





### proNGF BINDING TO p75NTR ACTIVATES PRO-INFLAMMATORY PATHWAYS

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Al-Shawi et al., 2007

## **NGF receptor system**



Bracci-Laudiero and De Stefano, Curr Top Behav Neurosci 2015

## **NGF** action on **PNS**

#### Embryo peripheral neurons precursor proliferation survival differentiation





Levi-Montalcini Science 1964

#### **Adult peripheral neurons**

neurotransmitter levels synaptic plasticity target innervation

#### **NGF effects on immune system**



basal expression of TrkA and NGF in MNC is enhanced after activation

increased NGF synthesis at the inflammatory site

#### TrkA expression in differentiated immune cells



mediator release

survival

Mast cells

oxidative burst activity cytokine release

Bracci-Laudiero L, PhD Thesis 1999



- 🔆 Activates innate immunity cells
- Influences APC antigen presentation

#### Induces lymphocytes proliferation

## 🔆 Contributes in mantaining immunological memory

In vitro data suggest that NGF keeps the immune cells in an "alert mode" so that they are ready to react against dangerous signals and activate an inflammatory response more efficiently

### **NGF and inflammatory diseases**

High levels of NGF are found in blood and in inflamed tissues of patients with chronic inflammatory diseases.

This increase is correlated with the extend of the inflammatory response

Multiple Sclerosis: Bracci-Laudiero et al. Neurosci Lett. 1992 Rheumatoid Arthritis: Aloe et al. Arthritis Rheum. 1992 Systemic Lupus Erythematosus: Bracci-Laudiero et al. NeuroReport 1993 Vernal Keratocojunctivitis: Lambiase et al. IOVS 1995 Asthma and allergic inflammation: Bonini et al. PNAS 1996 <u>Crohn's disease and ulcerative colitis:</u> Di Mola et al. Gut 2000 Atopic Dermatitis: Toyoda et al. Br J Dermatol. 2002 Psoriasis: Raychaudhuri et al. Prog Brain Res. 2004



#### NGF protects against autoimmune encephalomyelitis



## In vivo NGF effect

• <u>Marmoset and murine models of autoimmune</u> <u>encephalomyelitis (EAE)</u>



Villoslada et al. 2000 Arredondo et al. 2001

• Models of rats with colitis



# A dual role for NGF?



Activation of immune responses

# Working hypothesis

NGF is involved in vivo in the balance between pro- and anti-inflammatory responses??

### **NGF receptor expression in JIA patients**



p75NTR is the main NGF receptor expressed in JIA MNC TrkA is the prevalent NGF receptor in PBMC of healthy donors

#### p75NTR and disease severity



High levels of p75NTR mRNA expression in the SFMC of JIA patients are associated with the most severe subtype and with disease activity

#### proNGF binds with high affinity to p75NTR/sortilin complex that signals indipendently from TrkA



Since p75NTR and sortilin are expressed in JIA MNC, is there any proNGF in the inflammatory site?

## In synovial fluids of JIA and RA patients, the predominant NGF form is proNGF and not mature NGF



# What is the effect of proNGF binding to p75NTR/sortilin complex?

- Apoptosis as in neurons?





Annexin V FITC-A

# proNGF addition to LPS-activated JIA SFMC does not change cell viability

#### Nerve Growth Factor Downregulates Inflammatory Response in Human Monocytes through TrkA

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#### In JIA SFMC proNGF induces release of IL-6



#### Which cells produce proNGF in the inflamed synovia?



Fibroblast-like synoviocytes express and release NGF

## Summary

- Increased expression of p75NTR and concomitant decrease of TrkA lead to a highly abnormal ratio between p75NTR and TrkA.
- P75NTR expression levels are related with JIA disease severity and activity
- ProNGF is the highly prevalent NGF form in the inflamed synovium and it is actively synthetized by synoviocytes more than by mononuclear cells.
- ProNGF activates the pathways involved in regulating inflammatory cytokine expression
- The pro-inflammatory action of proNGF is mediated through its binding to p75NTR and not through TrkA.

## Conclusions

Relative level of expression of TrkA and p75NTR plays a key role in the inflammatory response and directs the immune cells towards a pro-inflammatory or an anti-inflammatory response.









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