Serum soluble IFNAR2 levels in autoimmune diseases suggest that chronic IFN signaling leads to elevated levels of sIFNAR2

Taher Fatakdawala[1], Michael Skawinski[1], Tara Stauffer[1], Jonathan Ferreira[2], Thomas B. Lavoie[1]

1. Product R&D and Assay Services, PBL InterferonSource, Piscataway, NJ, United States.

2. Quality Control, PBL InterferonSource, Piscataway, NJ, United States.

Abstract:

The Type I Interferon (IFN) receptor consists of a heterodimer of chain 1 (IFNAR1) which is required for signaling and chain 2 (IFNAR2) which binds tightly to IFN. Soluble forms of the IFNAR2 (sIFNAR2) can be produced either by proteolytic cleavage or production of an alternatively spliced transcript. Soluble IFNAR2 can be found in serum and urine however its role and regulation are poorly understood. Studies have suggested that sIFNAR2 is elevated in MS patients, advanced cancer patients and hepatitis C infected patients. Using a newly developed ELISA for sIFNAR2 we have examined commercially sourced serum/plasma samples from autoimmune patients in comparison with normal donors. In comparison to 100 normal donors, MS patients on IFN therapy (n=29) had significantly (p=0.0004) increased levels of sIFNAR2 while those on other therapies (n=25) were not different from the normal population but were significantly different than those MS patients on IFN therapy (p=<0.0001). sIFNAR2 levels showed no correlation with treatments such as vitamin-D, copaxone or natalizumab. Systemic Lupus patients (n=67) had elevated sIFNAR2 (p=0.013) while rheumatoid arthritis patients (n=16) were not significantly different from normal nor were Sjogren's patients (n=11) and scleroderma patients (n=10) Although evidence of Type I IFN activation has been observed in RA, Sjogren's and Scleroderma patients, the intensity is thought to be less than that for MS patients on IFN-therapy^ and Systemic Lupus. These data suggest a model where long term IFN signaling above a certain threshold leads to elevated sIFNAR2.

Introduction:

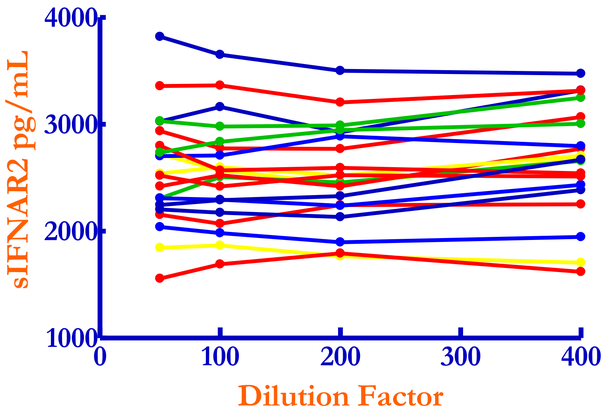
Interferons (IFN) have been identified as important immuno-modulators in autoimmune diseases. IFN-beta, for one, is a front line treatment for multiple sclerosis (MS) and has shown to decrease relapses, brain lesions, and slow neuro-degeneration in patients [1]. However, the clinical response to IFN-beta 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. Type I interferon has also been implicated in the etiology of other autoimmune diseases such as Systemic Lupus Erythematosis [3].

Type I 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 (IFNAR2b and IFNAR2c) which can be proteolytically cleaved to produce soluble forms and a soluble form (IFNAR2a) arising from the alternative splicing of the mRNA [4]. IFNAR2a may act as an antagonist or serve to stabilize Type I IFN by the formation of a complex *in vivo* [5]. Increased transcript levels of IFNAR2a have been noted for MS patients on long term therapy [6].

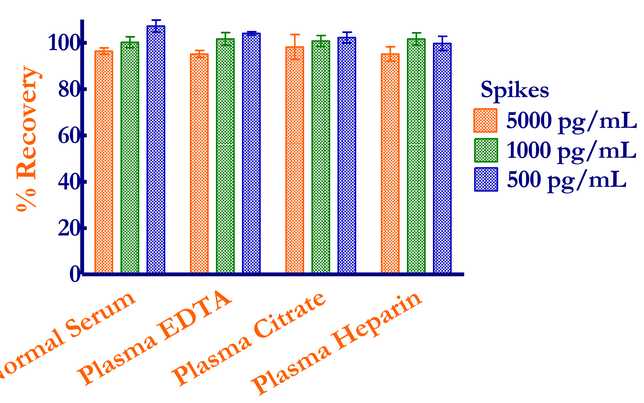
We measured the concentrations of sIFNAR2 and IFN-beta in the sera/plasma of 100 normal human donors, 25 MS patients not on IFN therapy, and 29 MS patients on IFN therapy (Avonex, Rebif, or Betaseron). Type-I IFN activity in the MS samples was also measured using a cell based assay. A panel of other cytokines was also examined using a 16-plex and a 9-plex ELISA assay.

We surveyed other autoimmune diseases by examining samples from patients with SLE (n=67), RA (n=17), Sjogren's syndrome (n=11) and scleroderman (n=10). Only Lupus patients displayed elevated sIFNAR2 levels.

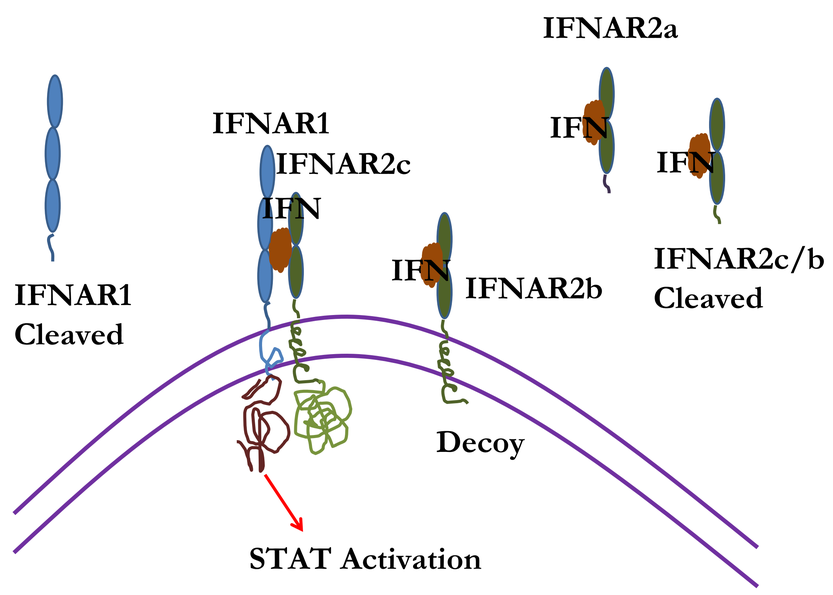
sIFNAR2 ELISA Linearity of Dilution for 20 Normal donors



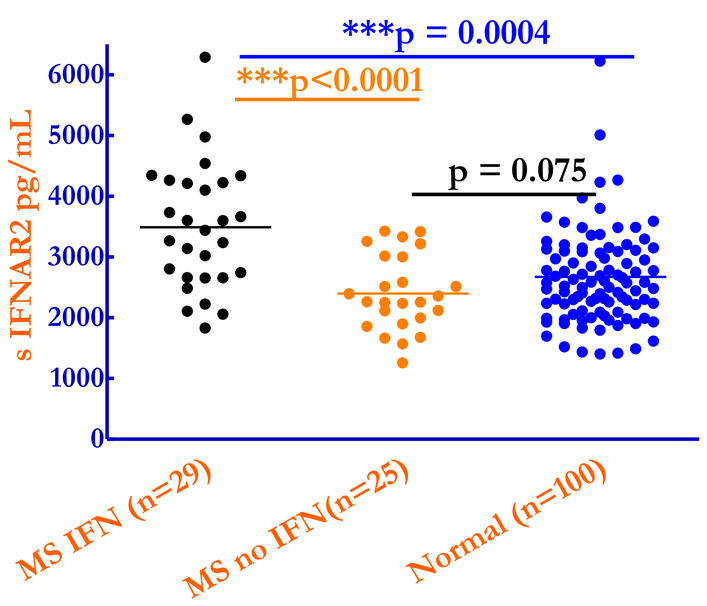
sIFNAR2 Spike Recovery in Human matrices



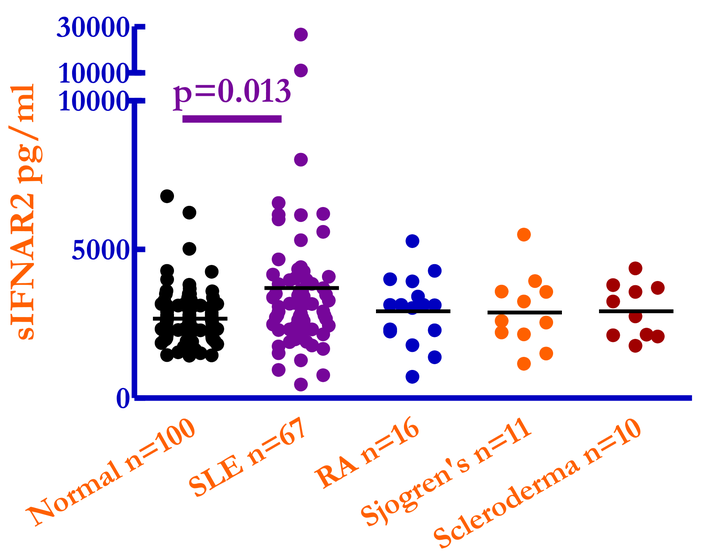
Type I Interferon Receptor Proteins



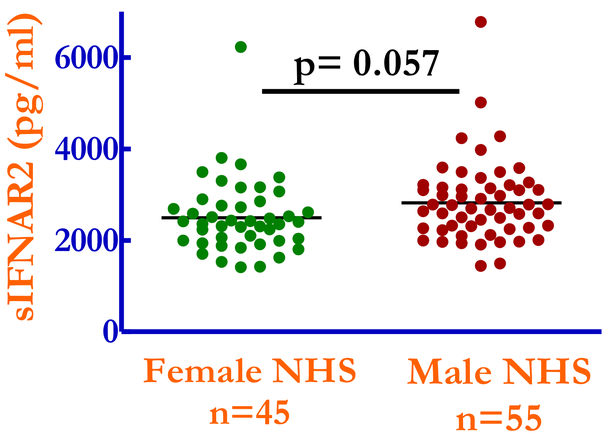
sIFNAR2 is elevated in Multiple Sclerosis with IFN treatment



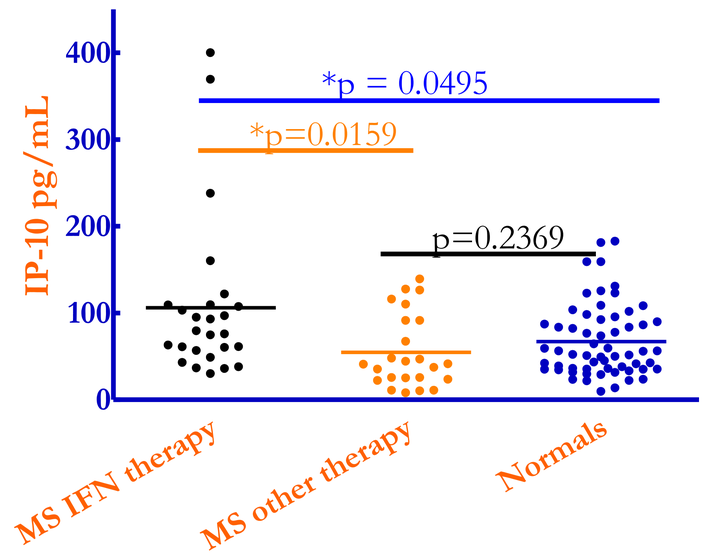
sIFNAR2 Levels in Autoimmunity



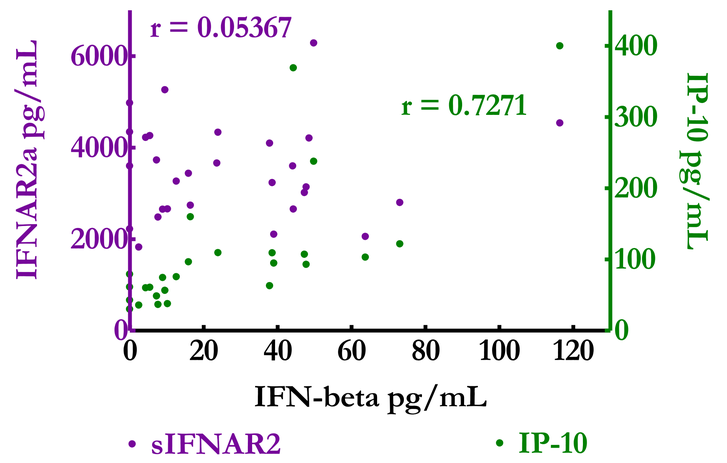
sIFNAR2 levels in Normal Donors



IP-10 is elevated in Multiple Sclerosis with IFN treatment



IP-10 & sIFNAR2 vs IFN-beta in Multiple Sclerosis



Conclusions:

sIFNAR2 is elevated in MS with IFN-Beta treatment.

sIFNAR2 is elevated in Lupus but not in these RA, Sjogren's or Scleroderma datasets.

sIFNAR2 trends toward elevation in Males.

IP-10 levels in MS are correlated with IFN-Beta levels, but sIFNAR2 levels are not. sIFNAR2 is not an acute marker?

No correlations are observed with IL-1α, IL-4, IL-5, IL-6, IL-7, Il-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-23, TNFα

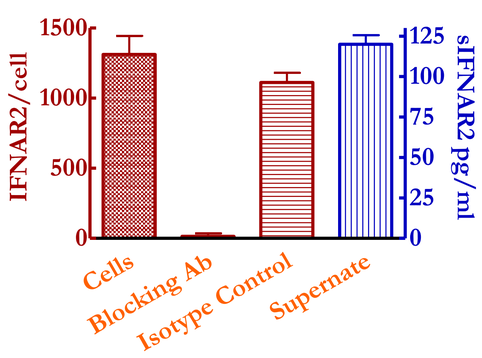
Future direction:

Expand sample sets,

Other disease states.

Are cell surface levels of IFNAR2 altered?

IFNAR2 on cells and in Supernates



References

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