Published in final edited form as:

Immunol Rev. 2012 July ; 248(1): 23–35. doi:10.1111/j.1600-065X.2012.01131.x.

Janus-like effects of type I interferon in autoimmune diseases

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Summary

In multiple sclerosis, type I interferon (IFN) is considered immune-modulatory, and recombinant forms of IFN- β are the most prescribed treatment for this disease. This is in contrast to most other autoimmune disorders, since type I IFN contributes to the pathologies. Even within the relapsing-remitting multiple sclerosis (RRMS) population, 30–50% of MS patients are nonresponsive to this treatment and it consistently worsens neuromyelitis optica (NMO), a disease similar to RRMS. In this article, we discuss the recent advances in the field of autoimmunity and introduce the theory explain how type I IFNs can be pro-inflammatory in disease that is predominantly driven by a Th17 response and are therapeutic when disease is predominantly Th1.

Keywords

interferon; Th17; Th1; autoimmunity; IL-7

Introduction

Type I interferons (type I IFNs) were first discovered by Isaacs and Lindenmann (1) when they observed that viral infected chick embryo cells produced a factor that interfered with subsequent viral infections. This cytokine family has expanded to include the IFN- α molecules, IFN- β , as well as the newly characterized IFN- ϵ , IFN- κ , IFN- τ , IFN- δ , and IFN- ζ (2). Interferons are integral in combating viral infections and tumors, and recombinant versions of type I IFN are used for treating hepatitis and melanomas (3, 4). But in autoimmune conditions, type I IFN has both beneficial and detrimental effects, depending on the disease context.

It is widely accepted that type I IFN is anti-inflammatory in the relapsing-remitting multiple sclerosis (RRMS) patient population (5). Recombinant IFN- β is most prescribed treatment for RRMS. In general, IFN- β is well tolerated and is thought to reduce relapse rate by 30%. But the most troublesome problem for IFN- β therapy is that up to 50% of RRMS patients do not respond to treatment, and in a subset of patients, this treatment might actually induce relapses.

In other autoimmune diseases, type I IFNs, including IFN- β , actually have inflammatory functions that contribute to disease symptoms; these diseases include systemic lupus erythematosus (SLE), neuromyelitis optica (NMO), and psoriasis (6–10). Collectively, these

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The authors have no conflicts of interest to declare.

observations demonstrate that type I IFN can either inhibit or promote autoimmunity and inflammation depending on the disease context. This review explores the recent research advances in the field of autoimmunity to gain an understanding of why type I IFN is anti-inflammatory and therapeutic in some diseases and pro-inflammatory and pathogenic in others.

IFN- β treatment in RRMS

In RRMS, it is widely accepted that type I IFN is anti-inflammatory to the general RRMS patient population (5). IFN- β is the most widely prescribed treatment for MS and clinicians now prescribe one of the four available interferons on the market (Avonex, Biogen Idec; Rebif, Merck Serono; Betaferon, Bayer; and Extavia, Novartis) when the patient is first diagnosed (11). In general, IFN- β therapy is well tolerated and reduces the relapse rate by 30% in patients with RRMS. In fact, there are some patients for whom this treatment works exceptionally well, and they remain relapse free for several years while on this treatment. A common side effect of IFN- β therapy is moderate to severe flu-like symptoms. In some severe cases, IFN- β can cause liver damage that requires the patients to either reduce the dose or change to an alternative therapy such as glatiramer acetate (12). The biggest drawback with IFN- β therapy is that up to 50% of MS patients do not respond to treatment. There has recently been a major research effort to determine biomarkers that can identify responders and non-responders prior to or shortly after the initiation of IFN- β therapy (13–16). This would eliminate the treatment of individuals who would have no benefit from this expensive drug.

Mode of action of IFN- β : insights from EAE

The mode of action of IFN- β treatment of RRMS is unclear, and there still is no definitive predictive marker to establish responsiveness to treatment. Tackling these biological questions is a formidable task. Obtaining tissues samples taken at various stages of disease from a sizable patient population with extensive recorded clinical histories is very rare. In addition, the specimens taken from these cohorts are usually limited to serum or plasma and not from the cerebrospinal fluid (CSF), which is anatomically adjacent to the active lesions. Furthermore, the experimental approaches to human diseases outside of clinical trials are very much observational and many consider these as stamp collecting exercises. There is a growing amount of evidence that strongly suggests that RRMS symptoms are initiated by a T-helper (Th) cell response to myelin in the central nervous system (CNS). First, the human leukocyte antigen-DR (HLA-DR) locus, which encodes for the major histocompatibility complex (MHC) class II molecule, has the strongest genetic association with RRMS (17). Secondly, many studies have identified CD4⁺ T cells in both the spinal fluid and in brain lesions from MS patients (18). Moreover, animal models of MS, collectively called experimental autoimmune encephalomyelitis (EAE), have similar pathological features of RRMS that are initiated by T-helper cells (19). Given the obstacles for conducting research directly on RRMS experiments with EAE, primarily done with mice, have been an effective way to model this disease and to study the mode of action for IFN- β therapy.

Experiments using type I IFN to treat EAE date back to 1982, where researchers demonstrated that injection of recombinant IFN- β suppressed demyelination in mice immunized with myelin antigens in complete Freund's adjuvant (20). Later, other studies confirmed the inhibitory effects of IFN- β in EAE using IFN- β knockout mice (21). More recently, two sets of experiments described a potential mechanism by which type I IFN inhibits neuro-autoimmunity. One publication by Prinz *et al.* (22) demonstrates that the local production of endogenous IFN- β is elevated in the CNS during EAE. These researchers created a panel of conditional type I IFN receptor (IFNAR) knockout mice. They found that

mice with myeloid cells deficient in IFNAR had increased disease symptoms compared to control animals, while disease was not significantly altered in mice deficient in IFNAR in T cells, B cells, or neurons. Also, they discovered that the myeloid cells from these conditional knockouts had increased expression of pro-inflammatory chemokines, suggesting that type I IFN attenuates CNS inflammation by inhibiting the ability of macrophages and microglia cells to produce chemokines. In another related study, Guo *et al.* (23) also examined the how endogenous type I IFN signaling affects EAE. They too demonstrated that IFNAR deficiency resulted in defective myeloid cell function. But in contrast to Prinz *et al.*, they concluded that the anti-inflammatory effects of type I IFN was due to the elevation IL-27 which subsequently inhibits the differentiation of the inflammatory Th17 cells. In spite of the differences in these two publications, these researchers independently describe that endogenously expressed type I IFN suppresses inflammation and autoimmunity in the CNS by acting on cells in the myeloid lineage. However, the myeloid lineage is comprised of many functionally different cell types such as macrophages, microglia, dendritic cells, and granulocytes, and thus, the specific target cell for IFN- β therapy remains to be elucidated.

Prinz (22) and Guo (23) have begun to elucidate the effects endogenous type I IFN play in neuro-autoimmunity. Other studies have used EAE to show how IFN- β as a treatment inhibits disease symptoms. Two studies have used a model of EAE that requires immunization of mice with myelin antigens in complete Freund's adjuvant to assess the effects of IFN- β treatment (21, 24). These experiments demonstrated that IFN- β treatment reduced EAE symptoms, and this treatment effect was correlated with decreased amounts of both Th17 and Th1 cells and induction of Th2 and regulatory T cells.

Th1 and Th17 pathways determine response to IFN- β in EAE

Several different classifications of effector T helper cells have been presented: Th1, Th2, Th3, Th9, and Tfh (25–27). Here we discuss the three major subsets, Th1, Th2 and Th17. These subsets have been classified based on their function in immunity and by the cytokines they produce. The Th1 subset is involved in antiviral immunity and is driven by IL-12 to secrete IL-2, IFN- γ , and tumor necrosis factor (TNF) and is involved in antiviral immunity. Th2, driven by IL-4, produce IL-4, IL-5, and IL-13 and is essential for clearing parasites. The relatively new Th17 subset develops in the presence of IL-6, transforming growth factor- β (TGF- β), and IL-23 and secretes IL-17A, IL-17F, and IL-22 and defends against bacterial and fungal infection (28).

RRMS and EAE were originally thought to be Th1-mediated diseases. IFN- γ was found in the CSF of patients with MS and spinal cords from mice with EAE (29). Mice deficient in T-bet, an essential Th1 transcription factor, are resistant to EAE (30). Mice given myelin-specific Th1 cells develop severe EAE symptoms (13, 31). Finally, IFN- γ treatment of RRMS patients induced severe relapses (32).

However, confounding data using the EAE model showed that treatment with IFN- γ reversed paralysis, and blockade of IFN- γ and IL-12 worsened disease in mice (33). This observation led to the discovery of the Th17/IL-23 pathway. Since the Th17 pathway is strongly inhibited by IFN- γ (34) and deletion of IL-23 protects mice from EAE (35), Th17 overtook Th1 as the inflammatory Th cells in neuro-inflammation. Since then, several papers have disputed the predominance of Th17 in causing inflammation in EAE and MS (36, 37). Transcriptional and fluorescence-activated cell sorting (FACS) analyses demonstrated that Th1 and Th17 cells are present in brain lesions and in blood of MS patients (38, 39). It has been demonstrated that both the Th1 and Th17 cells are capable of inducing EAE symptoms in mice (13, 31, 40). Therefore, it is generally accepted that both

Th1 and Th17 cells are inflammatory in EAE, and many researchers now feel that these cells play a major role in the pathogenesis of MS.

Studies by several independent researchers have indicated that type I IFN can inhibit Th1 and Th17 functions in cell culture experiments using human and mouse tissue (34, 38, 41, 42). It could be concluded that both Th1-driven and Th17-driven autoimmunity would be attenuated by IFN- β therapy. In our own publication in 2010, we also conducted T-cell culture assays to determine how IFN- β treatment alters Th cell differentiation (13). In concordance with Guo *et al.* (23), we found that in Th1 conditions, IFN- β directly induced IL-27 in antigen-presenting cells, which subsequently led to the elevation of IL-10 in the Th1 cells. In addition, we observed that IFN- β potentially inhibited Th17 differentiation in culture.

Based on our *in vitro* experiments and those done by others, it could be concluded that IFN- β has the potential to be anti-inflammatory in both Th1 and Th17 driven EAE. To directly test this hypothesis, we administered recombinant mouse IFN- β to mice with EAE induced by the transfer of either myelin-peptide specific Th1 or Th17 cells (13). IFN- β treatment effectively reduced disease symptoms in mice with EAE induced with Th1 cells. In congruence with our cell culture experiments, IFN- β increased the amount of IL-10 made by splenocytes from mice with Th1 EAE. Unexpectedly in Th17-induced EAE, we observed that IFN- β therapy worsened disease symptoms in mice.

This observation that Th17 EAE was exacerbated with IFN- β treatment was very surprising. A popular theory on the mode of action of IFN- β therapy is that it inhibits the Th17 differentiation to attenuate disease (38, 43). In fact, our *in vitro* and *in vivo* EAE experiments showed that IFN- β did inhibit IL-17 production in T cells (13). Yet, this treatment actually worsened Th17-induced disease. The reason why Th17 auto-immunity is exacerbated by type I IFN is not currently known, but we discuss possible mechanisms below.

Determining response to IFN- β therapy in RRMS patients

The clinical trials that led to the approval of IFN- β in RRMS patients indicated that some individuals experience clinical breakthrough from treatment, which means that they did not respond to well to the treatment (16). There could be many reasons why these patients did not respond to IFN- β therapy (reviewed in 44). Some of the postulated mechanisms are a decrease in IFNAR expression or decreased expression of signal transducer and activator of transcription 1 (STAT1) and STAT2, transcription factors activated by type I IFN. Another theory speculates that there is an increase in the suppressor of cytokine signaling (SOCS) proteins, which inhibit type I IFN signaling. These are very interesting and plausible reasons for non-responsiveness to treatment, but there has not been any clinical data to support these hypotheses.

Non-responsiveness could be explained by the theory that these patients have poor bioavailability of IFN- β . One well known theory for the decreased bioavailability is the development of antibodies to IFN- β (45). Several studies have identified that in some non-responders repeated injections of recombinant IFN- β elicits an antibody response against the cytokine, and in theory, these antibodies neutralize IFN- β 's beneficial effects (46–48). However, there are studies showing that the development of anti-IFN- β antibodies has no effect on the clinical outcome of the treatment (49). This demonstrates that there is still much to be learned about anti-IFN- β antibodies in MS treatment. Other biomarkers have been shown experimentally to have utility for the determination of IFN- β responsiveness. These include a bioassay for antiviral cytopathic effects and molecular assays (50), such as

measuring the inducible expression of the IFN-inducible genes like myxovirus resistance 1 (MxA)(51).

Another intriguing hypothesis that has been supported by experimental data is that IFN- β non-responders have elevated levels of endogenous type I IFN prior to treatment. Comabella and colleagues (14) found that myeloid cells from the blood of non-responders had elevated STAT1 phosphorylation and expression of IFN-inducible genes. They also found that type I IFN itself was elevated in the serum of the patients. This demonstrates that type I IFN signaling is already activated in these non-responders prior to the initiation of IFN- β therapy. It can be speculated that the non-responders displaying upregulated type I IFN is an attempt by the body to counteract the inflammation. Since type I IFN expression is already high, administering more in the form of IFN- β treatment would be ineffective. Yet, Comabella *et al.* (14) proposed that the endogenous type I IFN actually drives the pro-inflammatory effects in these patients, similar to what is seen in systemic lupus erythematosus (10). For this reason, IFN- β treatment would be ineffective in these patients and it would likely worsen symptoms.

Other researchers have also come to the conclusion that IFN- β may play a direct role in inducing inflammation in non-responders. Rani *et al.* (52) show that the population of RRMS patients has a varied molecular response to IFN- β treatment, where even 'non-responders' show transcriptional activity after IFN- β treatment. In a follow up paper, this research group actually found that patients classified as 'poor responders' had an 'excessive' transcriptional response after IFN- β treatment, which was also qualitatively different from that of the 'good-responders' (53). These data provide more support for theory that type I IFN contributes to the disease process in non-responders.

In our exploratory biomarker study of 26 RRMS patients, 12 responders and 14 non-responders, we discovered a subset of non-responders that had high serum concentrations of IL-17F (a Th17 cytokine) prior to the initiation of IFN- β therapy (13). Th17 cells from both humans and mice produce high levels of IL-17F, which suggests that this group of non-responders had a Th17-driven pathology (13, 36). It should be noted that there are many other cell types, including neutrophils, macrophages, natural killer T (NKT) cells and others, that can produce Th17 cytokines (54, 55). In addition to IL-17F, these non-responders also had elevated levels of endogenous IFN- β compared to responders. In fact we found that the patients with high serum IL-17F were the patients who also had high IFN- β concentrations in the serum. This association suggests that there is a biological link between these two cytokines. This observation is congruent with our experiments that demonstrate that mice with Th17 EAE do not respond to IFN- β treatment (13). It is also congruent with data from Comabella *et al.* (14) who demonstrate that type I IFN is elevated in non-responders prior to IFN- β treatment.

Since our publication in 2010, we have been a part of two collaborations: one with Biogen Idec and the other with Bayer pharmaceuticals. Both pharmaceutical companies have a large collection serum specimens taken from patients enrolled in clinical trials for Avonex and Betaseron. One aspect of this collaboration was to confirm or refute our initial IL-17F results. The results from the Bayer collaboration are concordant with our initial observation. Although differences in IL-17F levels were not statistically significant in responders and non-responders, the patients with very high IL-17F levels were non-responsive to Betaferon. Responding patients were defined by either as having no clinical relapses or no new magnetic resonance imaging (MRI) gadolinium-enhancing lesions while on treatment (unpublished data, manuscript in preparation). In the Biogen Idec collaboration, the measurements from our original sample set were independently validated, but their larger cohort did not confirm that elevated IL-17F is associated with non-responsive to Avonex

(manuscript in press in the *Journal of Neurology*). In this study, responsiveness to treatment was based only upon clinical evaluation of the patients and not by MRI. In addition, patients that developed neutralizing antibodies to therapy were excluded (patients with neutralizing antibodies were included in the Bayer cohort and in our initial study). So, there are conflicting results from Bayer with Betaseron and Biogen with Avonex regarding elevated levels of IL-17F in non-responders. There are four differing aspects of these two larger studies: (i) The definition of responders and non-responders. Bayer used MRI to assess responsiveness, whereas Biogen Idec used clinically defined relapses. (ii) The Biogen study excluded patients that developed antibodies to IFN- β , whereas the Bayer study included those patients. (iii) Avonex and Betaseron are different formulations of IFN- β . Avonex is IFN- β 1a and is a recombinant protein made in mammalian cells. Bayer is IFN- β 1b and is produced in *E. coli*. (iv) The dosing of Avonex and Betaseron differ. Avonex is 30 micrograms of IFN- β given once per week intramuscularly. Betaseron is 250 micrograms of IFN- β given every other day subcutaneously. These differing aspects could account for the discordant results with IL-17F non-responders and further studies will be needed to address all of these issues.

Both type I and type II IFNs have been shown to directly inhibit IL-17A production and Th17 differentiation(34). In fact, two studies have shown that IFN- β treatment has been shown to inhibit IL-17A production from CD4⁺ T cells from RRMS patients (38, 43). The authors conclude that this is the therapeutic mechanism of IFN- β in RRMS. In our *in vitro* and *in vivo* experiments, we also found that IFN- β decreases IL-17A in mice (13). Therefore, this appears to contradict our hypothesis that type I IFN and IFN- β treatment exacerbates Th17 induced inflammation. Nevertheless, we find that IFN- β and IL-17F are both elevated in non-responders and that Th17 EAE is exacerbated by IFN- β . These data provide strong evidence that type I IFN drives inflammation in a Th17-induced disease. This phenomenon, where type I IFNs promote diseases predominantly driven by Th17, also occurs in other human autoimmune diseases.

Role of Type I IFN in other autoimmune diseases

Systemic lupus erythematosus

SLE is a highly variable autoimmune disease that may affect the skin, joints, kidneys, brain, and other organs. Currently, very few biological therapeutics have shown efficacy in this disease. Most recently, belimumab, an anti-BAFF antibody, has received US Food and Drug Administration approval and is now commercially available (56). Several decades ago it first was demonstrated that patients with SLE had increased type I interferon activity in their serum (57). More recently, gene expression technologies have demonstrated that hundreds of type I IFN-inducible genes are active in PBMCs from SLE patients (10), demonstrating that this disease has a type I IFN signature. Genetic data also supports this theory. Outside of HLA, genes in the type I IFN pathway are highly associated with SLE risk (58–61). There is also direct evidence that type I IFN plays a pathogenic role in this disease. Animal models of lupus have shown that blockade of type I IFN reduces symptoms (62, 63), and conversely treatment with type I IFN worsens disease (64, 65). These preclinical studies have led to a phase 1 clinical trial using a monoclonal antibody to IFN- α (66). Data from this trial are promising and show that this treatment reduces the type I IFN signature in SLE patients (67).

Th17 cells have also been implicated in the pathogenesis of SLE. The frequencies of Th17 cells as well as levels of IL-17A and IL-17F are elevated in blood from SLE patients (68). The associated granulocyte molecules, which are induced by Th17 cytokines, are also activated in lupus (10, 61). Furthermore, blockade of IL-17 and IL-23 inhibits SLE symptoms in mouse models. In the clinic, IL-6, a cytokine in the Th17 pathway, is a drug

target with great potential in SLE. IL-6 is involved in a positive feedback loop with Th17. IL-6 is critical for the differentiation of Th17 cells (69) and the expression of IL-6 is driven by IL-17 signaling (70, 71). Tocilizumab, an anti-IL-6 antibody, is a drug that is showing promise in a small clinical trial in SLE where it decreased autoantibody levels and overall disease activity (72). Currently, there are no other Th17 cytokine blockers in clinical trials for SLE. Still, there is a case report of a patient with sub-acute lupus erythematosus who was successfully treated with ustekinumab (an IL-23 blocking antibody), and this drug may be another potential candidate for SLE therapy (73).

Neuromyelitis optica

NMO is a neuro-inflammatory disease that has many similarities to MS and at one time was considered a variant of RRMS. NMO is characterized by the presence of severe inflammation in the spinal cord and optic nerves (74). Lesions are also found in the brain of 60–70% of patients (75, 76), but MRI imaging demonstrates that they are not consistent with the Barkhof/Tintore criteria for RRMS diagnosis (16, 77). In addition, antibodies against aquaporin 4 (AQP4) are present in 80–90% of NMO, and the presence of AQP4-Ig is one clinical feature that is used to distinguish NMO from RRMS (47).

Another striking difference in NMO to RRMS is that NMO lesions have an abundance of infiltrating granulocytes, including both eosinophils and neutrophils, which are rarely seen in RRMS (74). In NMO, IL-17, IL-6, and the granulocyte chemo-attractant, IL-8/CXCL8, are elevated in the CSF compared to RRMS (78, 79). The frequency of Th17 cells in the blood is elevated in NMO compared to RRMS (80). IL-17 signaling is known to upregulate chemokines that recruit and activate granulocytes (40, 81, 82). Therefore, the high levels of IL-17 in the CNS of NMO patients are likely to induce the local expression of chemokines that recruit granulocytes to the CNS. In addition, we have recently published that NMO patients have elevated serum levels of the Th17 cytokines (IL-17A and IL-17F), the neutrophil chemo-attractants (CXCL5 and CXCL8), and neutrophil proteases, which further supports the hypothesis that the Th17/granulocyte axis is contributing to the pathology of this disease (in press in the *Multiple Sclerosis Journal*). In contrast, the majority of RRMS, except for a subset of IFN- β non-responders, may resemble a Th1-driven demyelinating disease.

In addition to Th17 and granulocytes, type I IFN has also been implicated as an important mediator of NMO pathology. Since NMO was at one time considered a version of MS, it was logical at the time to try IFN- β treatment in this disease. However, clinical trials of IFN- β therapy for NMO showed no therapeutic benefit (9), and in fact, several case reports have demonstrated that IFN- β treatment can induce severe relapses and exacerbations in this disease (8, 83, 84). A recent study also described that NMO has elevated interferon signature compared to RRMS (85). The elevated granulocyte signature and interferon signature in NMO reflect what is seen in SLE (10, 85). There are many cases in which NMO patients develop anti-nuclear antibodies (ANA) and can have co-morbidities with SLE (74, 86). In contrast, there are rarely any associations with RRMS and ANA or SLE co-morbidities.

Psoriasis

Psoriasis is another autoimmune disease where type I IFN and Th17 appears to drive pathology. This synergy between Th17 and type I IFN in psoriasis has been shown in mouse experiments (87). In this disease, it is thought that autoreactive T cells initiate chronic inflammation and cause the abnormal proliferation of keratinocytes to form psoriatic lesions and in some cases cause psoriatic arthritis. The IL-23/Th17 pathway has been implicated in the pathogenesis of psoriasis. Genetic studies have identified that polymorphisms in the IL-23/12p40 and IL-23R are risk factors for developing psoriasis (88, 89). In mice

intra-dermal injections of IL-23 induce inflammation in the epidermis which resembles psoriasis (90). Moreover, ustekinumab, a monoclonal antibody (mAb) therapy that blocks IL-23 signaling, had success in clinical trials of psoriasis (91). Ustekinumab is now on the market to treat moderate to severe cases of this disease. Interestingly, this same treatment failed in RRMS, and this suggests that the majority of the RRMS population is not driven by the IL-23/Th17 pathway (92). Other Th17 cytokines have been found in psoriatic lesions, including IL-17A, IL-22, IL-8, and IL-17F (93, 94). In addition, results from advanced clinical trials using neutralizing antibodies to IL-17A mAb is showing efficacy as a treatment for psoriasis (95).

There is strong evidence that type I IFN has an important role in initiating inflammation in psoriasis. Like SLE and NMO, the type I IFN transcriptional signature is activated within the psoriatic plaques (96). Studies have shown that plasmacytoid dendritic cells (pDCs) are found in high numbers in pre-psoriatic plaque areas (6). pDCs are known for producing large quantities of type I IFN (97). Therefore, it is thought that pDCs are recruited to the pre-plaque area and secrete large quantities of IFN- β and IFN- α to perpetuate the inflammatory response. Experimental models have shown that blocking type I IFN signaling reduces psoriatic symptoms in animals (98). Several cases of psoriasis have developed after type I IFN was administered to treat RRMS and hepatitis, which is the most convincing evidence that type I IFN promotes psoriasis (99–104).

Ulcerative colitis

Trials with IFN- β and other type I IFNs have shown some efficacy in ulcerative colitis (UC) (105), but endpoints for the phase II clinical trials using Avonex for UC did not reach statistical significance (106). However, investigators at the US National Institutes of Health conducted a small study to assess the biological differences between UC patients who had responded well to IFN- β compared to patients who did not respond (107). Their observation was strikingly similar to our data in mice and RRMS (13). They observed that those patients who were non-responders to IFN- β had significantly greater Th17 population in the blood and lamina propria compared to responders.

How does Type I IFN exacerbate autoimmune diseases?

The mechanism by which IFN- β promotes symptoms in Th17 driven autoimmune diseases is currently unknown. However, several studies have reported many effects that could contribute to this phenomenon (Fig. 1).

Type I IFN has a pro-inflammatory effect on granulocytes, which are commonly found in Th17 driven pathologies. It has been stimulates neutrophils to release neutrophil extracellular traps (NETS)(108), and we recently found that that IFN- β does as well (manuscript in press). These NETS have destructive proteases such as neutrophil elastase and cytokines that would promote inflammation and destroy inflamed tissues(109).

B cells could be affected by type I IFN to exacerbate symptoms. The B-cell-stimulating cytokine BAFF is known to be induced by type I IFN (110–112). Levels of BAFF are found to be elevated in SLE and NMO, and these increases have been attributed to the IFN signature in these diseases (113, 114). In line with this, MS patients also have elevated levels of BAFF after IFN- β therapy (110). BAFF functions to promote B-cell development, survival, and differentiation to plasma cells (115). Recently, it has been shown that IL-17 from Th cells plays an important role in autoantibody production by promoting the formation of germinal centers (116, 117). Therefore, in Th17 driven diseases, elevated BAFF induced by type I IFN would synergize with IL-17 to produce a robust autoreactive

B-cells response, increase the production of autoantibodies and exacerbate diseases such as SLE and NMO.

Signaling from other Th17 cytokines, other than IL-17A and IL-17F, could be augmented by type I IFN. Recently, it has been shown that the receptor for IL-22, a cytokine produced by Th17 cells (25), is elevated in epidermis of psoriasis lesions compared to normal controls (118). Furthermore, they demonstrated IFN- α induces the expression of IL-22R on epidermal keratinocytes in culture (119). This IFN-induced increase in IL-22 signaling may lead to increased defensin and complement expression in leukocytes and epithelial cells in psoriasis and also contribute to the breakdown of the blood brain barrier in NMO (120–122).

How does IFN- β attenuate RRMS?

As we discussed earlier in this review, two recent articles demonstrated that modulating cytokine and chemokine expression in monocytes and macrophages is an anti-inflammatory property of type I IFN (22, 23). Currently, we do not fully understand the mode of action of IFN- β therapy, but there are many studies in the literature that provide alternative theories (Fig. 2).

It has been speculated for some time that MS is caused by a viral infection (123); therefore, IFN- β could attenuate disease by clearing the virus. However, IFN- β successfully treats EAE (13, 20, 21, 24), a non-viral model of this disease. So, the antiviral effects of IFN- β may not be as essential as its anti-inflammatory properties. Several reports have identified potential anti-inflammatory functions that may contribute to the efficacy of IFN- β treatment. These include blockade of lymphocytes trafficking to the CNS, inhibiting metalloproteinase expression, increasing levels of soluble adhesion molecules in blood, reducing expression of MHC class II molecules, attenuating T-cell proliferation, and altering the cytokine milieu from pro-inflammatory to anti-inflammatory (44).

One fascinating alternative hypothesis suggests that the therapeutic mechanism of IFN- β is very similar to the new oral MS drug fingolimod (Gilenya, Novartis) (124, 125). Shiow *et al.* (125) demonstrated that type I IFN upregulates CD69 expression on CD4⁺ T cells during an immune response. They show that CD69 associates with and inhibits the function of the sphingosine 1 phosphate receptor (S1P1), the receptor targeted by fingolimod (124). Blocking S1P1 traps lymphocytes in lymphoid organs, preventing them from circulating and infiltrating into target tissues such as the MS brain.

Another interesting hypothesis is that the elevation in BAFF levels by IFN- β treatment could contribute to its therapeutic effects. Inhibition of BAFF has been shown to be effective in treating SLE and is currently one of the few drugs on the market for this disease (56). Data from a recent clinical trial showed that atacicept, a BAFF blocker, exacerbated symptoms in RRMS (126), and BAFF-deficient mice get worse EAE (127). This provides direct evidence that BAFF is anti-inflammatory in RRMS, and it is speculated that it is inducing a regulatory B-cell population (128). It has been shown that IFN- β treatment increases BAFF levels in RRMS patients (110), and furthermore, type I IFN has been shown to induce regulatory B cells in a mouse model of sepsis (129). Therefore, it is conceivable that BAFF may be an important molecule for effective IFN- β therapy.

The suppressive effects of IFN- β have been attributed to the activation of the transcription factor ISGF3, which is a complex that is comprised of STAT1, STAT2, and IRF9 and binds to interferon stimulatory response elements (IRSE) (130). Yet, IFN- β can also induce the activation of other STATs (131, 132). The pathways activated by IFN- β depend on the relative concentrations of the STAT molecules within the cell and other cytokines and factors can have an influence on type I IFN signaling (133–135). Our mouse studies

demonstrated that Th1 pathways are critical for the anti-inflammatory effect of IFN- β (13). Inhibition of EAE symptoms by IFN- β treatment requires IFN- γ , which is produced by autoreactive Th1 cells. We also published that IFN- β requires IFN- γ signaling to induce a sustained STAT1 response (13), but we recently have found that STAT4 activation is not affected by IFN- γ deficiency (unpublished observation). This is a noteworthy observation. STAT4 is essential for the induction of EAE (136), but STAT1 has anti-inflammatory effects in EAE, since mice deficient in STAT1 have exacerbated disease (30). Thus, the balance of the STAT1-STAT4 signaling induced by IFN- β could dictate the pro- or anti-inflammatory effects of this therapy.

These experiments showed that Th1 pathways are critical for the anti-inflammatory effect of IFN- β in mouse. However, this phenomenon is not obvious when we assessed biomarkers that correlate with a favorable response in RRMS patients. In our recent study (137), we found that serum levels of IL-7 are inversely correlated with IL-17F in RRMS patients. Moreover, high levels of IL-7 prior to treatment were associated with a good response to IFN- β therapy. In the past few years, several independent collaborations around the world identified that the IL-7 receptor gene has polymorphisms that confer a risk for developing RRMS (138, 139). In addition, expression of both IL-7R and IL-7 mRNA are significantly greater in the CSF of MS patients compared to patients with non-inflammatory neurological diseases (139). IL-7 signaling is critical in T-cell development and for the homeostasis of naive and memory T cells (140–142). Therefore, some researchers have concluded that IL-7 is a contributing factor for the progression of RRMS symptoms. This hypothesis was supported by mouse models. We and others (137, 143) have demonstrated that recombinant IL-7 treatment exacerbates EAE, and conversely, blocking IL-7 signaling with neutralizing antibodies or genetic deletions reverses EAE symptoms.

Our observation that high levels of IL-7 predicts a good response to IFN- β therapy does not appear to support our hypothesis that Th1 driven diseases respond favorably to this treatment (137). Furthermore, our hypothesis came under even more scrutiny, since it was reported that IL-7 aids in the differentiation of Th17 cells and not Th1 cells (143). However, in our experiments, we found that IL-7 has no effect on Th17 differentiation and actually promotes Th1 differentiation, even in the absence of IL-12 (137). Other studies have corroborated our results. Davis *et al.* (144) showed that culturing cord blood T cells with IL-7 promotes the survival and expansion of IFN- γ secreting Th1 cells. The biological relationships between Th1, IFN- γ , and IL-7 have also been demonstrated. First, IFN- γ directly induces the transcription of IL-7 in stromal cells (145, 146). Secondly, IL-7 is a critical factor for anti-viral immunity, the main function of the Th1 immune pathway (147). It is possible that together IFN- γ and IL-7 are involved in a positive feedback loop to maintain a Th1 immune response. We are currently identifying how this IL-7/Th1 axis is linked to a favorable response to IFN- β treatment. We have preliminary data demonstrating that IFN- β synergizes with both IFN- γ and IL-7 to upregulate IL-27 in macrophages, which in turn upregulates IL-10 (unpublished observation). The upregulation of IL-10 could then decrease chemokine/cytokine production from macrophages/microglial cells as observed by Prinz and Guo (22, 23). This synergy with IL-7 and IFN- β has been seen also in studies of human immunodeficiency virus. It is now speculated that the combination of IL-7 and IFN- β could be in full or in part responsible for the lymphopenia in HIV patients (133).

The biology of IL-7 signaling in MS is complex and is likely to be quite important in the pathophysiology of MS. To date, MS is the only autoimmune disorder where IL-7 signaling has been linked in genome-wide association studies (148). Furthermore, preclinical EAE studies, conducted by us in collaboration with Pfizer and independently by GlaskoSmithKlein, indicate that the pharmaceutical industry is considering this therapeutic approach for RRMS (137, 143). IL-7 signaling may actually have protective effects in

RRMS. First, we find that patients with high IL-7 respond to IFN- β treatment, and therefore blocking IL-7 during IFN- β treatment could counteract the therapeutic effects (137). In addition, the IL7R polymorphisms suggest that blocking IL-7 may even harm RRMS patients. The polymorphism that confers risk for RRMS encodes for a splice variant of IL-7R that generates a soluble version of this receptor (138). This soluble receptor can then act as a molecular decoy in the plasma and in tissue. This could mean that RRMS patients have a decrease signaling initiated by IL-7, or the other IL7R ligand TSLP, and contributes to the development of RRMS.

Concluding remarks

The disease categorized as MS is a highly heterogeneous population, and it is gaining acceptance that RRMS is a collection of different syndromes that are under the same disease umbrella. The clinical unpredictability of this disease is exemplified by the variation in response to therapy, which makes it especially difficult for clinicians to choose the appropriate drug for their patients' specific conditions. It is a great challenge for researchers to discover unique ways to identify responsiveness to therapy early after treatment begins or better yet before treatment is initiated.

In this review, we discussed data from preclinical experimental models, biomarker studies, and clinical trials from MS and other autoimmune diseases. As a whole, these observations demonstrate that MS is unique compared to other autoimmune disorders. In many autoimmune diseases, with the notable exception of MS, type I IFN is known to be pro-inflammatory and contributes to tissue destruction (3, 8, 85). In these autoimmune diseases, where type I IFN drives disease, blockade of TNF, BAFF, and IL-23 are therapeutic (56, 149). In the MS community, type I IFN is considered anti-inflammatory and is used to treat RRMS patients (5, 44). Remarkably, blockade of TNF, BAFF, and IL-23 failed to improve RRMS in clinical trials (92, 126, 150). In fact, the blockade of BAFF and TNF, two cytokines that belong in the TNF molecular family, worsen MS symptoms (126, 150).

Understanding the molecular similarity and differences in these diverse autoimmune diseases provides insight into the molecular pathologies of RRMS. Furthermore, it may provide some rationale on how clinicians can stratify RRMS patients and begin predicting treatment response.

Acknowledgments

This study was funded by a US National Institutes of Health grant 1K99NS075099-01 to R.C.A.

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Fig. 1. Potential mechanisms of how type IFN exacerbates autoimmune diseases

Autoimmune diseases initiated with the IL-23/Th17 response secrete high levels of IL-17A and IL-17F. IL-17A and IL-17F initiate granulocyte infiltration to the site of inflammation as well as orchestrate germinal center formation and B-cell maturation in lymphoid tissues. Endogenously expressed or therapeutically administered IFN- β could exacerbate Th17 diseases by directly stimulating granulocytes to release tissue destructive proteases and cytokines or by elevating BAFF to enhance the production of autoreactive antibodies and memory B-cells. Type I IFN also upregulates IL-22 receptor on skin epithelial cells in psoriatic skin and BBB endothelium in NMO. IL-22 can contribute to inflammation by promoting the release of defensins and breaking down tight junctions at the BBB.

Fig. 2. Potential mechanisms on how type I IFN protects in RRMS

Autoimmune diseases initiated by Th1 cells have high levels of IFN- γ that drive lymphocytic and macrophage infiltration in to sites of inflammation. IFN- γ upregulates IL-7 expression in lymphoid tissue stromal cells during T-cell differentiation and provides signals to expand and maintain the Th1 population. IFN- β treatment synergizes with both IFN- γ and IL-7 to attenuate inflammation by upregulating the anti-inflammatory cytokines, IL-27 and IL-10, and decrease chemokine production from macrophages/microglial cells. Type I IFN also induces BAFF expression. BAFF then could directly or indirectly induce the differentiation of IL-10-producing regulatory B cells.