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Increased Sensitivity of ras-trnasformed Cells to Capsaicin-induced Apoptosis

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During the last decade, enormous progress has been made on the biological significance of apoptosis. Since ras is among the most central molecule in signaling, we asked if ras regulates apoptotic pathway. We have previously shown that H-ras, but not N-ras, induces an invasiveness and motility in human breast epithelial cells (MCF10A), while both H-ras and N-ras induce transformed phenotype. In this study, we wished to seek a chemopreventive agent that effectively induces apoptosis in H-ras-activated cells. Here we show that capsaicin, the major pungent phytochemical in red pepper, induces caspase 3-involved apoptosis selectively in H-ras activated MCF10A cells while the parental MCF10A cells are not affected. In order to study the molecular mechanisms for the increased sensitivity of H-ras MCF10A cells to capsaicin-induced apoptosis, activation of ras downstream signaling molecules, mitogen-activated protein kinases (MAPKinases), upon capsaicin treatment was investigated. Phosphorylated forms of JNK1 and p38 MAPKinase were prominently increased whereas activated ERK-1/2 was decreased by capsaicin in ras-activated cells. The parental cells did not respond to capsaicin, suggesting that capsaicin selectively induces apoptosis through modulating activities of ras downstream signaling molecules in H-ras-activated cells. Studies using chemical inhibitors (CPT-cAMP, SB203580 and PD98059) and dominant negative constructs of JNK1, p38 and MEK show that activation of JNK1 and p38 MAPKinase, but not ERK-1/2, is critical for ras-mediated apoptosis by capsaicin.