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Cancer therapy and prevention by green tea: role of ornithine decarboxylase

Review Article

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Summary. Green tea which is widely consumed in China, Japan and India, contains polyphenolic compounds, which account for 30% of the dry weight of the leaves. Most of the polyphenols are flavanols, of which (−)-epigallocatechin-3-gallate (EGCG) is most abundant. Epidemiological studies revealed that the incidences of stomach and prostate cancers are the lowest in the world among a population that consumes green tea on a regular basis. It has also been reported that the quantity of green tea consumed, plays an important role in reducing cancer risk and in delaying cancer outbreak and recurrence. Various systems were used to confirm anti-cancer activities of green tea and/or EGCG. These included experimental animals in which cancer was induced chemically. Cultured cells transformed chemically or by oncogenes were also used. These studies clearly demonstrated that green tea or EGCG have anticancer and cancer preventive properties. The mechanisms of these activities have also been studied in details. It has been shown that green tea and its active components interfere with signal transduction pathways. Thus the activities of various protein kinases are inhibited, the expression of nuclear proto-oncogenes declines and the activity of ornithine decarboxylase (ODC) is reduced. ODC, which catalyzes the rate-limiting step in the biosynthesis of polyamines is closely linked with cellular proliferation and carcinogenesis. Inhibitors of ODC, like α-difluoromethylornithine (DFMO) have long been used for cancer prevention and therapy. It has been suggested that polyamine depletion by green tea could offer one explanation for its anti-cancer activities.

Keywords: Amino acids – Green tea – Polyphenols – (−)-Epigallocatechin-3-gallate (EGCG) – Polyamines – Ornithine decarboxylase (ODC) – Cancer prevention – Cancer therapy

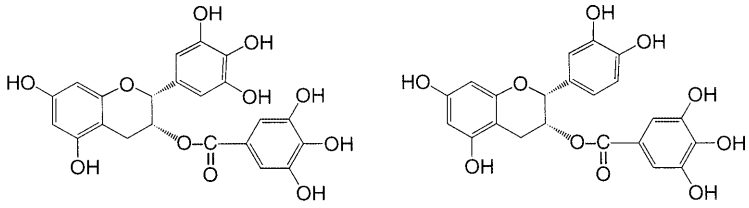
Introduction

The American Cancer Society estimated that in the 1980s more than 4.5 millions of Americans died of cancer. In addition, there were nearly 9 million new cases and about 12 million people were under medical care for cancer (Brown, 1999). Prostate cancer is the most commonly diagnosed solid tumor and is the second leading cause of cancer mortality in American men (Landis et al., 1999). According to an estimate by the American Cancer Society, approximately one fifth of the male population in the United States will develop prostate cancer during their lifetime (Jones, 1993). In modern medicine, methods to prevent disease are gaining considerable attention. The concept of treatment and prevention of cancer using naturally occurring substances that could be included in the diet became one of the foundations of the alternative medicine. Indeed, a wide array of phenolic substances, particularly those present in dietary and medicinal plants, have been reported to posses substantial anti-carcinogenic activities. These substances, which include green tea, have been used in the Far East for over 4,000 years (Weisburger, 1997), are consumed repeatedly, and apparently posses limited toxicity.

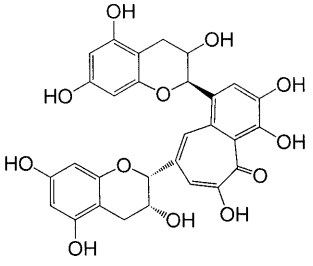
Green and black tea

The tea plant *Camellia sinensis* is native in Southeast Asia but is now cultivated in more than 30 countries around the world (Mukhtar and Ahmad, 2000). Tea is consumed world-wide. Next to water, tea is the most consumed beverage in the world. Different types of tea can be produced according to the processes of drying and fermentation. For the production of black tea, the fresh leaves are allowed to wither until the moisture is reduced to about 50% of the original leaf weight. This results in the concentration of polyphenols in the leaves (Mukhtar and Ahmad, 2000). The leaves are then rolled and crushed and the polyphenols are fermented. This results in the formation of the black tea, which is consumed in the Western countries. On the other hand, green tea is mainly consumed in China, Japan and India. Steaming freshly harvested tea leaves, causes the inactivation of enzymes which are responsible for fermentation processes. This yields a dry and a stable product, which contains most of the polyphenols and which gives the green tea its characteristic color and taste.

Green tea contains polyphenolic compounds, which account for 30% of the dry weight of the leaves. Most of the polyphenols of the green tea are flavanols, commonly known as catechins (Balentine et al., 1997). These include epicatechin, epicatechin-3-gallate, epigallocatechin and (−)-epigallocatechin-3-gallate (EGCG). These polyphenols do not occur in black tea (Fig. 1). EGCG was used in most of the studies aimed at the elucidation of the pharmacological and physiological effects of green tea.



Major Green Tea Polyphenols



Major Black Tea Polyphenol

Fig. 1. Major polyphenols of green tea and black tea

Prevention of cancer by green tea and by EGCG

Epidemiological studies demonstrated that the incidence of stomach cancer is low among tea drinkers in Shanghai (Yu et al., 1995). Similarly, the incidence of prostate cancer in China, a population that consumes green tea on a regular basis, is the lowest in the world (Gupta et al., 1999). It has been reported that in Japan the onset of cancer in females who had consumed 10 cups of green tea per day was 8.7 years later and 3.0 years later among males, compared with patients who had consumed under 3 cups per day (Fujiki et al., 1998). Japanese investigators also found that the consumption of 4–5 cups of green tea caused a decrease in the recurrence of stages I and II of breast cancer (Nakachi et al., 1998; Fujiki, 1999; Fujiki et al., 1999). To find out whether genetic or environmental factors are responsible for the reduced cancer risk among Asian tea drinkers, the incidence of breast and prostate cancer was studied among Japanese immigrants in Los Angeles. It has been shown (Shimizu et al., 1991) that for prostate cancer, the incidence rates in Los Angeles was significantly higher than that in the homeland (Japan). For breast cancer, the incidence rates in Los Angeles were also high compared with those of the homeland. The timing of immigration was important in determining breast cancer risk. These finding suggested that environmental and not genetic factors are important in the etiology of cancer among the Japanese immigrants (Shimizu et al., 1991). Consumption of green tea in Japan could certainly be one of the environmental factors, which control carcinogenesis.

The epidemiological evidence for the lower incidence of digestive tract cancers among green tea drinkers has recently been reviewed (Blot et al., 1996).

Systems used to study the mode of action of EGCG

To elucidate the mode of action of green tea, aqueous extracts of the leaves or EGCG have been used in the following systems (Table 1).

Polyamines and cancer

The naturally occurring polyamines, putrescine, spermidine and spermine are widespread in nature and they have been detected in all cells studied.

Table 1. Systems used to study the mode of action of EGCG

Human cell lines	
breast carcinoma	Valcic et al., 1996
	Liang et al., 1999b
	Chen et al., 1998
chondrosarcoma cells	Islam et al., 2000
colon carcinoma	Valcic et al., 1996
epidermal carcinoma	Liang et al., 1999a
	Ahmad et al., 1997
	Ahmad et al., 2000
glioblastoma cells	Ahn et al., 1999
	Sachinidis et al., 2000
hepatoma cells	Yu et al., 1997
leukemic cells	Asano et al., 1997
	Otsuka et al., 1998
lung tumor epithelial cell	Okabe et al., 1997
	Yang et al., 1998
	Suganuma et al., 1999
	Steele et al., 2000
lymphoid leukemic cells	Achiwa et al., 1997
	Thatte et al., 2000
melanoma	Valcic et al., 1996
prostate cells	Ahmad et al., 1997
	Paschka et al., 1998
	Gupta et al., 1999
	Lyn-Cook et al., 1999
stomach cancer	Hibasami et al., 1998
	Okabe et al., 1999
	Katdare et al., 1998
T lymphocytes	Li et al., 2000
Other cell lines	
Ehrlich acites tumor cells	Kennedy et al., 1998
	Kennedy et al., 1999
	Chen et al., 1999
	Ahn et al., 1999
mammary epithelial cells	Araki et al., 1995
mouse erythroleukemia	Lea et al., 1993

Table 1. *Continued*

pancreatic tumor cells	Lyn-Cook et al., 1999
rat glioma cells	Serenelli et al., 1997
rat hepatoma	Lea et al., 1993
rat smooth muscle	Ahn et al., 1999
Animals	
Mice	Hu et al., 1995
	Sadzuka et al., 1998
	Fujiki et al., 1998
	Conney et al., 1999
	Suganuma et al., 1998
Rats	Yamane et al., 1995
Carcinogens and oncogenes	
fibroblasts transformed by *sis*	Ahn et al., 1999
human fibroblasts transformed by SV 40 virus	Chen et al., 1998
lung neoplasia	Katiyar et al., 1993a
mouse epidermal cells transformed with H-*ras*	Chung et al., 1999
mouse epidermal cells transformed by uv	Nomura et al., 2000
mouse skin carcinogenesis	Katiyar et al., 1993b
	Hu et al., 1995
	Katiyar and Mukhtar, 1997
	Dong et al., 1997
rat colon carcinogenesis	Narisawa and Fukaura, 1993
rat stomach carcinogenesis	Yamane et al., 1995
	Yamane et al., 1996

Ornithine decarboxylase (ODC, EC 4.1.1.17), catalyzes the conversion of ornithine into putrescine (Fig. 2). This is the major rate limiting step in the biosynthesis of polyamines (Russell, 1985). Polyamines are intimately linked with growth processes; they accumulate in embryonic cells (Caldarera and Moruzzi, 1970) and their concentrations increase in cancer cells (Pegg, 1988). Similarly, the activity of ODC is high in proliferating cells (Pegg, 1986) and is elevated during chemical (O'Brien, 1976) and virus-induced malignant transformation (Don and Bachrach, 1975; Gazdar et al., 1976). Recent studies suggest that ODC can be defined as a proto-oncogene (Auvinen et al., 1992) and over-production of this enzyme resulted in malignant transformation (Hibshoosh et al., 1991; Auvinen et al., 1992; Moshier et al., 1993; Holtta et al., 1994; Shantz and Pegg, 1994). Moreover, polyamines have been shown to trigger the transformation of normal cultured cells. In the presence of polyamines, fibroblasts grew in soft agar and became anchorage independent (Tabib and Bachrach, 1998; 1999). It is therefore not surprising that various drug companies attempted the production of drugs, which would inhibit polyamine synthesis. One of them is the suicide inhibitor of ODC, α-difluoromethylornithine (DFMO), which was found to inhibit the proliferation of cancer cells (Metcalf et al., 1978) and the growth of parasites (Bacchi et al., 1980). Recent studies also suggested that DFMO can be used for chemoprevention of cancer by blocking polyamine biosynthesis (Meyskens and Gerner, 1999).

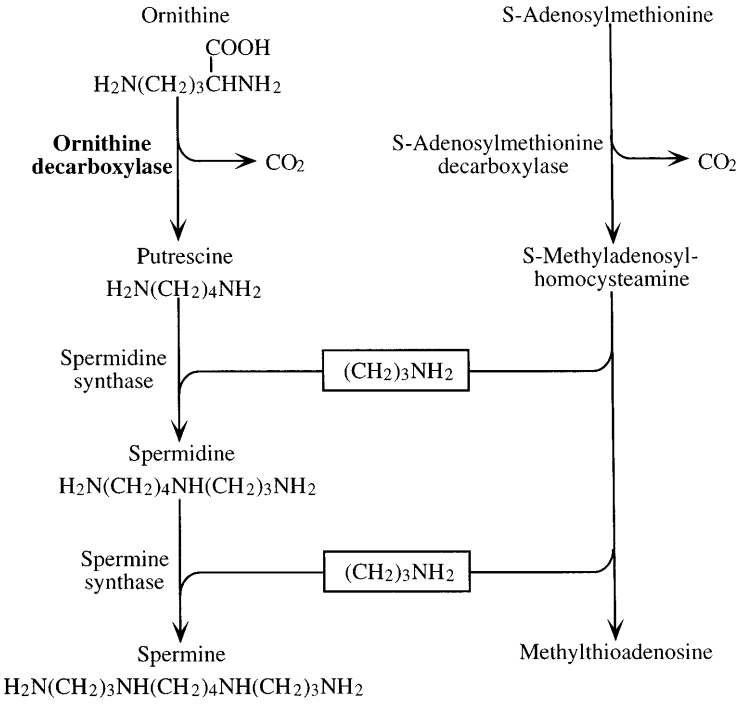


Fig. 2. Biosynthesis of the naturally occurring polyamines

Involvement of ornithine decarboxylase in cancer prevention and therapy by EGCG

As stated above, polyamines and their biosynthetic enzyme-ODC are intimately involved in carcinogenesis and in malignant growth. Inhibition of that enzyme led to cancer prevention and therapy. It could be speculated that the anticancer and the chemopreventive activities of EGCG could also be explained by inhibiting ODC activity. To test this assumption, skin tumor was induced in rodents by carcinogens. As expected the activity of ODC increased. Topical application of EGCG prevented the appearance of the tumor and inhibited the expression of ODC (Katiyar et al., 1992; Han, 1993; Hu et al., 1995; Katiyar and Mukhtar, 1997). Carcinogens were also used to induce gastric cancer in rats. Again, EGCG prevented the formation of the tumors. This was accompanied by a reduction in tissue ODC activity and in celullar spermidine levels (Yamane et al., 1995). Other studies (Agarwal et al., 1993) showed that EGCG protected hairless mice from ultraviolet induced skin carcinogenesis. This resulted in a decrease in ODC activity (Agarwal et al., 1993). A similar reductions in ODC activity by EGCG was also obtained with cultured Ehrlich ascites tumor cells (Kennedy et al., 1998), or with human lung tumor epithelial cells, treated with green but not with black tea (Steele et al., 2000).

Of special interest are the studies dealing with prostate chemoprevention by green tea (Gupta et al., 1999). Feeding mice with green tea polyphenols for

7 days abolished the typical over-production of ODC in prostate cancers. DFMO, which also inhibits ODC activity demonstrated a similar chemopreventive effect (Gupta et al., 2000). Polyamine depletion by ODC inhibition has been suggested to be a logical target for cancer prevention and inhibition (Pegg et al., 1995; Marton and Pegg, 1995). DFMO, which is a relatively nontoxic inhibitor of ODC, has been used for cancer chemoprevention. Various studies showed that oral administration of DFMO prevented colon cancer (Singh et al., 1992, 1993; Meyskens and Gerner, 1995; Meyskens et al., 1998), prostate cancer in experimental animals (Gupta et al., 2000), human skin tumor (Love et al., 1993) and cervical neoplasia in human (Nishioka et al., 1995; Mitchell et al., 1998).

Discussion

It has been well established that growth factors (mitogens) bind to specific receptors located on the cellular membrane. The mitogen-receptor complexes then trigger a cascade of events including the activation of Ras (Fig. 3). The activation of protein kinases is regarded to be the next step in signal transduction. MAPKs are phosphorylated by MAPK/ERK kinases (MEKs), which are, in turn, activated by Raf. MAPKs, next trigger the expression of the nuclear oncogenes, *myc*, *jun* and *fos* (Fig. 3), which function as transcription factors, stimulating proliferation and the expression of the ODC gene (Bello-Fernandez et al., 1993; Wrighton and Busslinger, 1993). Polyamines, which are formed by ODC, enhance the expression of protein kinases (Flamigni et al., 1999) and of nuclear oncogenes (Tabib and Bachrach, 1994). DFMO, which inhibits polyamine synthesis, prevents the expression of protein kinases (Flamigni et al., 1999) and of the nuclear oncogenes (Tabib and Bachrach, 1994). In analogy to DFMO, ECGC also inhibited MAPK activity (Chung et al., 1999). The inhibition of the syntheses of Jun and Fos by EGCG has also been reported (Okabe et al., 1999; Lu et al., 1998; Nomura et al., 2000). Unlike DFMO, green tea and/or EGCG are natural products, which can be consumed at large quantities without any harmful side effects. All these results suggest that the consumption of green tea is a practical and effective cancer preventive both before cancer onset and after cancer treatment (Suganuma et al., 1999). These considerations led to clinical trials in which the usefulness of green tea and/or EGCG in treatment of cancer was evaluated. Mukhtar and Ahmad (2000) have recently reported that the MD Anderson Cancer Center in collaboration with the Memorial Sloan-Kettering Cancer Center has conducted the clinical trials. To examine the safety of green tea, 10 cups were given daily to 30 cancer patients with advanced solid tumors. It is very likely that parallel studied will also be conducted by using EGCG instead of large quantities of green tea. If these treatments will appear beneficial, then new horizons will be opened to improve the treatment and prevention of cancer.

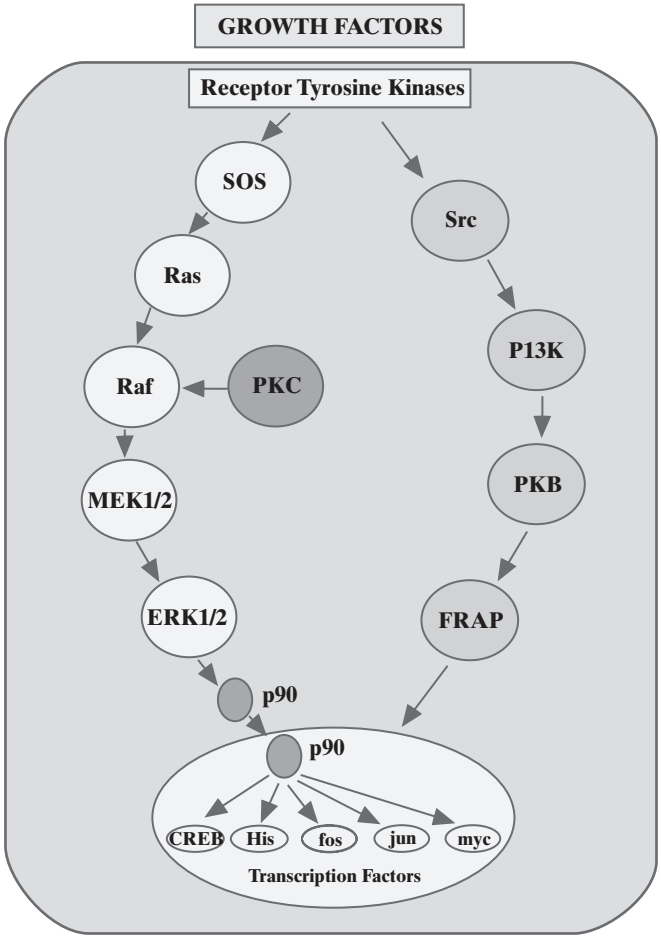


Fig. 3. Signal transduction pathway from the cellular membrane to its nucleus

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