

題名:Switch activation of PI-PLC downstream signals in activated macrophages with wortmannin

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摘要:Phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P₂)

has been known to serve as a substrate for phosphatidylinositol 3-kinase (PI3K) and phosphoinositide-specific phospholipase C (PI-PLC), which can produce PtdIns(3,4,5)P₃ and inositol 1,4,5-trisphosphate (Ins(1,4,5)P₃) and

diacylglycerol (DAG), respectively. In this study, we elucidated the role of PI-PLC during the LPS-activated mouse macrophages RAW264.7

treated with PI3K inhibitor wortmannin. First, wortmannin treatment enhanced Ins(1,4,5)P₃ production and iNOS expression in LPS-activated macrophages. Inhibition of PI3K by p85 siRNA also showed an enhancement of iNOS expression. On the other hand, overexpression of PI3K by ras-pl10 expression plasmid significantly decreased iNOS expression in LPS-activated macrophages. In addition, overexpression of wild-type or dominant-negative Akt expression plasmid did not affect the iNOS expression in LPS-activated macrophages.

Second, treatment of PI-PLC inhibitor U73122 reversed the enhancement of iNOS expression, the increase of phosphorylation level of ERK, JNK and p38, and the increase of AP-1-dependent gene expression in wortmannin-treated and LPS-activated macrophages. However, NF- κ B activity determined by EMSA assay and reporter plasmid assay did not change during LPS-

activated macrophages with or without wortmannin. We propose that the inhibition of PI3K by wortmannin in mouse macrophages enhances the PI-PLC downstream signals, and subsequently increases the LPS induction of iNOS expression independently of Akt pathway.