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## INHIBITION OF CARCINOGENESIS BY TEA

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The inhibition of carcinogenesis by tea has been demonstrated in animal models on many organ sites. These include cancers of the skin, lung, oral cavity, esophagus, stomach, liver, small intestine, pancreas, colon, bladder, prostate, and mammary glands. The most well studied sites are the skin and lung. These experiments indicate that tea has broad inhibitory activity against both spontaneous and chemically-induced lung tumorigenesis, and it is effective when administered during the initiation, promotion, or progression stages of carcinogenesis. Recent results demonstrated that oral administration of green tea to hamsters with oral hyperplasia and dysplasia (caused by treatment with DMBA for 6 weeks) inhibited the development of oral squamous cell carcinoma. In both the mouse lung cancer and hamster oral cancer models, inhibition of cell proliferation, enhancement of apoptosis, and inhibition of angiogenesis were observed. Inhibition of chemically- and UV-induced skin carcinogenesis by tea and tea constituents has also been demonstrated under different experimental protocols. Although EGCG and other tea polyphenols have been postulated to be the active constituents, the contribution of caffeine could be very important in some model systems (e.g., UV-induced complete skin carcinogenesis in mice and NNK-induced lung tumorigenesis in rats).

A key issue is the bioavailability of tea polyphenols at the target organ site. The systemic bioavailability of EGCG is rather low in humans and mice, but extremely low in rats. The peak human plasma levels of EGCG after tea consumption are in the range of 0.1 to 1  $\mu$ M. After ingestion, the tea polyphenols are extensively methylated and glucuronidated. Some ring fission metabolites produced by the intestinal microflora also appear in the blood and urine. The biological activities of these metabolites need to be studied. Many mechanisms for the inhibition of carcinogenesis by tea have been proposed. Recent studies indicate that tea polyphenols inhibit MAP-kinase, AP-1, NF  $\kappa$  B, and other

signal transduction pathways or transcription factors, modulating cell cycle regulatory proteins, and block ligand binding to certain receptors. These activities may lead to the inhibition of cell transformation, proliferation, tumor invasion, and angiogenesis as well as apoptosis. Most of these activities were observed *in vitro* with EGCG concentrations much higher than those observed *in vivo*. It is important to verify these proposed mechanisms in carcinogenesis models *in vivo*.

Many epidemiological studies have been conducted to investigate the effects of tea consumption on human cancer incidence. The results, however, are not conclusive. Whereas a protective effect of tea consumption on certain types of cancer are suggested by some studies, such an effect was not observed in some other studies. It is likely that the effect of tea consumption on humans depends on the etiological factors and modifying life-style factors involved in the specific cancer. More studies on the bioavailabilities and biological activities of tea constituents will enhance our understanding of the possible application of tea for the prevention of certain types of cancer (supported by NIH grant CA56673).