Peptidoglycan Induces Cyclooxygenase-2 Expression in Macrophages by Activating the Neutral Sphingomyelinase-Ceramide Pathway

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摘要.

Abstract

The sphingomyelin signal transduction pathway is known to play a role in mediating the action of various cytokines. Herein, we examined the role of neutral sphingomyelinase (nSMase)/ceramide in peptidoglycan (PGN)-induced NF-κB activation and cyclooxygenase-2 (COX-2) expression in macrophages. PGN-induced COX-2 expression was attenuated by an nSMase inhibitor (3-O-methyl-sphingomyeline, 3-OMS) and ceramidase, but not by an acidic SMase inhibitor (imipramine). C2-ceramide, bacterial SMase (which mimics cellular SMase activity), and a ceramidase inhibitor (N-oleoyl-ethanolamine) individually had no effect on COX-2 expression; however, they markedly enhanced PGN-induced COX-2 expression. PGN activated nSMase, but not acidic SMase, resulting in increased ceramide generation. PGN-induced nSMase activation and ceramide formation were inhibited by 3-OMS, but not by imipramine. PGN-induced COX-2 expression was inhibited by a p38 MAPK inhibitor (SB 203580) and dominant negative mutants of MAPK kinase (MKK) 3, MKK6, and p38 MAPKα. 3-OMS selectively inhibited PGN-induced p38 MAPK and MKK3/6 activation, but not JNK or ERK1/2. C2-ceramide, bacterial SMase, and N-oleoyl-ethanolamine all induced p38 MAPK or MKK3/6 activation. The PGN-mediated increases in κB-luciferase activity were also inhibited by 3-OMS and the p38 MAPKα DN, but not by imipramine. Furthermore, C2-ceramide caused an increase in κB-luciferase activity. Our data demonstrate for the first time that PGN activates the nSMase/ceramide pathway to induce MKK3/6/p38 MAPK activation, which in turn initiates NF-κB activation and ultimately induces COX-2 expression in macrophages. The nSMase/ceramide pathway is required but might not be sufficient for COX-2 expression induced by PGN.