# COMMENTS

# Hypothesis: Multiple Sclerosis is a Type I Interferon Deficiency Syndrome (44295)

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Multiple sclerosis (MS), a chronic demyelinating disease of the central nervous system (CNS), is in part an immune mediated disease (1). MS is clinically associated with periods of disability (relapse) alternating with periods of recovery (remission) but often leading to progressive neurological disability (2). White matter lesions in the CNS are associated with mononuclear infiltrates that consist primarily of T cells and macrophages and resemble the lesion produced by T-lymphocyte delayed type hypersensitivity (DTH) (2–3). Alternatively, T-cell infiltration may not be the "initial hit" but T cells may be recruited secondarily by the release of chemokines from activated macrophages (4). Activated immune cells in the CNS lead to inflammation and eventually demyelination. MS has been associated with abnormalities of immunoregulation (5).

We propose a unifying hypothesis of the etiopathogenesis of MS that mirrors the relapsing-remitting character of clinical MS and defines MS as a type I interferon (IFN) immunodeficiency syndrome. At the core of our unifying theory is the interaction between the two major components of the immune system, the older innate and the newer acquired immune systems. Foreign nucleic acids, cells, and bacteria cause type I IFN secretion by the innate immune system and act as the initial nonspecific antiviral, antibacterial, and antiproliferative defense system. Type I IFN secretion activates antigen-presenting cells, allowing the transition into antigen-specific humoral and cell-mediated immunity. However the products of the innate immune system, type I IFNs, can also function as immunomodulators to balance the effects of the acquired immune system. We hypothesize that under normal circumstances there is a dynamic interaction between the innate immune system that initially generates antiforeign and secondarily immunomodulating cytokines, including IFN-α/β (type I IFNs), and the acquired immune system that generates pro-inflammatory IFN-γ (type II IFN), resulting in a physiological downmodulation of the total immune response. In MS and possibly in other autoimmune diseases, there may be a deficiency of immunomodulation of the innate immune system.

All IFNs display antitumor, antiviral, and antiproliferative effects. However, their immunomodulatory properties differ significantly. Type 1 IFNs are composed of two highly homologous protein families, the IFN-α (leukocyte IFN) and IFN-β (fibroblast IFN), whose members have similar biological properties (6, 7). IFN-α and IFN-β interact with the same cell receptor (8–9). Type I IFNs can decrease the immune function of T cells in humans when given parenterally and can increase class I MHC expression and induce suppressive effects *in vitro*. In contrast, pro-inflammatory IFN-γ regulates the DTH response and inflammation, and enhances cell-mediated immune mechanisms by inhibiting immunomodulatory cell function or by promoting class II MHC expression on various cell types (10). The balance and mutual regulation of the IFN-α/β and IFN-γ actions on the immune system are critical and may provide a key to the underlying immune dysregulation of MS and possibly other autoimmune diseases.

We propose that every antigen is an IFNogen. Under normal circumstances, organisms do not produce IFN. However, exogenous antigen or altered self-antigen can induce an immune response that may lead to the production of IFN.

The secretion of IFN-α by cells of the monocyte-macrophage lineage (phase I–innate immunity) occurs after the introduction of antigen such as virus, tumor, or bacteria (11). The response is swift because there is no need for an accessory cell for IFN-α production. However, the antiviral and anticellular effects produced are short-lived (12). IFN-α plus antigen provide a signal for the synthesis of small amounts of IL-1 by the monocyte-macrophage cells. The combination of IFN-α, antigen, and IL-1 takes part in the presentation of antigen to T lymphocytes, allowing entry

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0037-9727/98/2184-0278$10.50/0

into a phase II response, the acquired immune system (13). In this phase, there is a selective activation of T lymphocytes through antigen-specific T cell receptors (TCR), and stimulation of IL-2 with an expansion of the T cell population. The antigen-sensitized T lymphocytes produce IFN-γ, beginning phase II of the IFN cycle and enhancing and broadening the immune response. IFN-γ production takes longer to reach a maximum, but its effects are stronger than those of IFN-α/β and last much longer (12). The concentration and kinetic complexities of IFN-γ production by T cells depend on the monocyte-macrophage accessory cell, both for induction and inhibition. IFN-γ induces a positive feedback on the monocyte-macrophage cells with the production of IL-1, and subsequently IL-2 and IFN-γ (13). The continual production of IFN-γ and the stimulation of acquired immune responses without an adequate counterregulatory immunomodulation may be responsible for the perpetuation of immunity resulting in autoimmune diseases.

Thus the positive actions of the IFNs on the immune system may be divided into two phases: *phase I* (innate immunity) associated with the production of low quantities of IFN-α during the initiation of the immune response and *phase II* (acquired immunity), associated with the production of IFN-γ, that reinforces immunity through an intense and broadened antigen-specific response that can recruit bystander immune cells for inflammatory purposes (13).

For every response, there is an equal and opposite physiological reaction. IFNs are unusual proteins. The response to different amounts of one and the same IFN may upregulate or downregulate the immune system. Low levels of IFN-α/β are important in the innate immune response, allowing entrance into acquired immunity. However, the ability of the organism to generate relatively high levels of counterregulatory anti-inflammatory IFN-α/β may prevent the continuation of inflammatory responses.

The dynamic imbalance of type I versus type II IFNs and the inability to engender sufficient quantities of counterregulatory anti-inflammatory IFN-α/β may define the immune pathophysiology of MS. The production of and response to IFNs *in vivo* and *in vitro* have been assessed in patients with MS. In most patients the capacity of peripheral blood leucocytes (PBL) *in vitro* to produce IFN-α/β or IFN-γ after induction by virus or mitogens was reduced. The reduction was consistent with defective production of IFN in MS. Despite low production levels, over prolonged periods of time serum IFN-α was detectable in the vast majority of patients without evidence of detectable IFN-α activity in control healthy subjects. However, the activity of 2′-5′-oligoadenylate synthetase (OAS), an IFN-induced enzyme, was elevated in PBL from only two-thirds of patients seropositive for IFN-α. The lack of IFN-induced enzymatic activity indicates that in some MS patients there was a failure of PBL to respond to endogenous IFN-α. The failure to respond may be related to defective transduction of IFN-induced signaling across cell membranes *via* type I IFN receptor molecules. The imbalance in MS includes both decreased IFN production, intermittent interferonemia, and a defective IFN-induced signaling response (14).

There also appears to be a correlation between IFN production and a distinct class II haplotype. IFN production by PBL after induction with viral antigens was studied in patients with stable MS and healthy controls. MS patients produced significantly less IFN-α after induction with mumps and measles virus antigens. The decreased ability to produce IFN-α was associated with the histocompatibility antigen Dw2, a class I haplotype found three times more frequently in patients with MS. The observed impaired IFN-α production in MS is at least partially linked to a high prevalence of Dw2 antigen (15).

Other investigators determined serial IFN serum levels and *in vitro* activated IFN production in eight patients with relapsing remitting MS (RRMS). There was a biphasic increase in the individual IFN-α and IFN-γ production over 12 months that correlated with clinical disease activity. ConA-stimulated IFN-γ synthesis by MS lymphocytes *in vitro* showed a significant augmentation prior to the onset of a new relapse, and Newcastle disease virus-induced IFN-α production showed a temporal delayed increase that was related to clinical remission. IFN-γ production decreased and returned to baseline levels at least 4 weeks after the clinical onset of the relapses. Compared to the IFN-γ secretion, viral-induced IFN-α production showed a delayed increase. The production of IFN-α rose and peaked approximately 2–4 weeks after the clinical manifestation of the relapse. The observed fluctuations in the individual production of both IFN subtypes were not reflected in the sera of the patients. The observed association between increased IFN-α production and clinical remission emphasizes a possible role for type 1 IFNs in the resolution of the MS relapse and potentially in the resolution of CNS inflammation (16).

Other serial studies have disclosed that before exacerbations, an increase of IFN-γ production preceded clinical symptoms by a maximum of 2 weeks. In benign cases, the increase disappeared rapidly, even before the appearance of symptoms, and neurological sequelae occurred whenever the increase persisted for weeks. IFN-γ, in concert with other pro-inflammatory cytokines, triggers exacerbations at a very early stage and may play a role in maintaining disease in chronic progressive forms (17).

A fourth set of investigations examined whether IFN production correlated with the stage of clinically stable disease in MS. MS patients were divided into three groups of mild, moderate, and severe patients according to the scores of disability status scale (DSS). Viral-induced PBL IFN-α production obtained from the patients was depressed in parallel with the severity of DSS of the patients. These results suggest that an increasing defect of IFN-α may underlie the clinical progression of the disease (18).

Rheumatoid arthritis (RA), a presumed autoimmune disease with similarities to MS, also has imbalances of the type I and type II IFN system. Markers associated with the production of and response to IFNs were studied in patients

with either inactive RA or active RA, and in healthy subjects. IFN activity was not demonstrable in the serum of any patient with RA. The viral-induced production of PBL IFN-α/β was low in active RA but high in inactive RA, fluctuations consistent with increased or decreased clinical activity respectively (19). However, others have demonstrated that both active and inactive RA exhibited a significantly reduced viral-induced IFN-α production when compared with normal blood donors, suggesting a persistent IFN-α production defect irrespective of clinical status (20). The activity of OAS in PBL was increased in inactive RA compared with healthy subjects, suggesting recent exposure to IFN-α during clinical remission. The production of IFN-γ by PBL in RA was lower than in healthy subjects, more so in active than in inactive RA (20). Thus RA in remission is marked by evidence of increased capacity of PBL *in vitro* stimulated IFN production than during preceding subclinical and clinical relapses. These findings indicate an IFN-α immunodeficiency of the circulating lymphocytes of RA patients and underscore the relevance of IFN-α production to clinical activity in RA (19–20). Therefore RA, in common with MS, demonstrates decreased IFN-α production that correlates to disease activity. However, RA differs from MS in that IFN-γ production is persistently defective and does not correlate with clinical activity.

Other autoimmune diseases share a defective production of IFN-α. Significantly lower levels of viral-induced IFN-α were found in stimulated cultures of IDDM patients compared to control children (21). IFN-α in Sjogren's syndrome (SS) was significantly decreased compared with age- and sex-matched healthy subjects, indicating the inability of SS patients to generate physiological levels of IFN-α (22). PBL of psoriatic patients showing moderate to severe disease activity and from healthy controls were stimulated with the mitogens PHA, ConA, and PWM; with PPD and tetanus antigen as IFN-γ inducers; with C. parvum, polyinosinic-polycytidylic acid {poly(I:C)}; and with Herpes simplex virus as inducers of IFN-α. Psoriatic patients showed a significantly decreased IFN-α and IFN-γ production to all the stimuli tested. The decreased IFN profile by leukocytes from psoriatic patients seems to parallel findings in RA (23).

Are there examples of the potential role of counterregulatory type I IFNs *in vivo* in MS? A classic *in vivo* example of the counterregulatory effects of type I and type II IFNs is suggested by analysis of IFNs in active lesions in the MS brain. CNS tissue from MS patients was examined for IFN-α, IFN-β, and IFN-γ. IFNs were detectable in active but not in inactive chronic MS lesions. In active chronic MS, labeling of cells for IFN-α, IFN-β, and IFN-γ was most pronounced at the lesion edge and displayed distinct distribution patterns. Overall, IFN-γ was more common than IFN-α and IFN-β, and was predominantly found on astrocytes. IFN-α was detectable mainly on macrophages. Distribution of IFN-β partially overlapped with that of IFN-γ and IFN-α, in that it was present on some astrocytes and on some macrophages. IFNs were rare in normal white matter remote from lesions and in the gliotic lesion center. Ia antigen and HLA class I on astrocytes were distributed similarly to IFN-γ and IFN-β, respectively. These findings indicate that IFN-γ may play a role in active lesion growth in multiple sclerosis, but could also indicate a triggering of production of IFN-α and IFN-β by macrophages with local immunomodulation (24).

Similar findings were reported in psoriatic lesions. The expression of mRNAs encoding IFN and IFN-inducible proteins was studied in psoriatic lesions and in noninvolved skin. Signals for the expression of IFN-γ mRNA were found exclusively in cells of psoriatic lesions, most likely representing a subpopulation of infiltrating leukocytes. Weak signals of IFN-α mRNA were detected throughout the hyperkeratotic epidermis. The expression of two IFN-α-inducible gene products, MxA, a type I IFN-specific signal and OAS, a type I and type II-induced signal, were studied as markers for the local activation of the IFN-α system. MxA and mRNA and protein were observed in psoriatic keratinocytes, but not in normal appearing keratinocytes adjacent to the lesions. Similarly, OAS expression was markedly elevated in psoriatic keratinocytes. The IFN-α system is selectively activated in psoriatic lesions and is another potential example of counterregulation of type I upon type II IFNs at sites of inflammation and in other autoimmune diseases [25].

Is there *in vitro* evidence that pro-inflammatory IFN-γ can induce counterregulating IFN-α/β? IFN-γ enhances the production of *in vitro* Sendai virus-induced IFN-α in human monocytes/macrophages that are efficient producers of IFN-α (26). *In vitro* experiments demonstrate that not only is the major antiviral mechanism of IFN-γ acting through IFN-α in mice but that IFN-γ can negatively regulate its own effects *via* IFN-α (27). The above demonstrates that *in vitro* systems, IFN-γ can downregulate its own activity by inducing a counterregulatory IFN-α/β response.

Is there direct *in vivo* evidence in animal models that type I IFNs, in particular IFN-α, counteract pro-inflammatory IFN-γ? During infections in mice with murine cytomegalovirus (MCMV), there is increased IFN-α/β expression. Neutralization of IFN-α/β in MCMV infected mice increases early IFN-γ protein production. Furthermore, during infections of mice with lymphocytic choriomeningitis virus (LCMV), blocking IFN-α/β activity revealed a previously undetected early IFN-γ protein expression. The effects of IFN-α/β neutralization on production of IFN-γ during the viral infections were detected in both serum samples and medium conditioned with splenic leukocytes isolated from infected animals. These results demonstrate a new mechanism for inhibition of IFN-γ immune responses *in vivo* (28). IFN-γ and IFN-α/β possess opposite activities *in vivo*, IFN-α/β modulating the immunity of IFN-γ.

If type I IFNs are immunomodulatory and capable of regulating the antigen-specific acquired immunity generated by IFN-γ, how do type I IFNs perform this function effectively? T-cell proliferation *in vivo* is presumed to reflect a TCR-mediated polyclonal response directed to various environmental antigens. However the primary immune re-

sponse to microorganisms is often intense and causes a marked enlargement of the secondary lymphoid tissue, even though the precursor frequency of the antigen-specific T cells is quite low. The activation of specific T cells by heterologous viruses suggests that a substantial component of the T-cell proliferative response is not antigen-specific. The massive proliferation of T cells seen in viral infections is suggestive of a bystander reaction driven by cytokines instead of the TCR. In mice, T-cell proliferation in viral infections preferentially affects the CD8+ T cells and is mimicked by injection of polyinosinic-polycytidylic acid {poly(I:C)}, an inducer of type I IFN, and also by purified IFN I; such proliferation was not associated with upregulation of CD69 or CD25 expression but upregulation of Ly-6C, a marker of IFN activation. This implies that TCR signaling is not involved. Type I IFN also potentiated the clonal expansion and survival of CD8+ cells responding to specific antigen. Therefore stimulation of CD8+ cells does not seem to require TCR ligation and appears to reflect release of type I IFN (29, 30).

The capacity of altered self-antigens or infectious agents (IFNogens) and subsequently of IFN-γ to induce non-antigen-specific stimulation of CD8+ T cells may play a role in boosting anti-inflammatory innate immunomodulation. Type I IFNs can activate non-antigen-specific CD8+ T cells that inhibit EAE, an animal model of MS. We have recently demonstrated that adoptively transferred CD8+ T cells from mIFN-α *fed* naive nonimmunized SWR donors inhibit clinical attacks in actively immunized SWR recipients (31). CD8+ T cells can be induced by type I IFN *in vivo* to regulate inflammatory disease.

Another 'deficiency' of MS lymphocytes appears to be a nonresponsiveness or resistance to the actions of IFN, in particular type I IFN. Under specific circumstances, circulating IFN may not transduce a signal *via* the type I IFN receptor (IFNABR), an IFN transducing complex consisting of a large transmembrane macromolecule assembly: ifnar1 (IFN α/β receptor gene 1–α subunit), ifnar2 (IFN α/β receptor gene 2–β subunit), cytoplasmic tyrosine kinases Tyk2 (*t*yrosine *k*inase) and Jak1 (*J*anus *a*ssociated *k*inase), at least one tyrosine phosphatase, and multiple Stat1 (p84), Stat2 (p91), and Stat3 (p113) proteins (*s*ignal *t*ransducer and *a*ctivators of *t*ranscription). As mentioned above, OAS activity is not elevated in PBL from one-third of patients seropositive for IFN-α, indicating a PBL nonresponsiveness or resistance to endogenous IFN-α (14). Abnormalities anywhere from the transmembrane receptor genes ifnar1 and ifnar2, interactions between ifnar1 and ifnar2, cytoplasmic proteins associated with the transmembrane receptor proteins, or the ultimate complex that interacts with IFN-sensitive response elements (ISRE) in the nucleus may be responsible for IFN resistance. Although the precise pathophysiological cascade of events that lead to type I IFN signal transduction blockade remain unclear, indications of possible underlying defects of signal transduction can be postulated from selective work using transformed cell lines and molecular constructs.

The comparison of the cDNA sequences from three melanoma cell lines by PCR, displaying a greater than 100-fold range in sensitivity to the antiproliferative effects of IFN-β, concluded that the cellular differences in responsiveness to IFN did not arise from the expression of variants of the cloned IFNABR subunits (32). Others have described normal and the variant α and β subunits in cell lines. In these cell lines, the normal β subunit has a molecular mass of approximately 100 kDa and the variant β subunit has a molecular mass of approximately 55 kDa. An IFN-α-resistant U-937 cell line expresses variant receptors and fails to downregulate and phosphorylate the α subunit on tyrosine residues. However, other cell lines YK-M2 and ML-2, expressing the variant form of the receptor, fail to downregulate and phosphorylate the α subunit on tyrosine residues, but are sensitive to the antiproliferative and antiviral effects of IFN-α2, indicating that expression of variant receptors is not necessarily a source of IFN-α resistance (33). These data suggest that differential responsiveness is most likely not related to alteration of transmembrane sequences, their interaction, or receptor subunit variants.

Intracytoplasmic proteins may regulate IFN-induced signal transduction. Low levels of the transcription factor ISGF3-α, the *i*nterferon-*s*timulated *g*ene *f*actor α consisting of three polypeptides (p113, p91, and p84), responsible for IFN-sensitive gene transcription at the ISRE, are detected in the cytoplasm and nucleus of untreated Daudi cells and increase markedly following IFN treatment. In contrast an IFN-resistant clone of Daudi cells, DIF8, showed no ISGF3-α, and only low levels after IFN-α treatment. A second clone of IFN-resistant Daudi cells, DIF3, also exhibited defective ISGF3-α production, which was restored to normal in the subclone DIF3REV5 that had reverted to high IFN sensitivity. Thus, the antiproliferative effect of IFN on Daudi cells and derived clones is closely related to the level of ISGF3-α present in the nucleus of these cells (34). Intracytoplasmic type I IFN receptor associated $Tyk2^-$ and $Jak1^-$ mutant cells are relatively resistant to IFN-α and IFN-α/β respectively. Truncation of KL (kinase function) domain within tyrosine kinases decreases binding affinity of the functional receptor unit for IFNs, demonstrating that different receptor activation or affinities may potentially be due in part to combinations of mutant or allelic forms of assembled proteins in the type I receptor complex (8).

Even in cells with the full complement of transmembrane and intracytoplasmic proteins, there are differences in antiviral and growth inhibitory effects. Low affinity interaction between IFN-α/β and cell surface receptors (IFNABR-α and IFNABR-β) results in ISGF3 activation and an antiviral response, yet no IFN-inducible growth inhibition in human cells expressing normal IFNABR, Jak 1, Tyk 2, and adequate levels of the cytoplasmic transcription factors Stat1, Stat2, and Stat3. Additional component(s) are required to confer high-affinity binding and IFN-inducible growth in-

hibition to cells that express the α and β subunits of the IFNABR (35). This may indicate another level of intracytoplasmic proteins necessary for transduction of specific type I IFN signals.

Our hypothesis is that MS and possibly other autoimmune diseases are type I IFN immunodeficiency diseases. The data above suggest that monocyte-macrophage lineage cells can produce adequate small amounts of IFN-α necessary for innate immunity, allowing progression into acquired immunity, but do not have the capability to produce sufficiently large amounts of IFN-α/β to regulate acquired immunity. As outlined above, our hypothesis is simple and more importantly testable. If interventions successfully immunomodulate the disease process underlying MS, and our hypothesis is correct, then there should be fluctuating IFN-α and IFN-γ production that correlates with disease activity.

Serial brain magnetic resonance imaging (MRI) detects 5–10 times more disease activity in RRMS and secondary progressive MS patients than is clinically apparent, and consequently MRI is a sensitive tool with which to monitor disease activity (36–41). Asymptomatic new lesions are frequent in stable and RRMS (42). Active lesions enhance with administration of Gd-DTPA (gadopentetate dimeglumine {Gd}) (43). Areas of enhancement are probably associated with active inflammation (44–47). This provides a powerful tool for investigating the potential of promising therapeutic agents in man. Monitoring MS patients with MR Gd scanning while measuring PBL induced IFN-α and IFN-γ production allows a direct test of our hypothesis of dynamic interaction of IFN-α/β (type I IFNs) versus pro-inflammatory IFN-γ (type II IFN). This test can be performed within short periods with limited numbers of patients because of the frequency of MR enhancements.

The reported abnormalities of production or response to type 1 IFN in autoimmune diseases have prompted clinical studies using type 1 IFNs as therapeutic agents in MS. Parenterally administered hrIFN-β in RRMS can decrease relapses by 18%–30% (48–49) and decrease brain inflammation as assessed by serial quantitative MRI (49–50). Similar clinical effects could be obtained at equivalent doses of IFN-α given by intramuscular injection with decreased spontaneous IFN-γ production (51). The beneficial effect of parenteral type I IFN treatment may be due in part to redressing the relative deficiency of type I IFNs in MS. The reduction of relapses and MR enhancements by IFN-β is impressive. However the resistance to treatment in a subset of patients could be related to late intervention in an ongoing chronic disease or intrinsic type I IFN receptor nonresponsiveness. It is unknown if another approved therapy for MS, Copaxone, can also increase type I IFN level responses.

There may be alternative theories about the etiopathogenesis of MS involving modulation of the acquired immune *via* antigen-specific or haplotypic-specific interventions. As yet, the clinical trials utilizing this understanding of antigen-specific acquired immunity have not born fruit. The dynamic theory of type I IFN versus type II IFN helps explain the benefits of parenteral type I IFN therapy in redressing the imbalances of innate and acquired immunity. The innate versus the acquired immunity theory conforms to recent theories about CNS demyelination as primarily caused by microglial activation, stimulated by T cells and IFN-γ (4). Our hypothesis allows the exploration of potential efficacies of successful interventions. We have recently demonstrated that ingested hrIFN-α is a biological response modifier (BRM) of ongoing immune responses in patients with RRMS (52). We are currently testing our hypothesis in a phase II randomized, placebo-controlled, double-blind trial of ingested IFN-α in patients with early RRMS and monitoring alterations in brain MR enhancements and PBL IFN-α and IFN-γ production. If successful, our trial will substantiate an underlying pathophysiology of MS and perhaps autoimmunity in general and provide an impetus to examine molecular mechanisms of IFN-α production and residual type I IFN resistance at the receptor level.


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