inflammation resulted in exacerbated disease suggesting that IFN γ is pro-inflammatory once fulminant inflammation is achieved [127, 134, 145, 146].

Overall, it is now clear that the outcome(s) of IFN γ signaling are largely controlled by the timing, localization, and cellular context of cytokine signaling. As such modulation of IFN γ activity in complicated disease states should be approached with great caution and consideration.

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