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Activation of C/EBPβ by PD98059 leads to the induction of GSTA2

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Induction of glutathione S-transferases is associated with cancer chemoprevention. We reported that PD98059, an MKK1 inhibitor, induces glutathione S-transferase A2 (rGSTA2). This report comparatively examines the role of CCAAT/enhancer binding protein (C/EBP) and Nrf-2 in the induction of rGSTA2 by PD98059. PD98059 at the concentrations effective for the inhibition of MKK1 increased the rGSTA2 protein and mRNA levels in H4IIE cells. PD98059 also induced rGSTA2 in cells stably transfected with dominant negative mutant of MKK1(-), providing that the inhibition of MKK1/ERK1/2 by PD98059 was not responsible for rGSTA2 induction. PD98059 caused nuclear translocation of C/EBPβ and increased C/EBP DNA binding, which was supershifted with anti-C/EBPβ antibody. Nrf2/antioxidant response element was not activated. PD98059 increased the luciferase reporter gene activity in cells transfected with the C/EBP-response element-containing 1.65 kb flanking region of the *rGSTA2* gene. Deletion of the C/EBP site or overexpression of dominant negative mutant of C/EBP abolished the reporter gene activity. Flavone also induced rGSTA2, which accompanied nuclear translocation of C/EBPβ and C/EBP-response element-mediated *rGSTA2* gene expression. These results demonstrated that PD98059 and flavone induce nuclear translocation of C/EBPβ and activate the C/EBP-response element present in the *rGSTA2* gene, irrespective of the inhibition of MKK1/ERK activity.