Stimulation of inducible Nitric Oxide Synthase by Monosodium Urate Crystals in Macrophages and Expression of iNOS in gouty arthritis. Nitric Oxide

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摘要

Abstract

From the studies on the involvement of iNOS in arthritis, it is clear that attention has focused primarily on rheumatoid arthritis (RA) and osteoarthritis (OA). To date, little is known about the role of iNOS in the pathophysiology of gouty arthritis (GA). Here, we investigated the significance of iNOS expression in cell culture system as well as in GA patients. Gouty crystals monosodium urate (MSU) appeared to up-regulate inducible nitric oxide synthase (iNOS) mRNA and protein expression in a concentration- and time-dependent manner in RAW264.7 macrophages. This increase of iNOS expression is attributable to the activation of multiple signaling pathways. Evidence for this was initially established by inhibitor treatment of cells in the presence of MSU. While the JAK inhibitor AG490, the PI3K inhibitor LY294002, and the NFkappaB inhibitor PDTC abrogated almost completely the expression of iNOS induced by MSU, the ERK1/2 inhibitor PD98059 was only partially effective. Furthermore, the effect of MSU on the activation of PI3K/Akt, JAK/STAT, ERK1/2, and NFkappaB signaling molecules was carefully examined. Moreover, it was shown that GAS and NFkappaB motifs are required for iNOS expression mediated by MSU. In addition, synovial tissues obtained from GA patients displayed enhanced expression of iNOS when compared with normal synovium. Taken together, these findings provide the first evidence for the potential importance of iNOS in the pathogenesis of GA as well as RA and OA, and in turn raise the possibility that iNOS may be an ideal target for preventive therapy in human arthritis.