Furthermore, IL-1 stimulates its own production perpetuating its downstream effects, and osteoarthritis chondrocyte express higher levels of the IL-1 receptor, increasing their sensitivity to IL-1 (Martel-Pelletier et al., 1999).

Roles of IL-1 in the pathophysiology of osteoarthritis are:

1. Triggering cartilage breakdown (catabolic pathway): IL-1 induces increased chondrocyte production of catabolic factors, such as matrix metalloproteinases (MMPs) and nitric oxide (NO). Chondrocyte and synoviocytes possess the inducible form of NO synthase (iNOS), which can be stimulated by inflammatory cytokines such as IL-1. IL-1 stimulates chondrocytes to produce inducible NO in amounts comparable to that produced by macrophages. IL-1 stimulates chondrocytes to produce inducible NO in amounts comparable to that produced by macrophages. IL-1 also reduces expression of enzymes that inhibit MMP activity (tissue inhibitor of metalloproteinases or TIMPs), further contributing to their catabolic activity (Carmona and Prades, 2009). NO is a free radical that can damage the extracellular matrix, in part though activation of MMPs in articular chondrocytes. In addition, increased production of NO decreased the concentration of the natural inhibitor of the IL-1 receptor, interleukin-1 receptor antagonist (IL-1ra). This causes an increase in the activity of IL-1, thus contributing to a positive feedback loop. NO is also one of the most powerful inducers of the immune response and significantly activates and stimulates immune cell migration (Carmona and Prades, 2009). As the monocyte/macrophage system is the major cellular source of IL-1 this can lead to a substantial increase in the local concentration of IL-1. In turn, IL-1 can induce the synthesis of potent enzyme activators such as urokinase-like plasminogen activator (uPA), while the level of its inhibitor (PAI-I) is reduced. When bound to