The effects of NGF, proNGF forms and their receptor inhibition on immune response in chronic inflammatory diseases

Inflammation is a central feature of many chronic diseases. The specific characteristics of the inflammatory response in each disease differ but all involve activation of inflammatory cells and increased expression of cytokines and chemokines. Between the factors involved in inflammation, high levels of nerve growth factor (NGF) were detected in inflamed tissues of a variety of inflammatory diseases (1). It has been clearly demonstrated that NGF production is induced by inflammatory cytokines as IL-1β, IL-6, TNF-a in several cell types (1).

However, the effects of NGF and its immature proNGF forms (2,3) in regulating immune cell activity and mediator release during inflammatory responses are still largely unknown. The discovery that enhanced levels of the high affinity proNGF receptor, p75NTR, characterize immune cells (4) and inflamed synoviae of chronic arthritis patients (5), correlating with inflammatory disease parameters, has allowed us (CNR and Ospedale Pediatrico Bambino Gesu’ joint project) to define a new inflammatory mechanism induced by p75NTR activation and prospect p75NTR inhibition as a novel therapeutic tool (6).

Blocking of p75NTR receptor using neutralizing monoclonal antibodies or non peptidic antagonists (Prof Frank Longo, Stanford University CA, USA) results in a reduced activation of several signal transduction pathways associated with the initiation and progression of inflammation. These pathways control the production of several inflammatory cytokines that plays a major role in maintaining chronic inflammation. Blocking p75NTR triggers cascade events that influence simultaneously the production of different inflammatory cytokines with the final result of dampening the inflammatory response (4,5 and manuscript in preparation). This up-stream effect of p75NTR on the reduction of several inflammatory cytokines is very important considering the frequently redundant and interchangeable role of inflammatory cytokines.

Confirms of this hypothesis are emerging from the preliminary in vivo studies study using animal models of chronic arthritis. Inhibition of p75NTR reduces or even abolish the expression of IL-6, IL-1b and IL-8 in the inflamed joints, rapidly decreasing the swelling and limiting inflammatory infiltrate in the synovia with a reduction of articular cartilage loss. These cytokines play a pleiotropic role in the inflammatory response and are the target of several biological drugs currently used to treat chronic inflammatory diseases.

References:


3) International patent PCT/IB2019/051753 Neurotrophic peptide for use in the therapeutic treatment of neurodegenerative and/or inflammatory diseases. Inventors: Luigi Manni, Marzia Soligo, Luisa Bracci Laudiero. Registration 05.03.2019


6) European patent EP2667895 A1 “Use of at least one p75ntr receptor inhibitor, alone or in association with at least one trka receptor activator, or of at least one trka receptor activator, for the treatment of chronic inflammatory diseases.” Inventors: Luisa Bracci Laudiero and Fabrizio de Benedetti Registration 04.12.2013
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