題名:Dipyridamole activation of mitogen-activated protein kinase phosphatase-1 mediates inhibition of lipopolysaccharide-induced cyclooxygenase-2 expression in RAW 264.7 cells

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摘要:Dipyridamole is a nucleoside transport inhibitor and a non-selective phosphodiesterase inhibitor. However, the mechanisms by which dipyridamole exerts its anti-inflammatory effects are not completely understood. In the present study, we investigated the role of mitogen-activated kinase phosphatase-1 (MKP-1) in dipyridamole's anti-inflammatory effects. We show that dipyridamole inhibited interleukin-6 and monocyte chemoattractant protein-1 secretion, inducible nitric oxide synthase protein expression, nitrite accumulation, and cyclooxygenase-2 (COX-2) induction in lipopolysaccharide (LPS)-activated RAW 264.7 macrophages. Dipyridamole inhibited the nuclear factor kappa B (NF-kappaB) signaling pathway as demonstrated by inhibition of the inhibitor of NF-kappaB (IkappaB) phosphorylation, IkappaB degradation, p65 translocation from the cytosol to the nucleus, and transcription of the reporter gene. Dipyridamole also inhibited LPS-stimulated p38 mitogen-activated protein kinase (p38 MAPK) and IkappaB kinase-beta (IKK-beta) activities in RAW 264.7 cells. A p38 MAPK inhibitor, SB 203580, inhibited LPS-stimulated COX-2 expression and IKK-beta activation suggesting that LPS may activate the NF-kappaB signaling pathway via upstream p38 MAPK activation. Furthermore, dipyridamole stimulated transient activation of MKP-1, a potent inhibitor of p38 MAPK function. Knockdown of MKP-1 by transfecting MKP-1 siRNA or inhibition of MKP-1 by the specific inhibitor, triptolide, significantly reduced the inhibitory effects of dipyridamole on COX-2

expression induced by LPS. Taken together, these data suggest that dipyridamole exerts its anti-inflammatory effect via activation of MKP-1, which dephosphorylates and inactivates p38 MAPK. Inactivation of p38 MAPK in turn inhibits IKK-beta activation and subsequently the NF-kappaB signaling pathway that mediates LPS-induced cyclooxygenase-2 expression in RAW 264.7 cells.