Lipoteichoic acid induces nuclear factor-kB activation and nitric oxide synthase expression via phosphatidylinositiol 3-kinase, Akt, and p38 MAPK in RAW 264.7 macrophages

林建煌
Kao SJ;Lei HC;Kuo CT;Chang MS;Chen BC;Chang YC;Chiou WT;Lin CH

Abstract

We previously demonstrated that lipoteichoic acid (LTA) might activate phosphatidylcholine-phospholipase C (PC-PLC) and phosphatidylinositol-phospholipase C (PI-PLC) to induce protein kinase C activation, which in turn initiates nuclear factor-kappaB (NF-kappaB) activation and finally induces inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) release in RAW 264.7 macrophages. In this study, we further investigated the roles of tyrosine kinase, phosphatidylinositiol 3-kinase (PI3K)/Akt, and p38 mitogen-activated protein kinase (MAPK) in LTA-induced iNOS expression and NO release in RAW 264.7 macrophages. Tyrosine kinase inhibitors (genistein and tyrphostin AG126), PI3K inhibitors (wortmannin and LY 294002), and a p38 MAPK inhibitor (SB 203580) attenuated LTA-induced iNOS expression and NO release in concentration-dependent manners. Treatment of RAW 264.7 macrophages with LTA caused time-dependent activations of Akt and p38 MAPK. The LTA-induced Akt activation was inhibited by wortmannin, LY 294002, genistein, and tyrphostin AG126. The LTA-induced p38 MAPK activation was inhibited by genistein, tyrphostin AG126, wortmannin, LY 294002, and SB 203580. The LTA-induced formation of an NF-kappaB-specific DNA-protein complex in the nucleus was inhibited by wortmannin, LY 294002, genistein, tyrphostin AG126, and SB 203580. Treatment of macrophages with LTA caused an increase in kappaB-luciferase activity, and this effect was inhibited by tyrphostin AG126, wortmannin, LY 294002, the Akt dominant negative mutant (AktDN), and SB 203580. Based on those findings, we suggest that LTA might activate the PI3K/Akt pathway through tyrosine kinase to induce p38 MAPK activation, which in turn initiates NF-kappaB activation, and ultimately induces iNOS expression and NO release in RAW 264.7 macrophages.