Inflammatory microcrystals induce murine macrophage survival and DNA synthesis

ABSTRACT

Murine bone-marrow-derived macrophages were treated in vitro with microcrystals, the cell numbers were monitored over time, and DNA synthesis was measured as the incorporation of [methyl-3H]thymidine (TdR). We report here that BCP, monosodium urate, talc, and, to a lesser extent, CPPD crystals promote macrophage survival and DNA synthesis; the latter response is particularly striking in the presence of low concentrations of macrophage-colony stimulating factor (M-CSF, CSF-1). Enhanced macrophage survival or proliferation may contribute to the synovial hyperplasia noted in crystal-associated arthropathies, as well as to talc-induced inflammation and granuloma formation. The crystals studied join the list of particulates having these effects on macrophages, indicating the generality of this type of response.

INTRODUCTION

Introduction Intra-articular basic calcium phosphate (BCP) (hydroxyapatite, octacalcium phosphate, tricalcium phosphate) crystal-deposition disease is associated clinically with severe degenerative arthritis characterized by hyperplasia of the synovial lining and loss of intrasynovial collagenous structures. The interaction of the crystals with inflammatory cells is believed to be a key factor in crystal-induced inflammation. Deposition of calcium pyrophosphate dihydrate (CPPD) crystals has been associated with the acute inflammatory arthritis of 'pseudogout'. Synovial thickening is a common clinical finding in the affected joints of patients with deposition of CPPD crystals. Histologically, synovial-cell hyperplasia and infiltration by mononuclear inflammatory cells are seen; CPPD crystals are phagocytosed by cells of the synovial lining. Gout, pseudogout, and acute articular and periarticular inflammation caused by BCP crystals can behave similarly, reflecting the fact that BCP and CPPD crystals share many of the fundamental mechanisms of cell activation utilized by urate crystals. Acute gout, even though initiated by deposition of monosodium urate (MSU) crystals in the synovium, is often associated with systemic inflammatory manifestations. Talc (magnesium silicate) crystals, present in aerosols of respirable talc and surgical gloves, can cause, respectively, inflammatory reactions in the lung or a granulomatous reaction with peritoneal adhesions. Exposure to talc leads to the development of granulomas containing macrophages. Injection of talc into rabbit knees induces synovitis. Macrophage-colony-stimulating factor (M-CSF), also called colony stimulating factor-1 (CSF-1), is an important regulator of the development and function of macrophage lineages throughout the body. There are in vivo data suggesting that both synovial and peritoneal macrophages are completely dependent upon CSF-1 for their development. One cell type that is normally resident in the synovium, and interacts in vivo with the various crystals mentioned above, is the macrophage (mononuclear phagocyte). We have previously shown that a number of particulates, including oxidized low-density lipoprotein (oxLDL), adjuvants, and β-amyloid and prion protein fibrillogenic peptides (manuscript in preparation), were able to induce macrophage survival; they could also induce a proliferative response, particularly in the presence of circulating concentrations of CSF-1. We report here that BCP, MSU, talc, and, to a lesser extent, CPPD all promote the survival of murine bone marrow-derived macrophages (BMMs) and the synthesis of DNA, the latter response being potentiated again by low (suboptimal) CSF-1

concentrations.

CONCLUSION

BCP, MSU, talc, and, to a lesser extent, CPPD all promote murine macrophage survival and DNA synthesis, the latter response being potentiated by low (suboptimal) CSF-1 concentrations. Such enhanced macrophage survival or proliferation may contribute to the synovial hyperplasia noted in crystal-associated arthropathies, as well as to talc-induced inflammation. The crystals mentioned above can therefore be included in the list of particulates having these effects on macrophages, indicating the generality of this type of response.