ProNGF BINDING TO p75NTR ACTIVATES PRO-INFLAMMATORY PATHWAYS

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We recently demonstrated in patients with Juvenile Idiopathic Arthritis (JIA) that a reduced expression of TrkA, the NGF specific receptor, results in decreased anti-inflammatory responses.

In this study, we focused on p75NTR and its specific ligand proNGF, the immature form of NGF, to assess their involvement in inflammatory responses.

Mononuclear cells from peripheral blood and from synovial fluids (SFMC) of JIA patients showed a significant increase in p75NTR levels when compared to healthy donors. We found that of p75NTR expression levels were correlated with disease severity and activity as documented by the direct correlation with JIA subtypes and with the number of active joints and C-Reactive Protein levels.

We also found that proNGF, and not the mature NGF, was the prevalent NGF form released in synovial fluids of JIA patients. In *ex vivo* experiments, the addition of proNGF in activated SFMC enhanced the expression and the release of pro-inflammatory cytokines. This effect was abolished when p75NTR activity was inhibited using either a neutralizing antibody or LM11A-31, a non-peptide ligand that blocks the binding site of p75NTR for proNGF.

Altogether, our results suggest that an active proNGF-p75NTR axis promotes pro-inflammatory mechanisms, contributing to amplifying inflammatory responses in chronic arthritis. The use of p75NTR inhibitors may represent a new therapeutic approach to treatment of JIA.