

## 【S-13】

**Cell Signaling Cascades as Prime Targets for Chemoprevention with Dietary Phytochemicals**

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Chemoprevention refers to the use of agents to inhibit, reverse, or retard tumorigenesis. Numerous phytochemicals present in edible plants have been reported to interfere with a specific stage of the carcinogenic process. Some antioxidative and anti-inflammatory substances derived from dietary or medicinal plants exert chemopreventive properties by targeting intracellular signaling molecules or events. Curcumin, a yellow colouring agent contained in turmeric (*Curcuma longa* L., Zingiberaceae), has been reported to possess strong anti-tumor promotional as well as anti-inflammatory and antioxidant activities. Recent studies from this laboratory have revealed that curcumin inhibits expression of cyclooxygenase-2 (COX-2) in mouse skin treated with the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) through inactivation of the redox-sensitive eukaryotic transcription factor NF- $\kappa$ B. Inhibition of NF- $\kappa$ B by curcumin appears to be mediated by blocking ERK1/2 and p38 MAP kinases. [6]-Gingerol, a pungent ingredient present in ginger (*Zingiber officinale* Roscoe, Zingiberaceae), inhibited TPA-induced tumor necrosis factor- $\alpha$  production, ornithine decarboxylase activity, and skin tumor promotion in female ICR mice. Its anti-tumor promoting effects appears to be associated with inhibition of p38 MAP kinase and of subsequent NF- $\kappa$ B activation. Capsaicin, a major pungent principle of hot chili pepper (*Capsicum annuum* L., Solanaceae) with potential anti-inflammatory and anti-tumor promoting properties, also suppressed TPA-induced activation of NF- $\kappa$ B and AP-1, in mouse skin *in vivo*. The soy isoflavone genisteine inhibits COX-2 induction in TPA- and TNF- $\alpha$ -stimulated human mammary epithelial cells by inactivating ERK1/2 and NF- $\kappa$ B. Resveratrol, a phytoalexin present in grapes and red wine, attenuated TPA-induced expression of COX-2 and activation of AP-1 in mouse skin. The green tea polyphenol epigallocatechin 3-gallate (EGCG) inhibited activation of NF- $\kappa$ B and AP-1 in the TPA-stimulated human mammary epithelial cell line. Under the same experimental

conditions, EGCG suppressed COX-2 induction, while it upregulated heme oxygenase-1 (HO-1). The molecular basis of reciprocal regulation of COX-2 and HO-1 by EGCG is under investigation.