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Interferon- β exacerbates Th17 inflammatory diseases

Robert Axtell^{*}, Chander Raman[^], and Lawrence Steinman^{*}

^{*}Stanford University, Dept. of Neurology and Neurological Sciences, Interdepartmental Program in Immunology

[^]University of Alabama, Birmingham, Dept. of Medicine

Abstract

Interferon- β (IFN- β) is the treatment most often prescribed for relapsing-remitting multiple sclerosis (RRMS). However, 30–50% of MS patients do not respond to IFN- β . In some cases, IFN- β exacerbates MS, and it consistently worsens neuromyelitis optica (NMO). In order to eliminate unnecessary treatment for patients non-responsive to IFN- β , and to avoid possible harm, researchers are identifying biomarkers that predict outcome prior to the initiation of treatment. These biomarkers reveal insights into mechanisms of disease. Recent discoveries on human samples from patients with RRMS, NMO, psoriasis, rheumatoid arthritis, systemic lupus erythematosus and ulcerative colitis, indicate that IFN- β is ineffective and may worsen the clinical status in diverse diseases when a Th17 immune response is prominent.

Relapse-remitting multiple sclerosis (RRMS) and Interferon- β (IFN- β) therapy: Unmet need for rational prescriptions

Type I Interferons (type I IFNs), which include the various IFN- β and IFN- α molecules, were first discovered in virally infected chick embryo cells¹. They bestowed cells with a resistance to virus. This pleiotropic cytokine family is now known to have anti-viral, anti-tumor and immune-regulatory functions. In autoimmunity and inflammation, type I IFNs possess both pro- and anti-inflammatory functions depending on the context of the particular pathology.

The various forms of recombinant IFN- β are collectively the most commonly prescribed treatment for RRMS. In general, IFN- β therapy is well tolerated and the various approved versions of IFN- β carry a label claiming that they reduce the relapse rate by 30%. Clinicians often refer to patients that remain relapse free for years while on treatment as “super responders”². The major side effects of IFN- β are moderate to severe flu-like symptoms and the potential for liver damage. But the most troubling problem for IFN- β is that 10–50% of RRMS patients do not respond to treatment³, thus delaying alternative and possibly

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beneficial treatments. And in some patients, treatment with IFN- β actually induces exacerbations⁴⁻⁶.

We do not fully understand the mode of action of IFN- β . One hypothesis is that multiple sclerosis (MS) is caused by a viral infection⁷; therefore IFN- β was thought to help attenuate disease by clearing the virus. However, IFN- β successfully reverses experimental autoimmune encephalomyelitis (EAE)⁸⁻¹⁰, a disease model devoid of a viral pathogenesis. Therefore, the anti-viral effects of IFN- β might not be as essential as its anti-inflammatory properties for the treatment of MS. In MS there is prominent perivascular lymphocytic infiltration and increased immunoglobulin synthesis within the CNS. Now, the favored theory is that IFN- β provides benefit for RRMS through its actions as an “immune modulator”. Several reports have identified potential anti-inflammatory functions of IFN- β that may contribute to its efficacy as a treatment¹¹. These include blockade of lymphocyte trafficking to the CNS, reduction of expression of MHC class II molecules on antigen presenting cells, attenuation of T-cell proliferation and alteration of the cytokine milieu from pro-inflammatory to anti-inflammatory.

In contrast to its role in RRMS, IFN- β has pro-inflammatory functions that contribute to the pathogenesis in other autoimmune diseases including system lupus erythematosus (SLE), neuromyelitis optica (NMO) rheumatoid arthritis (RA) and psoriasis^{4,12-17}. The role IFN- β treatment has in Th1 and Th17 diseases has been reviewed previously¹⁸. In this essay we will argue the case that IFN- β is a double-edged sword in autoimmune and inflammatory diseases, where it inhibits symptoms in diseases with a Th1 bias whereas it promotes the pathology in diseases with a predominant Th17 bias. Understanding these differences in the pro- and anti-inflammatory functions of IFN- β will be critical in understanding how this cytokine is therapeutic for RRMS. This understanding of its immune modulatory functions should also provide insights on how to discern which patients will respond to treatment with IFN- β .

Understanding the Mode of Action of IFN- β treatment: Lessons from EAE

Understanding the mechanism whereby IFN- β is effective in RRMS is formidable. Obtaining well-characterized MS tissue at various stages of disease, both before and during treatment is rare. Such specimens are usually limited to the blood. Given the barrier of obtaining such samples from RRMS patients, various models of EAE in rodents, primarily mice, have been used to dissect mechanisms of action for therapy with IFN- β ^{8-10,19,20}. However, identifying the mechanism whereby IFN- β attenuates EAE has been complicated for several reasons. First, EAE is a varied collection of models, involving different inciting antigens, different species and different genetic strains within a species. Moreover, so-called ‘active’ EAE is induced with different adjuvants, while no adjuvants are used for inducing ‘passive’ EAE in adoptive transfer protocols²¹. Analysis of disease mechanism must take into consideration processes occurring in various tissues (including the CNS) and cell types. To fully understand of the mechanism of action of IFN- β , the IFN- β receptor, IFNAR, must be analyzed. IFNAR is expressed in most tissues and cell types including, endothelial cells, neurons, glial cells and immune cells¹⁹.

EAE studies showed that *Ifnb1* (IFN- β) knockout mice had increased severity of clinical symptoms, demonstrating that endogenously expressed IFN- β acts as a brake on CNS inflammation²². Recently, two exciting sets of experiments described that the inflammatory functions of myeloid cells are targeted and regulated via endogenously expressed type I IFN, and that this interaction attenuates EAE. In a series of elegant experiments utilizing a panel of conditional IFNAR knockout mice, it was demonstrated that local expression of IFN- β is elevated in the CNS during EAE. In direct response to IFN- β , myeloid cells decrease expression of chemokines to inhibit disease¹⁹. The role of endogenous type 1 IFN signaling in EAE was also examined in another publication²⁰. Here the authors also demonstrated that IFNAR-deficient mice had defects in myeloid cell function. But, in contrast to the previous study, they concluded that the immunosuppressive effect of type 1 IFN is due to the upregulation of IL-27, which inhibits inflammatory Th17 cells (see Box 1). These two discoveries independently describe two key mechanisms whereby endogenously expressed type 1 IFN suppresses inflammation and autoimmunity in the CNS.

Box

T helper subsets in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis

RRMS symptoms are initiated by a Th response to myelin in the CNS. Several studies have identified CD4 T cells in the spinal fluid and in brain lesions from MS patients. Moreover, in animal models of MS, collectively called experimental autoimmune encephalomyelitis (EAE), disease is initiated by Th cells²¹. An ongoing research subject in the MS and EAE fields is to determine the subset of helper T cells critical for the pathogenesis of this disease. Effector Th cells have been categorized into the following subsets based on cytokine secretion and function in immunity: The Th1 subset is driven by IL-12 to secrete IL-2, IFN- γ and TNF and is involved in anti-viral immunity. Th2, driven by IL-4, produce IL-4, IL-5 and IL-13 and have a central role in clearing parasites. The newly discovered Th17 subset develops in the presence of IL-6, TGF β and IL-23 and secretes IL-17A, IL-17F, IL-22 and defends against bacterial and fungal infections⁷⁰.

Originally, both RRMS and EAE were regarded as a Th1-mediated disease based on several observations. First, IFN- γ has been found in considerable quantities in the cerebrospinal fluid (CSF) of patients with MS and in spinal cords from mice with EAE⁷¹. Second, mice deficient in the 'master' transcription factor for Th1 differentiation (T-bet) are resistant to EAE⁷². Third, myelin-specific Th1 cells transferred into mice produce severe EAE symptoms. And finally, an early clinical trial reported that IFN- γ treatment induced severe relapses in RRMS patients⁷³.

But discoveries using the EAE model catalyzed the discovery of the IL-23–IL17 pathway. Paradoxical data demonstrated that treatment of EAE with IFN- γ reversed paralysis in mice with EAE. Deletion of the gene encoding IFN- γ , IL-12 or administration of antibodies specific for these cytokines worsened disease⁷⁴. Given that Th17 differentiation is strongly inhibited by IFN- γ ⁷⁵ and deletion of IL-23 protects mice from EAE, the Th17 population gained notoriety as a highly inflammatory population of T helper cells in neuro-inflammation. In MS, transcriptional profiling and FACS analysis of

MS tissue demonstrated the presence of Th17 in lesions and T-cells from blood²⁵. IL-17 and interferon- γ transcripts are prominent in MS lesions. But since the discovery of the Th17 pathway, several papers have questioned the primacy of Th17 in causing inflammation in EAE and MS³⁰. Two papers have provided data that question the pathogenic potential of Th17 cells in neuroinflammation: first, mice with conditional deletion of IL-17 in T cells develop EAE normally; second, experimental uveitis is cured in rats by treatment with recombinant IL-17⁷⁶. However, it is now generally accepted that both Th1 and Th17 cells, as well as Th2 cells, can induce autoimmune demyelination and may also be pertinent to MS and its variants such as NMO^{47,77}. There may indeed be Th1, Th2 and Th17 variants of autoimmune demyelinating disease.

Other studies have utilized the EAE model to elucidate the mechanism of IFN- β as a treatment, using various active and passive transfer protocols. Two recent papers have used the active EAE model to assess the effects of IFN- β treatment^{9,10}. Active EAE experiments are conducted by immunization of mice with myelin antigens in complete Freund's adjuvant, often along with a boost of pertussis toxin. Procedures that use these complex adjuvants elicit both a Th1 and Th17 response^{23,24}. Depending on the specific experimental conditions the balance between Th1 to Th17 responses is quite variable. In these experiments, the investigators found that IFN- β does moderately attenuate EAE symptoms. This reduction in EAE correlated with decreased amounts of both Th17 and Th1 cells, and upregulation of Th2 and regulatory T cells.

Recently, T-cell culture assays were conducted using both mouse and human cells to determine how IFN- β treatment alters T helper differentiation⁸. In Th1 conditions, IFN- β directly induced IL-27 production in antigen-presenting cells, which subsequently led to elevated IL-10 secretion in Th1 cells. In addition, treatment with IFN- β during Th17 differentiation was inhibitory. These activities of IFN- β required functional IFN- γ signaling.

The in vitro experiments showed that IFN- β has anti-inflammatory effects that potentially applied to both Th1- and Th17-driven EAE. To directly test this, IFN- β was administered to mice with EAE that was passively induced with either Th1 or Th17 cells reactive to a myelin protein-derived peptide⁸. The 'passive' EAE approach induces disease without adjuvants or use of B. pertussis toxin that can be confounding variables. IFN- β treatment effectively reduced disease symptoms in mice with EAE induced by Th1 cells. In congruence to the in vitro experiments, IFN- β increased IL-10 production by splenocytes in Th1 EAE. In Th17-induced EAE, IFN- β treatment unexpectedly exacerbated disease symptoms. This observation was perplexing, intriguing and altogether a stunning surprise. A popular theory on the mechanism of IFN- β treatment in MS and EAE is that it attenuates disease by inhibiting the differentiation of Th17 cells^{9,10,20,25,26}. IFN- β did indeed inhibit IL-17 production both in vitro and in vivo; yet, IFN- β treatment was ineffective and actually worsened Th17-induced EAE. Only later was it learned that IFN- β also worsens human diseases where Th17 is prominent.

Understanding IFN- β Response in RRMS

The clinical trials that lead to the approval of IFN- β in RRMS patients indicated that some patients do not respond to treatment. One theory that explains the lack of response to treatment is poor bioavailability of IFN- β in these patients. One well known cause for the decreased bioavailability is the development of neutralizing antibodies to IFN- β . Several studies have identified that in some non-responders repeated injections of recombinant IFN- β elicits an antibody response against the cytokine and thereby this antibody neutralizes IFN- β 's beneficial effects²⁷. However, non-responsiveness to IFN- β could be due to other mechanisms that reduce the pharmacodynamic properties of IFN- β , for example: decreased expression of IFNAR or its downstream signaling molecules (STAT1 and STAT2), or increased expression of the IFNAR inhibitors such as the SOCS proteins^{11,27}. To assess IFN- β bioavailability, the standard bioassay is an antiviral cytopathic effect assay which is a sensitive assay to measure interferon activity. Recently, however, molecular assays, such as measuring the inducible expression of the IFN-inducible genes including myxovirus resistance 1 (MxA) and IP10 (CXCL10) and others are showing promise as biomarkers for treatment response^{28,29}.

Beyond simply being ineffective in some patients, there is the real possibility that IFN- β could have an active role in inducing inflammation in non-responders. A recent study using a cDNA array demonstrated that RRMS patients have a heterogeneous molecular response to IFN- β ²². Within the patient population, some non-responders had increased transcriptional activity in response to IFN- β , which was qualitatively different to that of the responders. It was concluded that IFN- β could contribute to the disease process. In a separate study of 26 RRMS patients (12 responders and 14 non-responders), a subset of non-responders (6 of 14) was identified that had high serum concentrations of the Th17 cytokine IL-17F before IFN- β therapy was initiated⁸. In both human and mouse, IL-17F is produced by Th17 cells, suggesting that this group of non-responders has a pathology for their type of disease that is skewed toward a Th17 phenotype^{30,31}. In addition, these subjects also had high endogenous levels of IFN- β compared to responders. In fact, a strong correlation was found between IL-17F and IFN- β concentrations in the serum suggesting there is a tight biological association between these two cytokines. This observation is congruent with the Th17 EAE mice, which are non-responders to IFN- β treatment. Moreover, they are also concordant with the identification of biomarkers to predict the response to IFN- β in RRMS were identified³². In this study, serum levels of type I IFN and the expression of type I IFN-regulated genes were elevated in non-responders prior to initiation of IFN- β therapy compared to responders. This suggested that the non-responders might have a similar disease process to SLE, which also has an activated transcriptional signature of type I IFN¹². It was further concluded that type I IFN might contribute to the neuro-inflammation in non-responding MS patients.

Two recent papers have shown that IFN- β directly inhibits IL-17A expression in PBMCs from MS patients, suggesting a mechanism for the positive therapeutic response of IFN- β in RRMS^{25,26}. As already discussed, IFN- β also decreases IL-17A in mouse T cell cultures. Therefore, observations that high levels of IFN- β correlate with high levels IL-17F are quite confounding. A possible difference is that we measured IL-17F and where as the other

investigators measured IL-17A. Even though IL-17A and IL-17F are located in the same region on the chromosome (Chr6 in human and Chr1 in mouse), the transcriptional regulation of these genes is quite different³³. This phenomenon where IFN- β and Th17 are tightly linked biologically can be explained by two hypotheses. It can be speculated that the non-responders displaying aggressive Th17-mediated disease up-regulate IFN- β to counteract inflammation. Because endogenous IFN- β expression is already high, administering IFN- β treatment would be ineffective. But we propose another theory that extends from the work showing that IFN- β non-responders had high³², where endogenous IFN- β drives the pro-inflammatory effects during Th17 biased disease. Therefore, not only would IFN- β treatment be ineffective in these patients, it could worsen symptoms. Our mouse studies provide evidence that type I IFN drives inflammation in a Th17 version of adoptively transferred EAE. A detrimental link between Th17 and IFN- β also occurs in other human autoimmune diseases.

The role of IFN- β in autoimmune diseases other than RRMS

RRMS is the one of the few known autoimmune diseases where the anti-inflammatory effects of IFN- β can be harnessed as a therapy. IFN- β was notably ineffective in rheumatoid arthritis (RA) for example³⁴. In fact it is striking that the main treatment for RA, TNF blockade, has been shown to worsen MS symptoms and this drug carries an FDA black box warning against this contra-indication³⁵. However, trials with IFN- β and other type I IFNs have shown some efficacy in ulcerative colitis (UC)³⁶. A recent study of IFN- β treatment of UC assessed the biological differences between responders and non-responders. These authors observed a result stunningly congruent to IFN- β responders vs non-responders in RRMS. Investigators at NIH found that prior to IFN- β therapy in UC, those patients who were non-responders to IFN- β had significantly higher IL-17 production from lamina propria T cells compared to responders³⁶.

In most other autoimmune disorders, including SLE, psoriasis, RA and NMO, type I IFN contributes to the pathogenesis of the disease¹²⁻¹⁴. It now emerges that Th17 also plays a pivotal role in these diseases³⁷⁻⁴¹. Here we will discuss three of these diseases in the context of Th17 and type I IFN: Neuromyelitis Optica, and Psoriasis.

Neuromyelitis Optica

NMO, also known as Devic disease, is a neuro-inflammatory condition which until recently was considered a variant of RRMS. Unlike MS, the lesions in NMO are rarely associated with the brain. Instead, extensive demyelination is found in the spinal cord and optic nerve of these patients⁴². Recent developments have show that NMO patients develop antibodies against the aquaporin 4 (AQP4) water channel and assays detecting AQP4-IgG are now used for making the NMO diagnosis⁴³. In addition to the lesion location and auto-antigens targeted in NMO, several groups have observed that the dominant infiltrating cells found in NMO lesions are granulocytes, a cell type which are largely absent in RRMS lesions^{42,44}. Strikingly, levels of IL-17 are elevated in the CSF of patients with NMO compared to RRMS⁴¹. The high level of IL-17 in the CNS of NMO patients likely induces the local expression of IL-8, G-CSF and Gro- α which in turn would recruit and activate

granulocytes^{45–49}. IFN- β has been tried as a therapy for NMO but has had devastating consequences. Not only are NMO non-responders to IFN- β treatment, several case reports have shown that this treatment induces severe relapses and exacerbations in this disease^{4,15–17}.

Psoriasis

In the dermatological disease, psoriasis, keratinocytes proliferate in an abnormal manner in response to a chronic inflammatory reaction. The IL-23–Th17 pathway (See Box) has been implicated in the pathogenesis of psoriasis^{39,50,51}. Genetic studies have identified polymorphisms in *IL23A*, *IL12B* and *IL23R* as risk factors for developing psoriasis^{52,53}. In mice intradermal injections of IL-23 induces inflammation in the epidermis that resembles psoriasis⁵⁴. Moreover, monoclonal antibody (mAb) therapy that blocks IL-23 signaling have been successful in clinical trials of psoriasis (interestingly this same treatment failed in RRMS)^{55–57}. Other Th17 cytokines identified in psoriasis include IL-17A, IL-22, IL-8 and also IL-17F^{39,40,50,51,58}. Neutralizing IL-17 with mAb, as with anti-IL-23, is showing promise as a treatment for psoriasis⁵⁹.

In addition to Th17, type I IFN has also been implicated as an important mediator of inflammation in psoriasis. Like SLE, the transcriptional signature of type I IFN is activated within the psoriatic plaques¹⁴. The cellular source of type I IFN is likely plasmacytoid dendritic cells (pDC). Among the first events that occur in this disease, is the recruitment of pDCs to the pre-plaque area where they are activated and secrete large quantities of IFN β and IFN- α ⁶⁰. Experiments using blocking antibodies and knockout mice have demonstrated that type I IFNs play a pathogenic role in psoriasis^{14,61}. Type I IFN has been identified as a key component for the pathology in several cases of psoriasis that developed in RRMS and Hepatitis C patients who received type I IFN as a treatment for their disease^{62–69}.

As a whole, the observations encompassing these pre-clinical experiments in mice and clinical studies in human diseases suggest that type I IFN and Th17 are a dangerous combination in autoimmune disease, where endogenous expression or therapeutic administration of IFN- β in conditions with a Th17 bias, only worsens the disease (see Fig). But the question remains, how does IFN- β exacerbate these Th17-mediated diseases? One hypothesis is that type I IFN could have a pro-inflammatory effect on granulocytes. In particular, it has been shown that IFN- α instructs neutrophils to release neutrophil extracellular traps (NETS) which contain destructive proteases and cytokines. However, B-cells may also be targeted in these diseases. It has been shown that the B-cell stimulating cytokine BAFF is elevated after in both NMO and MS patients after IFN- β therapy. This effect could promote B-cell mediated pathology which is thought to be of primary importance in NMO.

Concluding Remarks

RRMS is a complex disease that has an unpredictable clinical course, with variable pathological patterns. RRMS might not be a single disease, but rather a collection of different syndromes that cause inflammatory demyelination. This heterogeneity is illuminated by the variability in responses to IFN- β . This variability poses a challenge to

clinicians and researchers to develop ways to identify responsiveness early after treatment begins, or better yet, before treatment is initiated.

In this article, we have described the discovery of several biological markers that have great potential to address this important health care issue. However, as of publication there is no approved test to determine whether or not an MS patient should take IFN- β , glatiramer acetate or the recent FDA approved oral medication. Therefore, it should be a high priority for agencies to fund research that is geared to identify the mode of the action of these therapies, to discover biomarkers that predict response, and to develop reliable tests for clinical use. This would be a wise investment for the public for it would eliminate the unnecessary treatment of patients who are non-responders, and would streamline the way clinicians treat RRMS patients with these expensive drugs.

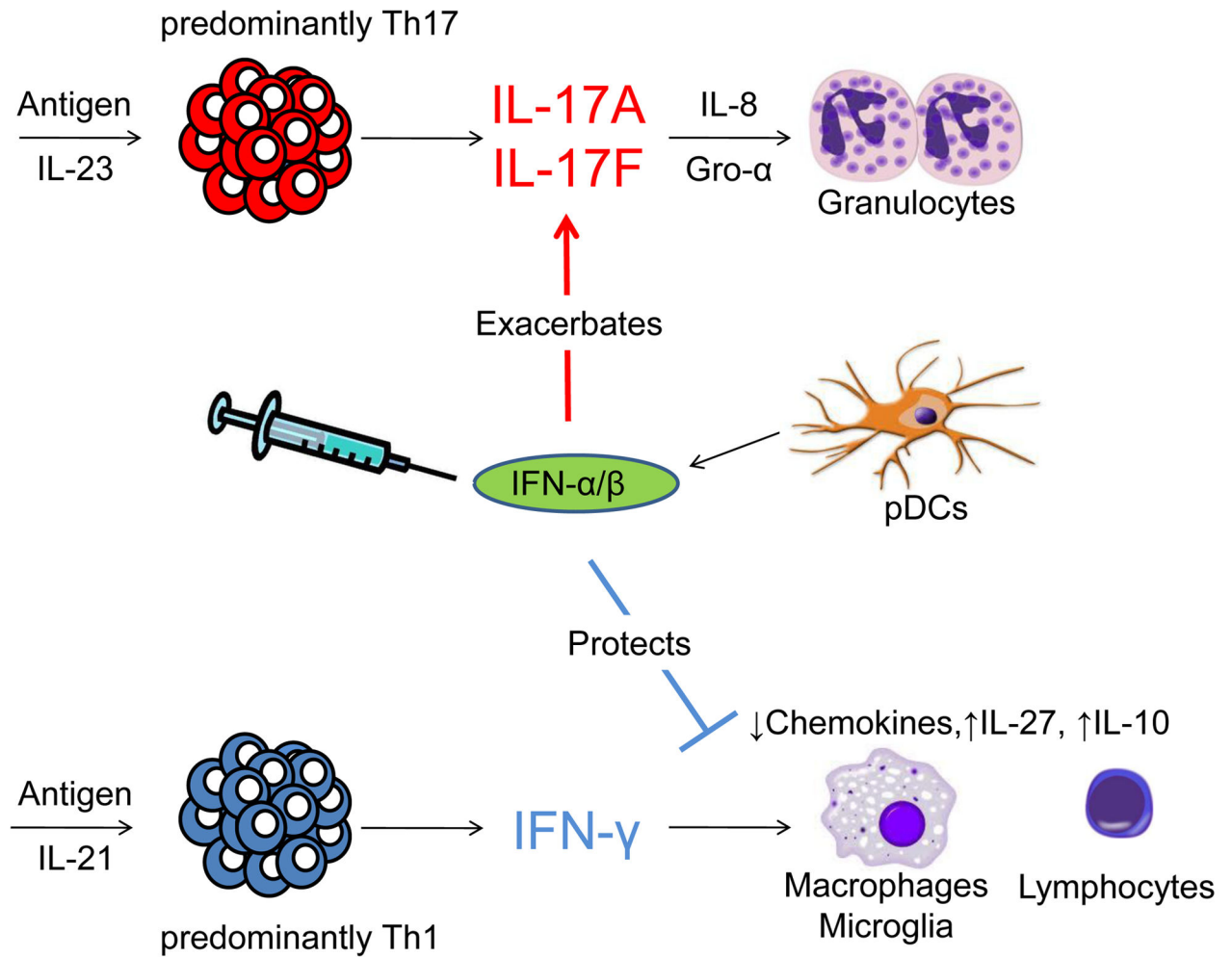
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**Figure.**

Autoimmune diseases with a predominately IL-23–Th17 response secrete high levels of IL-17A and IL-17F, which signals to the surrounding tissue to up-regulate granulocyte recruitment and activation factors, such as G-CSF, Gro- α and IL-8. Through a currently unknown mechanism, endogenous expression of IFN- β by plasmacytoid DCs or therapeutic administration of IFN- β , worsens Th17 disease. Conversely, predominantly Th1-mediated diseases have high levels of IFN- γ and have a lymphocytic and macrophage infiltrate. In Th1 disease, IFN- β , in concert with IFN- γ , drives anti-inflammatory responses such as upregulation of IL-27, IL-10 or inhibiting chemokine expression by macrophages.