

## Epigallocatechin 3-Gallate and Green Tea Catechins: United They Work, Divided They Fail

Perspective on Fu et al., p. 531

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Epidemiologic studies indicate that green tea consumption decreases cancer risk (1–3). These data are supported by the results of numerous preclinical studies, which have shown that green and black tea are potent inhibitors of carcinogenesis in various rodent models (4–6), including models for cancers of the skin, lung, esophagus, stomach, liver, duodenum, small intestine, pancreas, colon-rectum, and mammary gland (1, 4, 6–11).

Different tea preparations contain varying amounts of polyphenols, and epigallocatechin 3-gallate (EGCG) is the most abundant, best-studied, and possibly most potent (against cancer) polyphenol found in tea (4–6, 12–15). Besides EGCG, which may account for 50% to 80% of the total antioxidant polyphenols called catechins in tea (6, 12–16), other tea catechins include (–)-epigallocatechin, (–)-epicatechin gallate, and (–)-epicatechin. The achievable tissue concentrations of these polyphenols are in the low micromolar range, and therefore, anticarcinogenic effects observed with much higher concentrations *in vitro* may not be relevant to the *in vivo* anticarcinogenic process (4, 5, 17).

Green tea, EGCG, or other dietary components clearly have both direct and indirect effects. Numerous proteins that can directly bind with EGCG include the plasma proteins fibronectin, fibrinogen, and histidine-rich glycoprotein (18), which may act as carrier proteins for EGCG. EGCG also binds with Fas (19), which might trigger the Fas-mediated apoptosis cascade. Laminin and the 67 kDa laminin receptor (20, 21) also interact with EGCG, and this binding seems to regulate the biological functions of the 67 kDa laminin receptor that have possible implications for prion-related diseases. Other directly bound protein targets include the intermediate filament protein, vimentin (22),  $\zeta$  chain-associated 70 kDa protein (ZAP-70) kinase (23), Fyn (24), insulin-like growth factor-1 receptor (25), and the molecular chaperone glucose-regulated protein 78 (26; Fig. 1). All of these directly bound proteins play important roles in carcinogenesis. Zap-70 plays a critical role in T cell receptor-mediated signal transduction and in the immune response of leukemia cells, and Fyn plays a major role in malignant cell transformation. Insulin-like growth factor-1 receptor

plays a functional role in cell transformation and cancer formation, and glucose-regulated protein 78 is associated with the multidrug resistance phenotype of many types of cancer cells. The many targets of polyphenols that have been discovered and continue to be discovered are very likely dependent on the concentration of the tea polyphenol used and the specific cell, tissue, or organ—for example, proteins that bind EGCG in the lung, breast, colon, or skin might be very different from one another, and EGCG very likely targets multiple proteins in each tissue.

EGCG and other polyphenols also exert strong indirect effects on a number of important regulatory proteins and transcription factors, adding further complexity to these agents' multitargeted anticancer effects. In particular, EGCG inhibited tumor promoter-induced activator protein-1 (15, 27), signal transducers and activators of transcription (28), phosphatidylinositol 3-kinase/Akt (29), and nuclear factor- $\kappa$ B (30) activation. Phorbol ester tumor promoters such as 12-*O*-tetradecanoylphorbol-13-acetate are known to stimulate activator protein-1 activity through protein kinase C and the epidermal growth factor receptor (EGFR; ref. 31). Theaflavins and EGCG were reported to down-regulate the EGFR (32) or its phosphorylation (33). However, the direct target(s) of EGCG, theaflavins, and other polyphenols in suppressing EGFR, activator protein-1, signal transducers and activators of transcription, nuclear factor- $\kappa$ B, or other transcription factor activations have not yet been identified.

Polyphenon E (Poly E) is a well-defined pharmaceutical-grade mixture that contains at least five different catechins, including epicatechin, gallic acid, gallic acid gallate, epigallocatechin, epicatechingallate, and most abundantly, EGCG (~65%; refs. 34, 35). Poly E is the form of green tea used in clinical cancer trials funded through the National Cancer Institute to investigate the benefits of tea catechins in humans. Poly E has effectively inhibited lung cancer in a number of mouse model studies. Female A/J mice with benzo(a)pyrene-induced precancerous lesions formed over a period of 21 weeks received Poly E (1% in the diet) for an additional 25 weeks. Poly E treatment reduced the average tumor load per animal but did not significantly inhibit average tumor multiplicity (36). It is notable that Poly E reduced the largest carcinomas (compared with these tumors in untreated mice; ref. 36). Another study found that Poly E in the diet significantly reduced pulmonary adenoma multiplicity and tumor load in a dose-dependent fashion in A/J mice (37). Poly E in drinking fluid significantly reduced the incidence (by 52%) and multiplicity (by 63%) of 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumor progression from adenoma to adenocarcinomas in female A/J mice (38). The number of visible lung tumors was also reduced (38). These studies indicate that administration of

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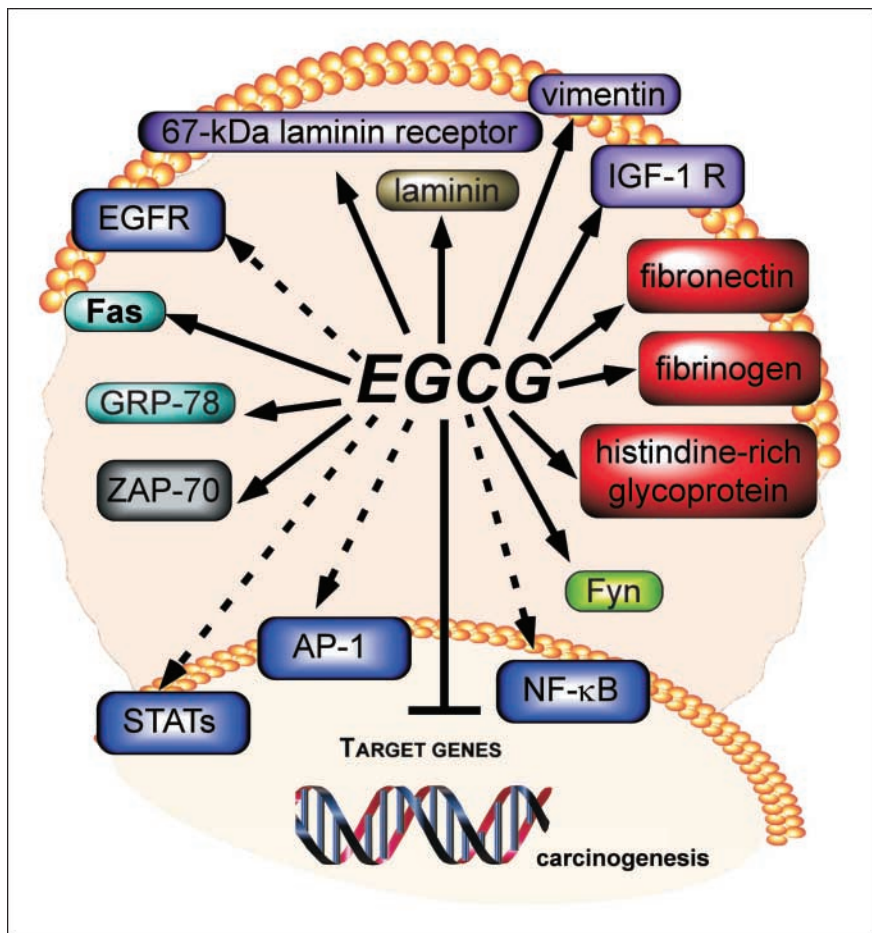
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**Fig. 1.** EGCG interacts with and binds numerous proteins to prevent carcinogenesis. EGCG has been reported to directly bind with the plasma proteins fibronectin, fibrinogen and histidine-rich glycoprotein, Fas, laminin and the 67 kDa laminin receptor, vimentin IGF-1R, and glucose-regulated protein 78 (GRP-78; *solid arrows*). EGCG also indirectly targets a number of other oncogenic proteins including EGFR and the activator protein 1 (AP-1), signal transducers and activators of transcription (STAT), and nuclear factor  $\kappa$ B (NF- $\kappa$ B) transcription factors. The net result is the inhibition of carcinogenesis in a variety of tissues.



Poly E in the diet or drinking fluid is effective in suppressing lung cancer in animal models.

In this issue of the journal, Ming You's group (Fu et al.) report a study of aerosolized Poly E (39) that builds on an earlier study by the same group. In the previous study, aerosolized Poly E or EGCG alone was administered to A/J mice beginning 2 weeks after carcinogen treatment and continued daily for 20 weeks. Poly E decreased tumor load by ~59%, whereas EGCG alone at the same or a higher dose failed to inhibit lung carcinogenesis (40). The new study reported in this issue of the journal tested Poly E versus Poly E stripped of its EGCG content, or Poly E-light, in A/J mice (39). Poly E decreased benzo (*a*)pyrene-induced tumor multiplicity by 53%, but the same dose of Poly E-light failed to inhibit lung carcinogenesis. Ineffectiveness for EGCG alone was shown in the first study and for Poly E minus its most abundant component, EGCG, in the second study, indicating that aerosolized Poly E may require all its components but certainly requires EGCG in order to be effective in treating or preventing pulmonary adenoma formation and growth in A/J mice.

These results are supported by studies of Poly E versus EGCG in other tissues. *Apc*<sup>Min/+</sup> mice fed Poly E (0.12% in diet) or EGCG (0.08% in drinking water) exhibited significantly decreased tumor multiplicity, suggesting that Poly E was more effective than was EGCG alone (41). It is notable that more EGCG was found in the small intestine of animals receiving Poly E than EGCG (41), suggesting that EGCG may be metabo-

lized more efficiently when given in a combination of catechins rather than alone. The effects of Poly E or EGCG might also be tissue-specific. For example, Poly E caused a dose-dependent decrease in palpable 4-hydroxybutyl(butyl)-nitrosamine-induced urinary bladder tumors but had little effect on the prevention of methylnitrosourea-induced mammary cancers (42). Relatively high levels of various polyphenols, but not EGCG, were found in the urine, and the levels of these polyphenols were ~50 to 1,000 times lower in serum. Therefore, the bioavailability of these tea polyphenols to different organ sites might contribute to the differential preventive efficacy of Poly E against urinary bladder and mammary cancers (42).

These results suggest what many have begun to suspect— isolating a single compound from complex foods may not be effective cancer prevention even at high, relatively toxic doses, whereas combinations of lower, less-toxic doses of each compound might be effective (43–47). Clearly, EGCG or other polyphenol chemicals may require interactivity or dependency on other components in the whole food source. This idea is supported by the general clinical findings that individual dietary components have not been very successful in preventing cancer. Results from the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study in Finnish men smokers at risk of lung cancer indicated that the incidence of lung cancer was not affected by  $\alpha$ -tocopherol and unexpectedly increased in men receiving  $\beta$ -carotene compared with those who did not

(48). Subsequent findings across subgroups of participants in the Alpha-Tocopherol, Beta-Carotene study supported these findings but also indicated that the adverse  $\beta$ -carotene effect might have been associated with heavier smoking and higher alcohol intake (49). The findings of the Beta-Carotene and Retinol Efficacy Trial in smokers, former smokers, and workers exposed to asbestos (50), similar with the Alpha-Tocopherol, Beta-Carotene Study, was that  $\beta$ -carotene (combined with retinol) had a higher risk of lung cancer compared with placebo (50). Folic acid did not prevent colorectal adenomas in patients with a recent history of colorectal adenomas and no previous invasive large intestine carcinoma (51). Furthermore, the Selenium and Vitamin E Cancer Prevention Trial showed that neither selenium nor vitamin E prevented prostate cancer (52). On the other hand, recent results of a phase III trial of low doses of combined sulindac (a nonsteroidal anti-inflammatory drug) and difluoromethylornithine prevented colon polyp recurrence by 70% overall and by 92% for the highest-risk, advanced adenomas (43).

The available clinical evidence suggests that Poly E is more bioavailable than is EGCG alone, which may explain the differences in efficacy between the two agents in different models. In general, the oral bioavailability of green tea catechins is low, which means that systemic catechin levels in humans are several-fold less than the effective concentrations determined in *in vitro* systems (53). Phase I pharmacokinetic studies have tested increasing single oral doses of EGCG or Poly E (decaffeinated) to assess their systemic availability. Following Poly E administration, EGCG was present mostly in the free form, whereas epicatechin and epigallocatechin were present at low/undetectable levels as glucuronide and sulfate conjugates in plasma or urine (53). Following EGCG administration in another study, none of these compounds were detectable (indicating the purity of the EGCG used), and the systemic availability of EGCG was increased at higher doses (54). In addition, oral administration of EGCG or Poly E under a fasting condition increased their bioavailability (53). A study of the safety and pharmacokinetics of 4 weeks of daily oral EGCG or Poly E (decaffeinated; ref. 55) found that healthy individuals can take green tea polyphenol products in amounts equivalent to the EGCG content of 8 to 16 cups of green tea and that a high daily bolus dose (800 mg EGCG or Poly E once daily) increased the systemic availability of free EGCG by >60% (55).

Cell culture studies suggest that EGCG alone is just as effective as is Poly E in inhibiting cancer cell growth. For example,

as little as 1  $\mu\text{g}/\text{mL}$  of EGCG or Poly E (containing ~65% EGCG) for 96 hours inhibited the growth of Caco2, HCT116, HT29, SW480, and SW837 colon cancer cells but had no effect on the FHC normal human fetal colon cell line (33). Poly E and EGCG alone had similar potencies to suppress EGFR and HER2 phosphorylation and downstream target activation with similar potency. Of note, as little as 1  $\mu\text{g}/\text{mL}$  of epicatechin combined with EGCG (10  $\mu\text{g}/\text{mL}$ ) had synergistic inhibitory effects on cell growth (33), suggesting an interdependency for optimal activity. Accumulating evidence from animal models strongly suggests that EGCG and perhaps other catechins are not as effective *in vivo* on their own as they are combined.

Clinical studies support the concept that combinations (such as Poly E) of chemopreventive compounds and agents may be superior to such agents used singly. Compared with purified chemicals such as erlotinib (tarceva; an EGFR inhibitor), celecoxib (a cyclooxygenase-2 inhibitor), or difluoromethylornithine (an ornithine decarboxylase inhibitor), compounds such as EGCG found in complex foods seem to be much less potent or toxic. Therefore, combinations of natural or synthetic agents for cancer prevention might be more effective and have fewer side effects because they likely will require lower doses of natural compounds such as EGCG or of molecular-targeted agents such as inhibitors of EGFR, cyclooxygenase-2, or ornithine decarboxylase. Indeed, a report by Amin et al. (56), in this issue of the journal, provides evidence that a combination of EGCG and the EGFR inhibitor erlotinib synergistically inhibited the growth of squamous cell carcinoma of the head and neck by suppressing nuclear factor- $\kappa\text{B}$  activation. Results of this type support the hypothesis that isolating single compounds such as selenium, vitamin E, and  $\beta$ -carotene may cause them to lose their potential anticancer and other beneficial effects, possibly even causing them to exhibit undesired cancer promotion effects, as in the case of  $\beta$ -carotene. Likewise, EGCG or other polyphenol chemicals may require their complex, natural combination forms to be active anticancer agents because they depend on interactions with other whole-food components for efficacy, illustrating the age-old principle—united they stand, divided they fall.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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