TUMOR NECROSIS FACTOR ALPHA TRIGGERS OSTEOGENESIS THROUGH THE INVOVLVEMENT OF Gs-COUPLED RECEPTOR SIGNALS

Simona Daniele, Letizia Natali, Chiara Giacomelli, Maria Letizia Trincavelli, Claudia Martini.

Department of Pharmacy, University of Pisa, 56126 Pisa, Italy

Tumor Necrosis Factor alpha (TNF-α) plays a role in several chronic immune and inflammatory diseases, where inhibition of TNF has led to significant clinical improvement. Actually, this cytokine is involved in bone healing by affecting mesenchymal stem cell (MSC) behaviour in a dose- and time-dependent manner[1,2]. Indeed, in the early inflammatory phase after fracture, low doses of TNF-α are required to favour MSC migration, survival and differentiation, thus initiating bone repair. At high dose, in the chronic uncontrolled phase of inflammation, the same cytokine has destructive effects on bone and contribute to bone loss[1,2].

As other soluble factors released in cell microenvironment, the cytokine modulates expression and functioning of different G protein coupled receptors (GPCRs) and of their regulatory proteins (GPCR regulated kinases, GRKs)[3], thus dictating the final biological outcome of these receptor proteins in controlling bone anabolic processes.

Herein, we investigated the effects of TNF-α low doses on the expression and functional responsiveness of A_{2B} adenosine receptor (A_{2B} AR), a Gs-coupled puringergic receptor that controls mesenchymal stem cell (MSC) differentiation to osteoblasts[4,5].

In our hands, TNF-α exerted a pro-differentiating action on MSCs, pushing towards an osteoblast phenotype, and without any effects on cell proliferation. The cytokine increased the A_{2B} AR-mediated pro-osteogenic effects, through the A_{2B} AR desensitization impairment mediated by GRK2 inhibition. These data i) support the anabolic effect of sub-massimal concentration of TNF-α in bone reparative processes and ii) demonstrate that the cytokine regulates GPCR responses by interfering with desensitization machinery and potentiating in turn the anabolic responses evoked by Gs-GPCRs. Overall these results indicated that manipulating MSC local environment by lregulates membrane receptors favouring bone remodelling.

[1]FRONT IMMUNOL 2014; 5:1-9; [2]J. CELL. PHYSIOL. 2010; 223:168-177; [3]MOL PHARMACOL 2006; 69:1311–1319. [4]J BIOL CHEM. 2012; 287:15718-27. [5]BIOCHIM BIOPHYS ACTA. 2014;1843:2957-66.