Interferon-beta therapy increases concentration of soluble Interferon alpha/beta receptor in Multiple Sclerosis patient serum.

Abstract:
Interferon (IFN) have been identified as important immuno-modulators in autoimmune diseases. Interferon-beta for one, is the most accepted bio-therapeutic for the treatment of multiple sclerosis (MS) and has shown to decrease relapses, brain lesions, and slow neuro-degeneration in patients [1].

However, the clinical response to IFN-beta therapy is highly variable [2]. Hence, understanding the mechanism of action of IFN-beta in MS treatment may prove to be highly valuable in improving the efficacy of this therapy.

IFN-beta activates various signaling cascades via its high affinity interaction with the multi-subunit type-I IFN cellular membrane receptor (IFNAR). The IFNAR2 subunit exists in two transmembrane isoforms (IFNAR2a and IFNAR2c) and a soluble form (IFNAR2a) arising from the alternative splicing of the mRNA and post-translational proteolytic cleavage of the transmembrane isoforms [3]. IFNAR2a may act as an antagonist or serve to stabilize IFN-beta by the formation of a complex in vivo [4].

We measured the concentrations of IFNAR2a and IFN-beta in the sera/plasma of 35 normal human donors, 25 MS patients not on IFN therapy, and 29 MS patients on IFN therapy (Avonex, Rebif, or Betaseron). Type-I IFN activity in the MS samples was also measured using a cell based assay. A panel of other cytokines were also examined using a 16-plex and a 9-plex ELISA assay.

Conclusions
Interferons exhibit a wide range of biological activities including antiviral, anti-proliferative, and other immunomodulatory effects. In the treatment of multiple sclerosis, IFN-beta is thought to play an anti-inflammatory role by regulating the movements of different immune cells across the blood brain barrier as well as promoting the production of other anti-inflammatory factors [5]. However, the exact mechanism of action is more involved and is still under investigation. In this study, we observed that the concentrations of the soluble version of the type-I interferon receptor were elevated in the serum samples from MS patients that received interferon therapy. This could be a response to neutralize excess interferon activity from prolonged interferon treatment because cellular receptors are known to undergo modification post-ligand binding to limit cell response. However, transcriptional regulation may also be one of the sources of the soluble receptor after IFN stimulation. An increase in the IFNAR2a mRNA in MS patients on long term IFN-beta therapy has been reported [7]. We were able to measure IFN-beta (mass) in 86% of the samples from IFN treated MS patients and noted that IFN-beta concentration in the samples did not correlate well to the IFNAR2a levels. This suggests a more indirect induction of soluble receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different. Nonetheless, IFNAR2a levels may be indicative to the extent of receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different. Nonetheless, IFNAR2a levels may be indicative to the extent of receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different. Nonetheless, IFNAR2a levels may be indicative to the extent of receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different. Nonetheless, IFNAR2a levels may be indicative to the extent of receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different. Nonetheless, IFNAR2a levels may be indicative to the extent of receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different. Nonetheless, IFNAR2a levels may be indicative to the extent of receptor expression from IFN treatment or that the half-lives of the two analytes are vastly different.

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