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PREVENTION OF CANCER BY DIETARY FACTORS: TARGETING MAP KINASE/AP-1 SIGNAL TRANSDUCTION PATHWAYS

Zigang Dong

The Hormel Institute, University of Minnesota, 801 16th Avenue NE, Austin, MN 55912 USA
Email: zgdong@hi.umn.edu Fax: +1 507-437-9606

MAP kinase/AP-1 signal transduction components are rapidly initiated by many extracellular stimuli, especially environmental carcinogens. We have investigated the role of MAP kinases (Erks, JNKs, and p38 kinases) and AP-1 signal transduction pathways in the process of cell transformation and carcinogenesis. Incubation of Cl 41 cells with tumor promoters such as TPA, EGF, arsenic, or TNF-α led to cell transformation and activation of MAP kinases. Introduction of the dominant negative mutant of JNK1, Erk2, or p38 kinase into JB6 Cl 41 cells specifically inhibited tumor promoter-induced activation of JNKs, Erks, and p38 kinases, respectively. Expressing dominant negative mutant JNK1 inhibited TNF-α-induced cell transformation but not EGF-induced cell transformation. Dominant negative Erk2, on the other hand, inhibited EGF-, TPA-, or arsenic-induced cell transformation. Our results also show that in *Jnk2*-/- mice, the multiplicity of papillomas induced by TPA was lower than that in wild-type mice. Papillomas on wild-type mice grew rapidly and were well vascularized compared with *Jnk2*-/- mice. After the 12th week of TPA treatment, the mean number of tumors per mouse was 4.5 in wild-type mice, but only 2 in *Jnk2*-/- mice. In embryo primary cells from the same mice, TPA induced AP-1 DNA binding activity in wild-type cells, but the binding was inhibited in *Jnk2*-/- cells. TPA-induced phosphorylation of Erks and p38 kinases were not affected in *Jnk2*-/- cells, while TPA-induced phosphorylation of glycogen synthase kinase 3 was strongly inhibited in *Jnk2*-/- cells. Additionally, in TPA-treated *Jnk2*-/- cells, the expression of some genes associated with the induction of apoptosis increased whereas some associated with the inhibition of apoptosis decreased. In agreement with the *in vitro* cell transformation data, a knockout of *Jnk1* (*Jnk1*-/-) did not inhibit skin tumor promotion by TPA.

Tumor promotion by various tumor promoters may be mediated by different signal transduction pathways. Many dietary factors show potent cancer preventive activity. These factors include tea polyphenols, retinoids, InsP6, resveratrol, and gingerol. These food factors and agents, such as aspirin and other COX_2 inhibitors can inhibit one or more of the MAP kinases and/or AP-1 activation. Our studies indicate that the chemopreventive effect of these factors may be mediated by their effects on different signal transduction pathways.