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PHOSPHATIDYLINOSITOL 3-KINASE REGULATES NUCLEAR TRANSLOCATION OF Nrf2 THROUGH ACTIN REARRANGEMENT

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Expression of phase II detoxifying genes is regulated by Nrf2-mediated antioxidant response element (ARE) activation. We previously showed that phosphatidylinositol 3-kinase (PI3-kinase) plays an essential role in ARE-mediated rGSTA2 induction by oxidative stress. In view of the fact that the signaling pathway of PI3-kinase controls microfilaments and translocation of actin-associated proteins, the current study was designed to investigate the role of this kinase in the rise of [Ca2+]i and actin-mediated nuclear translocation of Nrf2. tert-Butylhydroquinone (t-BHQ) stimulated a rise in [Ca2+]i and nuclear translocation of Nrf2 in H4IIE cells, which were prevented by pretreatment of the cells with PI3-kinase inhibitors. Chelation of [Ca2+]i suppressed Nrf2 migration and rGSTA2 induction. t-BHQ relocalized Nrf2 in concert with changes in actin microfilament architecture, as visualized by immunocytochemical staining. Furthermore, t-BHQ increased the level of nuclear actin, co-immunoprecipitated with Nrf2, which returned to that of control by PI3-kinase inhibition. Cytochalasin B, an actin disruptor, alone stimulated actin-mediated nuclear translocation of Nrf2 and induced rGSTA2. In contrast, phalloidin, an actin stabilizer, inhibited Nrf2 translocation and rGSTA2 induction by t-BHQ. Thus, the PI3-kinase signaling pathway regulates a rise in [Ca2+]i and rearrangement of actin microfilaments in response to t-BHQ. Also, depolymerization of actin causes actin-bound Nrf2 to translocate into nucleus.

keyword : Nrf2, actin, ARE, PI3-kinase