P-31

THE ESSENTIAL ROLE OF PHOSPHATIDYLINOSITOL 3-KINASE IN THE INDUCTION OF MICROSOMAL EPOXIDE HYDROLASE

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We have shown that PI3-kinase played an essential role in the ARE-mediated rGSTA2 induction by oxidative stress following sulfur amino acid deprivation (SAAD) (Kang et al., *Mol. Pharmacol.*, 2000). Microsomal epoxide hydrolase (mEH), which detoxifies a variety of epoxide intermediates produced from various xenobiotics, is inducible by oxidative stress. In the present study, we studied whether SAAD activated phosphatidylinositol 3-kinase (PI3-kinase)/Akt and induced mEH in H4IIE cells. The role of PI3-kinase activation on the mEH induction by SAAD was also investigated. PI3-kinase was activated from 10 min through 12 h after SAAD, the activity of which returned to control level at 24 h. The activation of PI3-kinase led to increases in the activity of Akt at the same time points. Northern and Western blot analyses revealed that the mEH mRNA level was 4-fold increased at 48 h, which accompanied the induction of mEH protein. Wortmannin or LY294002, PI3-kinase inhibitors, completely inhibited the increases in mEH mRNA and protein by SAAD. These results demonstrated that SAAD activated the PI3-kinase/Akt pathway at early times and induced mEH presumably as an adaptive response, and that the PI3-kinase/Akt pathway played a crucial role in the induction of mEH.