Noggin as a regulator of bone remodelling

Recombinant bone morphogenetic protein 2 (BMP2) has been used in orthopaedic surgery to promote bone healing. The biological efficacy of exogenous BMP-2, however, is decreased by the endogenous expression of antagonists. Thus, administration of high doses of BMP2 is necessary to induce bone formation. It has been shown that inhibition of noggin with L51P (an engineered BMP2 variant) resulted in higher biological efficacy of BMP2 and lower amounts of BMP2 were required for bone formation. Moreover, noggin was found to exert direct effects on osteoclastogenesis *in vitro*. The mechanism underlying this effect is not clear and its elucidation is the aim of his study. For the generation of osteoclast progenitor cells (OPC), bone marrow cells from *C57BL/6J* mice were incubated overnight in α-MEM supplemented with CSF1. Osteoblasts (OB) were isolated from murine calvariae using collagenase type I. OPC and OB/OPC co-cultures were supplemented with combinations of noggin, BMP2 and L51P and the development of osteoclasts (OC) was assessed. Cell viability was determined by XTT assay and osteoclast differentiation was quantified by TRAP (tartrate resistant acid phosphatase) staining and measuring TRAP activity. The expression of RANK and calcitonin receptor (CTR) was measured by Q-PCR. In cultures of OPC, noggin significantly induced the development of OC which was not reversed by addition of BMP2 and L51P. In co-cultures of OB and OPC, noggin significantly decreased OC differentiation. This reduction was reversed by the addition of BMP2 and L51P, to the cultures. Furthermore, the inhibitory effect of noggin overcame the exogenous addition of RANKL in OP/OPC cultures. RT-PCR results showed that the levels of transcripts encoding CTR were significantly downregulated by noggin, while RANK gene expression was not affected. The downregulation of CTR gene expression was reversed by L51P and BMP2. In summary, noggin exerts direct and indirect biological effects on OC lineage cells. In fact, noggin acts pro-differentiation on OC lineage cells. This effect can not be reversed by the addition of BMP2 and L51P to the cell cultures. In OB/OPC co-cultures, however, noggin inhibits the development of osteoclasts indirectly through OB. This action can be reversed by BMP2 and L51P. It remains to be elucidated, whether direct cell-cell contact between OB and OPC is required for the mediation of this inhibitory effect, or whether the effect is mediated through (a) soluble factor(s).