synoviocytes through induction of NO, which contributes to the loss of cartilage in osteoarthritis (Carmona and Prades, 2009). In culture, treatment with high concentrations of NO donors induced apoptosis of human osteoarthritis synovial fibroblasts through a COX-2 and tyrosine kinase-dependent pathway. The generation of reactive oxygen species, such as hydrogen peroxide and superoxide, also played a role in apoptosis of these cells. Endogenous NO production induced by a combination of cytokines, including IL-1ß, led to a reduction in apoptosis. This may reflect the lower concentration of NO produced in this way. In canine models of osteoarthritis, levels of chondrocyte apoptosis were higher in osteoarthritis cartilage compared with normal cartilage (Martel-Pelletier et al., 1999).

4. Triggering subchondral bone remodelling: in normal bone, there is a balance of formation mediated by osteoblasts and resorption mediated by osteoclasts, which maintains bone homeostasis (Carmona and Prades, 2009; Martel-Pelletier et al., 1999). Cytokines, including IL-1, can act on both osteoblasts and osteoclasts altering this balance. In vitro studies have shown that IL-1ß stimulates bone resorption and inhibits bone formation in rodent bone cultures. IL-1ß- mediated bone resorption has been linked, in part, to the conversion of plasminogen to plasmin and induction of MMPs in osteoblasts by IL-1, which would lead to degradation of the bone matrix. IL-1ß has also been shown to stimulate bone resorption and inhibit bone formation in adult rats in vivo. IL-1ß increased calcium excretion, osteoclast number and active resorption surface, but decreased bone apposition rate osteoclacin concentration. In this way, excessive activity of IL-1 in osteoarthritis may contribute to subchondral bone remodelling and loss (Martel-Pelletier et al., 1999).