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The effects of hypoxia and acidosis on bone cells

The importance of the blood supply for skeletal homeostasis has long been recognised, although the direct effects of oxygen tension on normal bone cell function were not investigated until the 21st century. Our own studies showed that the formation of osteoclasts from mouse marrow or human peripheral blood mononuclear cells was strongly stimulated when the cells were cultured in hypoxic environments (≤2% O_2) for 7-14 days, with corresponding increases in resorption pit formation. Surprisingly, the resorptive function of osteoclasts was unimpaired even in severe hypoxia (0.1% O_2), although cell survival was reduced. Thus osteoclasts (which contain abundant mitochondria) are, like other cells of the myeloid lineage, adapted to function in low O_2 environments. Conversely, we found that the growth, differentiation and bone-forming capacity of primary rodent osteoblasts was sharply reduced in hypoxia, with almost complete abolition of osteogenesis in severe hypoxia.

Our *in vitro* hypoxia experiments were performed in pH-clamped conditions but *in vivo*, tissue hypoxia due to reduced blood perfusion is usually accompanied by acidosis. Some 30 years ago, I observed that a small reduction in ambient pH (<7.2) is an absolute requirement for activation of mature osteoclasts to form resorption pits on bone surfaces. Activation of osteoclastic resorption appears to be more sensitive to stimulation by 'respiratory' acidosis (due to increased CO_2) than by 'metabolic' acidosis (due to decreased HCO_3^-). Osteoblast function, however, is inhibited by acidosis, via a selective blockade of mineral accretion into newly-formed bone matrix. *In vivo*, these highly-sensitive, reciprocal responses of bone cells to ambient pH could act to maximise the availability of OH^- ions in solution (rather than in deposited hydroxyapatite), where they can buffer excess H^+.

In summary, hypoxia directly stimulates osteoclast formation and thus bone resorption, whilst blocking bone formation by osteoblasts; acidosis directly activates mature osteoclasts but blocks bone mineralisation. The profound, linked effects of hypoxia and acidosis on bone cell function *in vitro* may help our understanding of the bone disturbances that occur in numerous *in vivo* settings, including ageing, inflammation, fractures, tumours, anaemias, kidney disease, diabetes, respiratory disease and smoking.