

6. Innate immunity

A88 ANALYSIS OF TNFR2-MEDIATED FUNCTIONS ON OSTEOCLAST PRECURSOR CELLS

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Background and Objectives The role of tumour necrosis factor (TNF) in the induction and maintenance of human rheumatoid arthritis is well established. However, the role of its two receptors, especially of TNFR2, is not sufficiently understood. The authors have previously demonstrated that lack of TNFR2 on haematopoietic cells leads to increased osteoclastogenesis

in vitro and in vivo in a TNF-dependent model of arthritis. It is therefore important to define specific functions of TNFR2 with respect to target genes and signalling cascades initiated by TNFR2. The authors investigated the role of TNFR2 on osteoclast precursor cells (pOCs).

Methods and Results To study the function of TNFR2, the authors used pOCs lacking TNFR1, leaving TNFR2 as the only TNF receptor expressed on these cells. The authors show that stimulation of TNFR2 with soluble TNF is not sufficient to induce activation of MAP-kinases p38 or ERK1/2 or AKT/PKB. However, crosslinking TNF and thereby mimicking membrane bound TNF, which has been reported to be a ligand for TNFR2, led to activation of ERK1/2 as well as AKT/PKB. In addition, crosslinked TNF but not soluble TNF induces TNF mRNA in pOC lacking TNFR1. To obtain information on the global transcriptional response initiated by TNFR2, osteoclast precursors lacking TNFR1 were stimulated with soluble as well as crosslinked TNF and RNA was isolated and analysed by microarray. The authors obtained approximately 50 genes specifically induced via TNFR2, including chemokines, surface receptors and many others.

Conclusion The authors show here that TNFR2 is capable of transmitting a TNF-dependent signal independent of TNFR1. They also characterise a TNFR2-specific gene signature which sheds light on the biological functions of TNFR2.