Review

Health-promoting effects of green tea

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(Communicated by Takao SEKIYA, M.J.A.)

Abstract: Green tea is manufactured from the leaves of the plant *Camellia sinensis* Theaceae and has been regarded to possess anti-cancer, anti-obesity, anti-atherosclerotic, anti-diabetic, anti-bacterial, and anti-viral effects. Many of the beneficial effects of green tea are related to the activities of (−)-epigallocatechin gallate (EGCG), a major component of green tea catechins. For about 20 years, we have engaged in studies to reveal the biological activities and action mechanisms of green tea and EGCG. This review summarizes several lines of evidence to indicate the health-promoting properties of green tea mainly based on our own experimental findings.

Keywords: green tea, catechin, health promotion, molecular mechanism, gene expression

Introduction

Green tea (*Camellia sinensis* Theaceae) was discovered in China in 3000 BC or earlier and has been known to have various medical effects.[1)] It was brought to Japan from China by Buddhist priests over a thousand years ago. In 1211, a Japanese Zen priest, Yeisai, published the book "Kitcha-Yojoki" (Tea and Health Promotion) in which the methodology of harvesting tea leaves, production processes for tea, and pharmacological effects were described. Nowadays, scientific evidence indicates that green tea is indeed beneficial to health and many of the components of tea have specific health-promoting effects.[1)–12)] For example, tea catechins (Fig. 1), especially (−)-epigallocatechin gallate (EGCG), are considered to be associated with the anti-cancer, anti-obesity, anti-atherosclerotic, anti-diabetic, anti-bacterial, anti-viral, and anti-dental caries effects of tea. Caffeine stimulates wakefulness, decreases the sensation of fatigue, and has a diuretic effect. Theanine and γ-aminobutyric acid act to lower blood pressure and regulate brain and nerve functions. Vitamin C is an anti-scorbutic, prevents cataracts, and strengthens the immune system.

For about 20 years, we have examined the biological activities of green tea and its major polyphenolic compound catechins. In the present article, we review the health-promoting beneficial effects of green tea mainly based on our own published results.

Anti-metastatic and anti-cancer activities

Much attention has been paid to the anti-cancer activity of green tea and tea catechins with animal and cell experiments.[1)–5),7)–12)] In 1993, we reported that EGCG, the major catechins in green tea, inhibited the adhesion of cancer cells to endothelial cell layers.[13)] We also found that EGCG prevented cancer cells from attaching to fibronectin[14)] and laminin,[15)] two components of the endothelial basement membrane.[16),17)] These findings suggested green tea to have an anti-metastatic effect (Fig. 2). Indeed, we found that a green tea infusion was effective at preventing cancer cell metastasis using *in vivo* and *in vitro* models.[18)] The peroral administration of green tea infusion reduced the number of lung colonies of mouse Lewis lung carcinoma cells in a spontaneous metastasis system. The experiments with artificially reconstituted basement membrane indicated that the green tea infusion and its constituent catechins prevented cancer cells from

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Abbreviations: EGCG: (−)-epigallocatechin gallate; G6Pase: glucose-6-phosphatase; HNF: hepatocyte nuclear factor; MMP: matrix metalloproteinase; NF-κB: nuclear factor kappa B; PEPCK: phosphoenolpyruvate carboxykinase; TNF-α: tumor necrosis factor-α.

doi: 10.2183/pjab.88.88

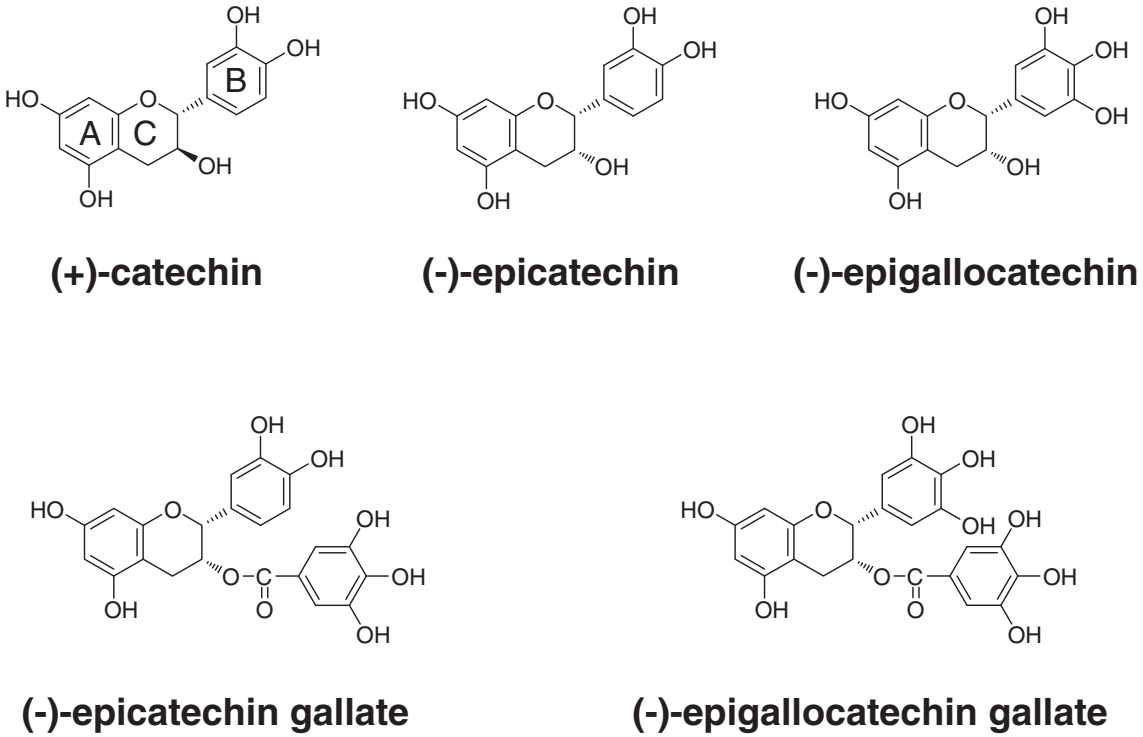

Fig. 1. Chemical structure of catechins. (−)-Epicatechin, (−)-epigallocatechin, (−)-epicatechin gallate and EGCG are major green tea catechins.

the penetration through the basement membrane. These findings were consistent with those of Taniguchi *et al.* who reported that EGCG inhibited lung metastasis in mouse B16 melanoma cell lines.[19]

Since the metastatic process includes the degradation of the basement membrane containing type IV collagen (Fig. 2), green tea catechins may inhibit collagenases or matrix metalloproteinases (MMPs). We observed that EGCG was a strong inhibitor for MMP-2 and MMP-9 derived from cancer cells[20),21] and MMP-3 (stromelysin).[22] Since EGCG binds to some proteins including fibronectin in blood plasma,[23),24] it could conceivably bind to MMPs directly to exhibit inhibitory activity. This was proven by an experiment using affinity chromatography.[20] In later experiments, we found that EGCG inhibited the gene expression of MMPs as well.[25),26]

Apoptosis is a programmed cell death and inducing apoptosis in tumor cells is a primary mechanism of action of certain anti-tumor drugs.[27),28] The anti-tumor mechanism of green tea appears to include the induction of apoptosis by EGCG through production of H_2O_2,[29] inhibition of cell-cycle progression,[30] inhibition of nuclear factor kappa B (NF-κB),[3),31] activation of the mitogen-activated protein kinase cascade[32] and binding to a 67 kDa laminin receptor.[8] In 1996, the first finding that catechins induce apoptosis was made by Hibasami *et al.*[33] in human leukemia Molt 4B cells. We observed that EGCG induced apoptosis in human lymphoma U937 cells as evidenced by the events including formation of apoptotic bodies and degradation of DNA into nucleosomal units.[34] There is a structure-function relationship in the apoptosis induction by catechins. The 5′(or 3′)-hydroxyl group in the B-ring plays an important role and a pyrogallol-type structure in a molecule is the minimum requirement for apoptosis induction[35] (see Fig. 1).

Consistent with the findings made *in vitro*, EGCG reduced numbers of colonic aberrant cryptic foci with an increase in apoptosis and enhanced the actions of the drug sulindac in an azoxymethane-induced model of colonic carcinogenesis.[36] Gupta *et al.*[37] showed that in autochthonous transgenic adenocarcinomas of the mouse prostate, oral infusion of green tea catechins inhibited prostate cancer development accompanied by enhanced apoptosis.

In addition, we have proposed that the involvement of the direct binding of EGCG to Fas, one of the death receptor proteins on the surface membrane

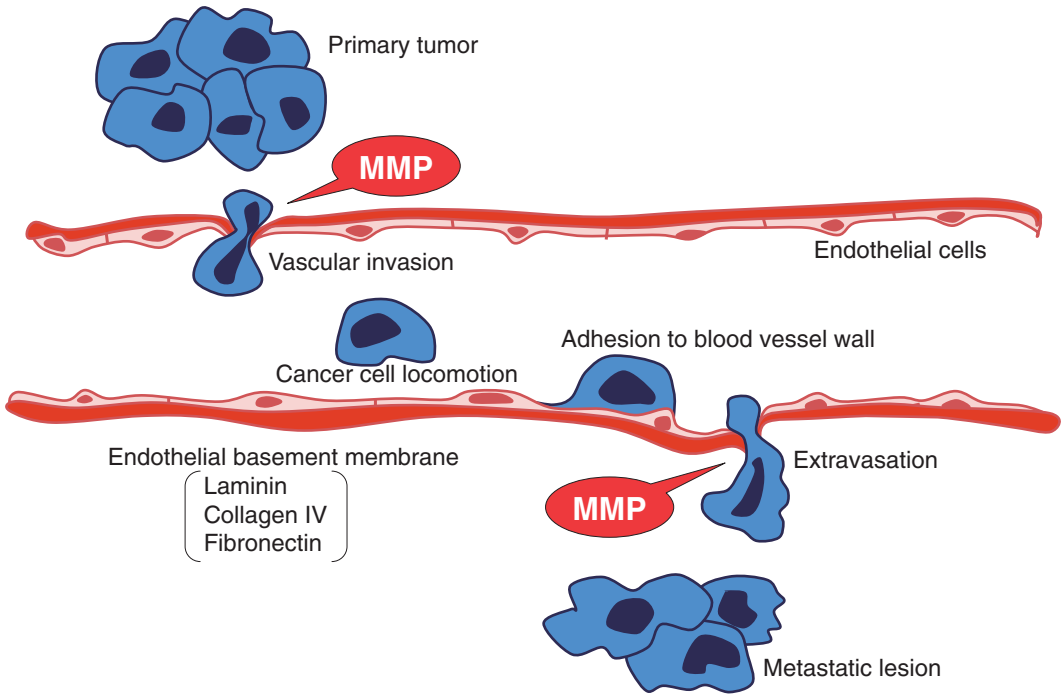

Fig. 2. A model depicting blood-borne metastasis of tumor cells. Cancer metastatic cells invade into the blood flow by degrading the endothelial basement membrane. After adhesion to the blood vessel wall, they extravasate by local degradation to form metastatic tumor colony. Tumor-associated proteinases such as MMPs have critical roles in degradation of the basement membrane containing laminin, collagen IV and fibronectin.

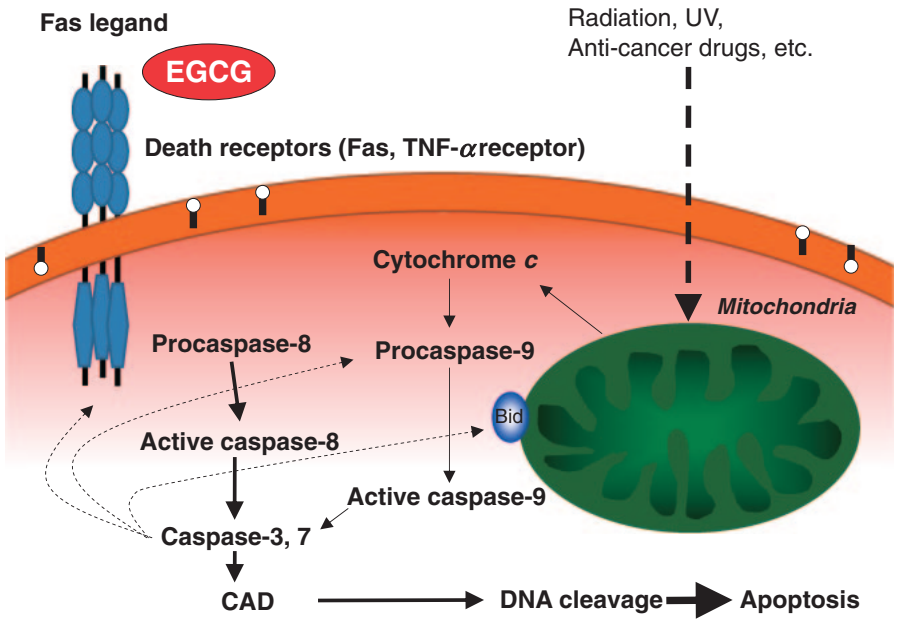

Fig. 3. A model depicting apoptosis through death receptor Fas and the action mechanism of EGCG. CAD, caspase-activated deoxyribonuclease. Binding of EGCG to Fas triggers apoptosis by activating the death receptor signaling.

of cells,[38] to initiate signal transduction for apoptosis (Fig. 3). The Fas-Fas ligand system is one of the major pathways operating in the apoptotic cascade. The EGCG treatment of human monocytic leukemia U937 cells resulted in elevation of caspase 8 activity and fragmentation of caspase 8. The DNA ladder formation caused by the EGCG treatment was inhibited by the caspase 8 inhibitor. These findings suggested the involvement of the Fas-mediated cascade in the EGCG-induced apoptosis in U937 cells. Affinity chromatography revealed the binding between EGCG and Fas. Thus, the results suggest that EGCG-binding to cell surface Fas triggers the Fas-mediated apoptosis in U937 cells. This study was the first to demonstrate that EGCG binds to cell surface protein to exert its biological action and confirmed the usefulness of affinity chromatography with EGCG immobilized on Sepharose 4B to find out the EGCG-binding proteins as used to identify those in serum.[23] The method was successfully used in several later studies to identify proteins involved in EGCG-mediated growth inhibition and apoptosis of cancer cells.[39)–44)] Recently, an alternate method using agarose-bound *m*-aminophenylsulfonyl boronic acid has been developed to search for EGCG-binding proteins.[45] Its use in combination with reduction-oxidation cycling staining made it possible to visualize EGCG-binding proteins. These methods[23),45)] have provided evidence that EGCG binds to several intracellular proteins such as vimentin and the ATP-dependent RNA helicase DDX5, indicating that EGCG can enter into the cell.

It has been well documented that cancer cells are more susceptible to apoptosis induced by EGCG than normal counterparts.[46),47)] There is a possibility that normal cells express larger amounts of several EGCG-binding, Fas-like *decoy* proteins on the cell surface than cancer cells, leading to a diminution in the concentration of EGCG available to bind Fas, resulting in resistance to apoptosis.[48] We also showed that differentiated HL-60 cells were resistant to EGCG-induced apoptosis as compared with undifferentiated cells, suggesting that EGCG induces apoptosis selectively in cancer cells.[49] However, the change in the expression of cell surface Fas-like *decoy* proteins after differentiation has yet to be examined.

The EGCG-induced change in the redox state of cancer cells[32] may also be involved in the mechanism. It is important to point out that green tea contains a high molecular weight fraction which induces apoptosis in cancer cells by a mechanism including cell cycle arrest.[50),51)] Thus, our results support the view that drinking green tea is useful to prevent cancer.

Epidemiological and intervention studies are important to reveal the anti-cancer effects of green tea and catechins. The first impressive result was reported in 1989 by Oguni *et al.*[52] who described that the rate of death from stomach cancer in males of the town of Nakakawane was about one fifth of the average for Japanese males overall and that this low rate might be related to the consumption of green tea. Later, it was reported that tea consumption did not correlate to the risk of stomach cancer.[53),54)] However, other studies revealed an inverse association between green tea consumption and distal gastric cancer among Japanese women[55] and a reduced risk of stomach cancer with intake of green tea.[56] The discrepancy in results may arise from factors such as differences in the type of tea consumed, in cancer etiology, in confounding lifestyle, and in genetic factors. Future epidemiological studies should include a measurement of urinary tea polyphenols, including epigallocatechin and epicatechin, and their respective metabolites to provide more reliable data on the relationship between tea consumption and cancer risk as exemplified by the study of Sun *et al.*[2]

More convincing data for the effects of green tea were presented by Bettuzzi *et al.*[57] who conducted a clinical trial to assess the safety and efficacy of green tea catechins for the chemoprevention of prostate cancer in individuals with high-grade prostate intraepithelial neoplasias. After 1 year of daily treatment consisting of three capsules containing 200 mg of catechin, only one tumor was diagnosed among the 30 catechin-treated men, whereas 9 cancers were found among the 30 placebo-treated men. Recently, a 15% ointment of Polyphenon® E, a defined extract of green tea catechins, proved to be efficacious and safe in the treatment of external genital warts which are non-malignant squamous cell tumors caused by infections of human papilloma viruses.[58),59)] These findings are encouraging further clinical studies on chemopreventive effects of green tea catechins.

Hepatoprotective effects

Galactosamine is known to induce hepatic injury in rats that is similar in pathophysiology to viral hepatitis and drug-induced hepatitis in humans.[60] Green tea has been shown to suppress galactosamine-induced liver injury in rats[61),62)] and one of the active components was identified as glycosidic flavonoids.[62] In our study, intraperitoneal injection of galactos-

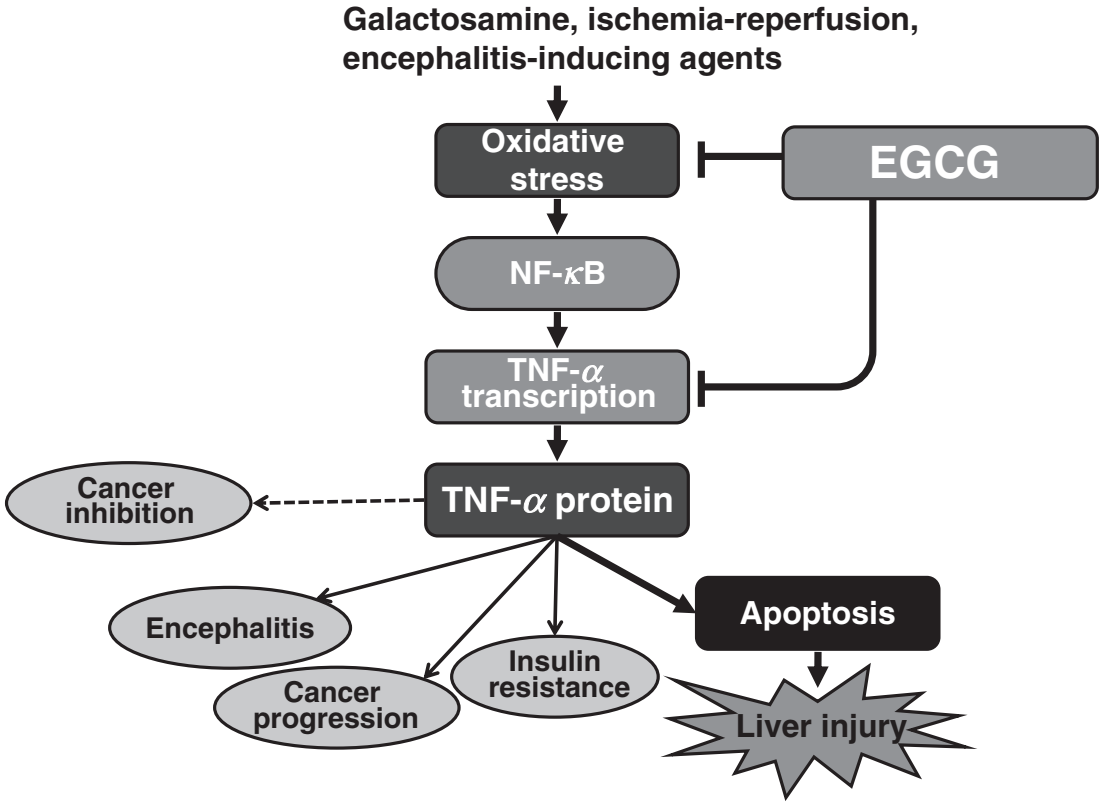

Fig. 4. The action mechanism of EGCG through inhibition of gene and protein expression of TNF-α. Liver injury induced with galactosamine or ischemia-reperfusion and encephalitis induced with proteolipid protein 139–151 are prevented by EGCG by reducing oxidative stress and/or decreasing TNF-α transcription. Anti-cancer effects of EGCG may include its suppression of TNF-α gene expression. EGCG may also have beneficial effects on TNF-α-associated diseases such as diabetes.

amine (500 mg/kg) induced liver injury with necrosis in rats and the oral administration of green tea rich in catechins inhibited the galactosamine's action. Green tea restored levels of several biomarkers in galactosamine-treated rats to near control values.[63] These biomarkers included serum transaminase activities, serum concentrations of tumor necrosis factor-α (TNF-α) and interleukin 1-β, and the hepatic mRNA expression of these inflammatory cytokines. The serum concentration in green tea-treated rats was about 55% of rats untreated after galactosamine injection. Since apoptosis of liver cells is involved in galactosamine-induced liver injury[64] and TNF-α induces apoptosis,[65] modulation of TNF-α appears to be a key action of EGCG (Fig. 4).

Hepatic ischemia-reperfusion activates Kupffer cells and initiates severe oxidative stress with enhanced production of reactive oxygen species (ROS) and TNF-α. Giakoustidis *et al.*[66] reported the hepatoprotective effect of EGCG in rats by inhibiting apoptosis through attenuation of the expression of NF-κB, c-Jun, and caspase-3 in an experimental model of severe hepatic ischemia-reperfusion. Similarly, Okabe *et al.*[65] demonstrated that green tea catechins induced growth inhibition and apoptosis by reducing TNF-α gene expression and TNF-α release, using the human stomach cancer cell line KATO III (Fig. 4). The EGCG's action to suppress TNF-α expression may also have beneficial effect on diabetes, since TNF-α is involved in developing diabetes.[67]

We also found that catechin-rich green tea prevented liver fibrosis after hepatic injury induced by galactosamine through the down-regulation of the gene expression of collagens.[68] Thus, green tea appears to have hepatoprotective effects. From a clinical point of view, the application of catechins to therapy for hepatitis C appears to be promising.[69] However, it should be noted that hepatotoxicity associated with supplements containing green tea has been reported,[70] although animal experiments showed no evidence of characteristic hepatotoxicity

in rats treated with very large amounts of different green tea extracts.[71]

Anti-diabetic effects

Research into the relationship between green tea and obesity-related insulin resistance syndrome has shown that green tea enhances insulin activity *in vitro*,[72] enhances insulin sensitivity in human subjects[73] and rats,[74] and reduces hypertriacylglycerolaemia in mice.[75] One of the hallmarks of diabetes is the inability of insulin to inhibit hepatic glucose production.[76] Increased gluconeogenesis is a main source of increased hepatic glucose production and the ability of insulin to regulate transcription of the rate-controlling gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), may contribute to this problem.

In experiments using rat hepatoma H4IIE cells, EGCG was shown to mimic the cellular effects of insulin including the reductive effect on the gene expression of these gluconeogenic enzymes.[76] It is very important to know whether or not such finding *in vitro* is relevant to the *in vivo* situation. We demonstrated that administration of EGCG caused a reduction in the level of mRNAs for these gluconeogenic enzymes in the mouse liver.[77] Green tea was also shown to down-regulate the gene expression of these gluconeogenic enzymes.[77] Wolfram *et al.*[78] reported a pronounced decrease of glucose levels in food-deprived db/db mice treated with EGCG. The results for gene expression in liver and adipose tissues of db/db mice supplemented with EGCG for 7 weeks showed that PEPCK expression was significantly down-regulated in the adipose tissue, although the down-regulation was not significant statistically in the liver.

Our recent findings indicate that EGCG down-regulates the gene expression of these gluconeogenic enzymes by reducing the gene and protein expression of hepatocyte nuclear factor (HNF)4α, a key transcription factor for PEPCK and G6Pase[79] (Fig. 5). Insulin is known to reduce the protein expression of HNF4α[80] and, therefore, EGCG has an insulin-mimetic property in this sense. EGCG also reduced the intestinal expression of these gluconeogenic enzymes in association with the down-regulation of HNF4α and HNF1α.[81]

In a more recent study, we showed that an EGCG-free fraction derived from a green tea infusion had effects similar to those of EGCG.[82] The hot water infusion of green tea leaves was separated into an ethanol-soluble fraction and an EGCG-free water-soluble fraction (GT-W). GT-W reduced the gene expression of G6Pase and PEPCK in H4IIE cells and caused a decrease in expression of the transcription factor HNF4α. Reduced levels of PEPCK and HNF4α proteins were demonstrated in the cells treated with GT-W. Administration of GT-W to mice for 4 weeks reduced the hepatic expression of G6Pase, PEPCK, and HNF4α. However, the action mechanism appears different because EGCG's action was attenuated by a reducing agent, *N*-acetylcysteine,[82] suggesting a change in the redox state of the cells to be involved, whereas the activity of GT-W was not affected by this agent.[83] These results suggest that green tea consumption and dietary supplementation with EGCG could potentially contribute to nutritional strategies for the prevention and treatment of type 2 diabetes mellitus through their effects to reduce the fasting blood glucose concentration by down-regulating the hepatic gene expression of gluconeogenic enzymes.[76),78]

A recent large-scale retrospective cohort study revealed that consumption of green tea, coffee, and total caffeine was associated with a reduced risk for type 2 diabetes mellitus.[84] Panagiotakos *et al.*[85] reported that long-term tea intake was associated with reduced levels of fasting blood glucose and a lower prevalence of diabetes, in a cohort of elderly people living on Mediterranean islands.

Anti-obesity and anti-atherosclerotic effects

In the book "Yojokun" published in the Edo period, Ekiken Kaibara described that according to the ancient Chinese medical doctor, long-term drinking of green tea would result in a lean body by removing body fat. Evidence has accumulated to show that the ingestion of green tea and tea catechins leads to a reduction in body fat as described in recent reviews.[86)–88] The stimulation of hepatic lipid metabolism might be a factor responsible for the anti-obesity effects of tea catechins. Tea catechins are suggested to inhibit cell growth by suppressing lipogenesis in human MCF-7 breast cancer cells through down-regulation of fatty acid synthase gene expression in the nucleus and stimulation of cell energy expenditure in the mitochondria.[89] The experimental data indicated that the suppression of fatty acid synthase gene expression by tea polyphenols may lead to down-regulation of EGFR/PI3K/Akt/Sp-1 signal transduction.

In addition to EGCG's effects described above, we observed that oral administration of an EGCG-

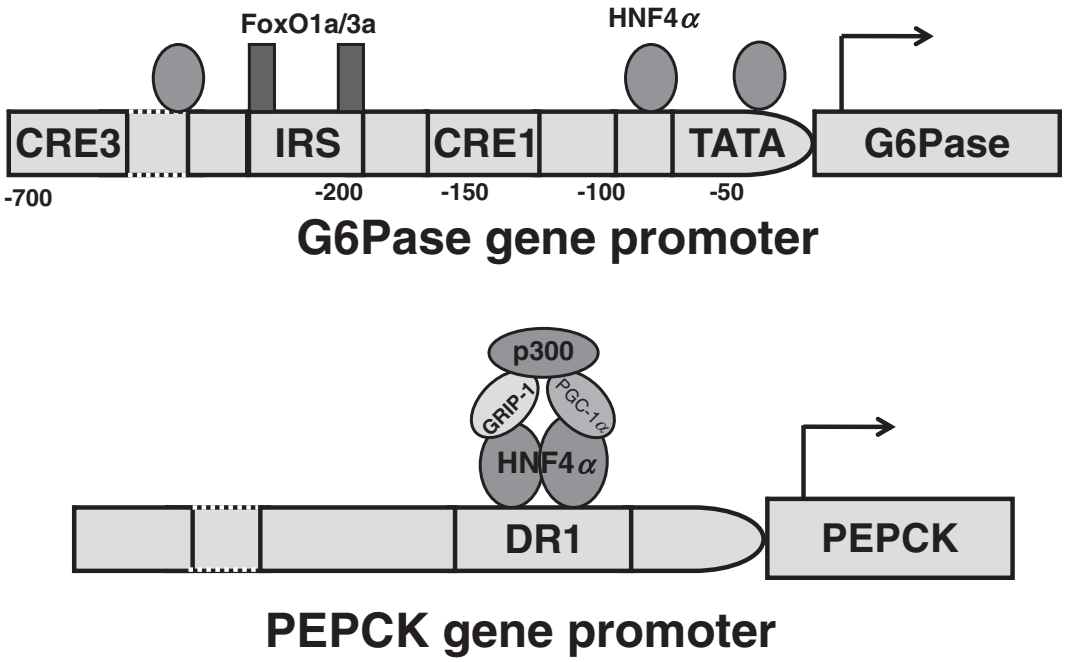

Fig. 5. HNF4α-mediated gene expression of gluconeogenic enzymes. The G6Pase gene promoter contains three HNF4α binding sites and the PEPCK gene promoter has the binding site of its dimer to which several co-factors bind. CRE, cyclic AMP responsive element; DR, direct repeat spaced by one nucleotide; FoxO, forkhead/winged helix box gene group O; GRIP, glucocorticoid receptor-interacting protein; IRS, insulin response sequence; PGC, peroxisome proliferator-activated receptor-γ coactivator.

free green tea fraction reduced the hepatic gene expression of PEPCK and G6Pase.[83] This fraction also reduced the hepatic gene expression of lipogenic enzymes such as fatty acid synthase, 4-hydroxymethylglutaryl CoA reductase, acetyl CoA carboxylase α, and ATP-citrate lyase in association with the reduced gene expression of sterol response element-binding factor (SREBF)-1 and SREBF-2, key transcription factors for the gene expression of lipogenic enzymes[90] (Fig. 6). In accordance with the results for these changes in hepatic gene expression of lipogenic enzymes, the plasma levels of triglycerides and cholesterol of mice given a diet containing the EGCG-free fraction were significantly reduced[90] (Table 1). The plasma glucose levels were not altered significantly, but tended to be reduced (Table 1). Thus, green tea contains some component(s) other than catechins which may have anti-obesity and anti-atherosclerotic effects.

Anti-atherosclerotic effects of catechins have often been reported. For example, Muramatsu *et al.*[91] found that tea catechins decreased plasma total cholesterol, cholesterol ester, and total cholesterol-HDL-cholesterol (VIDL-+LDL-cholesterol) levels and lowered the atherogenic index (VLDL-+LDL-cholesterol/HDL-cholesterol), indicating that they exert a hypocholesterolemic effect, in cholesterol-fed rats. Catechins have been shown to prevent vascular smooth muscle cell invasion by inhibiting MT1-MMP activity and MMP-2 expression.[92] The ability of green tea to prevent cell invasion and matrix degradation might contribute to its protective effect on atherosclerosis and cancer.

A recent report has revealed a potential role for green tea in the prevention of cardiovascular disease.[93] A population-based, prospective cohort study initiated in 1994 among 40,530 Japanese adults aged 40 to 79 years without a history of stroke, coronary heart disease, or cancer at baseline indicated that over 11 years of follow-up, 4209 participants died, and over 7 years of follow-up, 892 participants died of cardiovascular disease and 1134 participants died of cancer. The results of statistical analyses indicated that green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease.

Other effects

It was shown that EGCG suppressed experimental autoimmune encephalomyelitis induced by proteolipid protein 139–151 in mice.[94] EGCG reduced clinical severity when given at initiation or after the

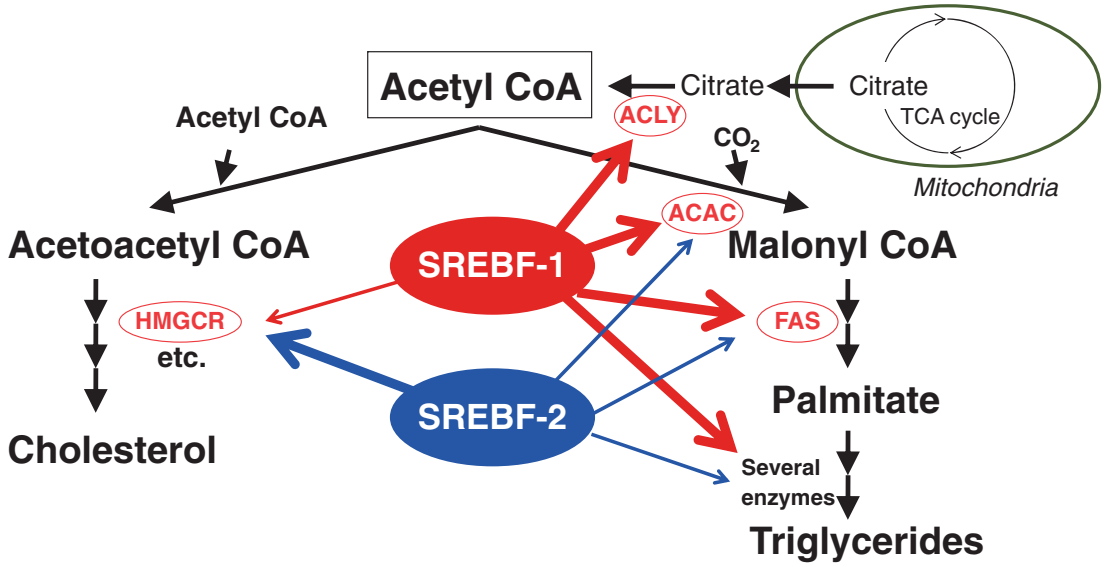

Fig. 6. Central roles of sterol response element-binding factors (SREBFs) in lipogenesis. Colored thick and thin lines represent the major and minor sites of action for SREBF-1 and SREBF-2, respectively. ACLY, ATP-citrate lyase; ACAC, acetyl CoA carboxylase; FAS, fatty acid synthase; HMGCR, 4-hydroxymethylglutaryl CoA reductase; TCA, citric acid cycle.

Table 1. Effects of a diet containing an EGCG-free green tea fraction on plasma levels of glucose, triglycerides and cholesterol

	0%	0.2%	0.5%
Glucose (mg/dl)	165.2 ± 9.1	152.5 ± 1.3	144.6 ± 6.9
Triglycerides (mg/dl)	164.7 ± 20.1	128.94 ± 10.4	101.13 ± 10.2*
Cholesterol (mg/dl)	107.8 ± 3.7	94.24 ± 2.4*	92.18 ± 2.7*

The plasma levels were determined for the mice (n = 5) given a diet containing 0.2% or 0.5% of an EGCG-free fraction derived from green tea and compared with those of control mice given a normal diet.[87] The results are expressed as the mean ± standard error of 3 determinations. *Significantly different from the control at $p < 0.05$.

onset of encephalomyelitis by both limiting brain inflammation and reducing neuronal damage. Mice given EGCG orally showed abrogated proliferation and TNF-α production in encephalitogenic T cells. Proposed models for signal transduction pathways modified by EGCG include: EGCG is capable of inhibiting both catalytic activities of the proteasome, including the activation of NF-κB, and the amount of ROS produced (Fig. 4). In lymphocytes, this leads to decreased proliferation and production of TNF-α, while in neurons, it results in less damage. Additionally, the antioxidative effects of EGCG on neurons might involve the NF-κB pathway as well, since an oxidative stress can induce production of NF-κB, which regulates the expression of a variety of factors contributing to cell proliferation, inflammation, and neuronal damage. Thus, a natural green tea constituent may open up a new therapeutic avenue for young disabled adults with inflammatory brain disease by combining, on the one hand, anti-inflammatory and, on the other, neuroprotective capacities.

Rezai-Zadeh *et al.*[95] showed that EGCG modulated cleavage of the amyloid precursor protein and reduced cerebral amyloidosis in Alzheimer transgenic mice. Daily consumption of green tea catechins may delay memory regression in aged mice as shown by Unno *et al.*[96] Thus, green tea catechins are expected to have beneficial effects on brain functions. A recent epidemiological study has indicated that consumption of green tea is associated with a lower prevalence of cognitive impairment in humans.[97]

Methylated EGCG ((−)-epigallocatechin 3-*O*-(3-*O*-methyl) gallate) was demonstrated to inhibit degranulation from cells that had been stimulated with the calcium ionophore A23187 in the human basophilic cell line KU812.[8),98] This result indicates that methylation of EGCG may be an effective means of modifying catechins to inhibit degranulation from human basophils and prevent clinical symptoms. In addition, EGCG and methylated EGCG were shown to have the ability to down-regulate Fc epsilon RI expression, and this suppressive effect may be due to a reduction of FcεRIα and γ mRNA levels.[8),99),100] However, caution is

needed for human application since EGCG has been identified as a causative agent in patients with green tea-induced asthma.[101)]

Theanine and γ-aminobutyric acid are also characteristic components of green tea. Using an *in vivo* brain microdialysis method, Yamada *et al.*[102)] demonstrated that theanine affects the release of neurotransmitters in the rat striatum. Recently, theanine was reported to enhance the synthesis of nerve growth factor and neurotransmitters during a nerve maturing period and promote maturation of the central nervous system.[103)] Electroencephalograms of volunteers who received 200 mg of theanine revealed the generation of α wave activity suggesting relaxation. γ-Aminobutyric acid is perhaps the most important inhibitory neurotransmitter in the brain, and its intake will affect brain functions. Thus, effects on brain function are a very important target for future investigations of green tea.

Conclusion

Modern scientific techniques have given the basis for the health-promoting effects of green tea, which have been recognized from ancient times. Many of the action mechanisms of green tea and its constituent EGCG are now known. For example, EGCG binds several enzyme proteins to inhibit their activities, induces oxidative stress in cells, and initiate signal transduction by binding to cell surface proteins. Our recent studies revealed that green tea and EGCG may cause changes in the mRNA levels of gluconeogenic and lipogenic enzymes by changing the expression levels of the respective transcription factors, HNFs and SREBFs. However, these findings pose new questions on the mechanism of how green tea and its constituents can induce changes in the level of the transcription factors. In addition, we demonstrated that an EGCG-free fraction of green tea had certain health-promoting effects, but the active entity remains to be determined. Although these and other questions await future investigations, epidemiological studies seem to indicate that ingestion of green tea contributes to human health-promotion. Future clinical intervention studies will provide more convincing evidence for effects of green tea.

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(Received Oct. 30, 2011; accepted Jan. 6, 2012)

Profile

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