Review Article

Prevention of obesity-associated colon cancer by (-)-epigallocatechin-3 gallate and curcumin

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Abstract: Obesity is now recognised as a major global health problem. It accounts for a large proportion of the population and is increasing in both developed and developing countries. Epidemiological evidence and studies in animal models showed that obesity increased the incidence of colon cancer. As obesity is difficult to prevent and treat, it is important to find effective approaches to prevent obesity-associated colon cancer. The prevention strategy should be different from that used for the treatment as clinically used drugs are not suitable for the prevention due to side-effects and cost. Phytochemicals are ideal for the prevention. This review summarises the effect of green tea component (-)-epigallocatechin-3 gallate and turmeric component curcumin in the prevention of obesity-associated colon cancer and the mechanisms for their preventive effects. Both agents have been demonstrated to reduce obesity increased polyp formation in animal models and inhibit PI3K/Akt and MAPK signal pathways.

Key Words: Obesity; colon cancer; (-)-epigallocatechin-3 gallate; curcumin; phosphoinositide 3-kinase/protein kinase B (PI3K/Akt); mitogen activated protein kinase (MAPK)

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Introduction

Obesity is now recognised as a major global health problem. It accounts for a large proportion of the population and is increasing in both developed and developing countries. Obesity can cause many co-morbidities including cancer, heart disease, osteoarthritis and diabetes (1-8). Among them, obesity-associated colon cancer has been studied extensively. Several epidemiological studies showed that obesity increased the incidence of colon cancer (9,10). This is further demonstrated in animal models. Two common animal models have been employed in colon cancer study: genetic defect model - *Apc*$^{min/-}$ and chemical azoxymethane (AOM)-induced colon polyp model (11,12). Obesity has been demonstrated to increase colon polyp formation in both models (13,14).

As it is difficult to prevent or treat obesity at present, prevention of obesity-associated colon is an important issue. To be able to prevent obesity-associated colon cancer, it would be great helpful to understand the mechanisms of the disease. Indeed, the mechanisms for obesity-associated colon cancer are now partially elucidated. It is known that multiple cancer risk factors that are increased in obesity are responsible for increased incidence of colon cancer cancer (1,15,16). The main increased risk factors include elevated levels of insulin, insulin-like growth factor-1 (IGF-1), leptin, interleukin (IL)-6, IL-17, tumor necrosis factor (TNF)-alpha and decreased levels of adiponection (14,17-24). These factors in turn cause activation of multiple signal pathways which play key roles in obesity-associated colon cancer such as, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) (25,26). Thus, inhibition of these factors and associated pathways can be used to prevent or treat obesity-associated colon cancer (27,28). Although many approaches can be used to

inhibit these pathways, phytochemicals may be the best to be used for the prevention due to low side-effects and low cost. This review focuses on the effects of green tea component (-)-epigallocatechin-3 gallate (EGCG) and turmeric component curcumin in the prevention of obesity-associated colon cancer and the mechanisms for such effects.

Signalling pathways in the initiation of obesity-associated colon cancer and prevention implications

Several studies showed that the PI3K/Akt pathway play a key role in obesity-associated colon cancer (25). A most recent study demonstrated the importance of the PI3K/Akt and MAPK in the initiation of obesity -associated colon cancer in A/J mice (29). High-fat diet was shown to increase AOM-induced colon carcinogenesis. In these mice, the activity of the PI3K/Akt pathway is increased as detected by phosphorylated Akt. Activation of MAPK pathway is indicated by p-ErK1/2. In addition, anti-apoptotic protein bcl-xl and cell cycle regulator cyclin D1 are increased. This study thus demonstrated that both pathways are important in the initiation of obesity-associated colon cancer and provide the basis for the prevention of obesity-associated colon cancer.

Various approaches have been used to inhibit these signalling pathways to prevent obesity-associated cancer. In energy restrict model, it has been shown that 30% decrease in energy could decrease AOM-induced polyp numbers markedly (30). Calorie restrict reduced IGF-1 and associated signal pathways (31). An angiotensin-converting enzyme (ACE) inhibitor captopril and angiotensin-II type 1 receptor blocker (ARB) telmisartan can also decrease AOM-induced colon cancer in obese mouse model (32). Pitvastatin and branch amino acids are effective in the prevention of colon cancer in db/db obese model (33,34). However, clinic drugs may be not practical to be used for the prevestion of obesity-associated colon cancer as they are expensive and have side-effects. Alternatively, phytochemicals may be ideal for prevention.

Effects of phytochemicals on obesity-associated colon cancer

Phytochemicals have been studied extensively for the prevention of cancer. It has been estimated that phytochemicals can reduce cancer risk as much as 20% via inhibition of cell cycle and increase of apoptosis as well as increase of host immune responses (35). Several phytochemicals have been shown to be effective on the prevention of obesity-associated colon cancer. Eskin *et al.* demonstrated that mustard mucilage was shown to inhibit obesity-associated colon cancer (36). A meta-analysis showed that coffee consumption decreased the incidence of colon cancer (37,38). Flavonoids (chrysin, quercetin and nobiletin) is also effective in AOM/db/db model (39). The effects of EGCG and curcumin are decribed in details in below sections.

EGCG

Green tea, made from the leaves of the plant *Camellia sinensis*, is a common beverage in China for thousands of years and now is popular worldwide. Many health beneficial properties of green tea have been revealed such as anti-inflammatry, anti-hypertensive, hypocholesterolemic, hypoglycemic, antidiabetic and anti-carcinogenic effects (40-43). The components of green tea include polyphenolic compounds (catechins): EGCG, (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC), and flavonols: quercetin, kaempferol and myricitin (44). EGCG is a main component of green tea and has been studied extensively in the prevention of cancer (45).

The preventive effect of green tea and EGCG in colon cancer carcinogenesis has been demonstrated in both *Apc*$^{min/-}$ and AOM animal models. Green tea extract alone or in combination with sulindac reduced intestinal tumour formation via down-regulation of beta-catenin in *Apc*$^{min/-}$ mouse model (12,46). Ju *et al.* showed that EGCG can effectively prevent colon cancer carcinogenesis in this model (47). EGCG was also demonstrated to reduce polyp formation in AOM model of colon cancer (48,49).

Several studies have extended the study of EGCG to prevent obesity-associated colon cancer. Shimiz *et al.* showed that EGCG at concentrations 0.01% or 0.1% in drinking water significantly decreased the number of total aberrant crypt foci induced by AOM in obese C57BL/KsJ-db/db mice, via reduction of beta-catenin (50). High-fat diet feeding is a common model for obesity-associated cancer which has been shown to increase colon cancer incidence. Ju *et al.* showed that 0.6% of EGCG in drinking water reduced AOM-induced abbarrant crypt foci formation in high-fat diet induced obese mice (51).

The mechanisms for the preventive effect of EGCG on carcinogenesis have been elucidated to be its properties to inhibit multiple signal pathways (52). EGCG can inhibit both PI3K/Akt and MAPK pathways (47) (*Figure 1*), which

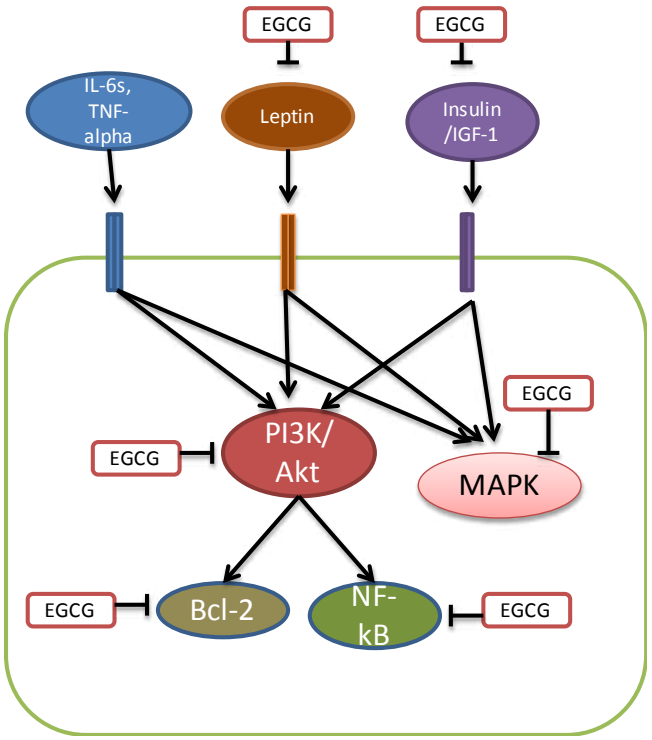

Figure 1 The effect of EGCG on signal pathways in obesity-associated colon cancer. EGCG inhibits multiple components of cancer risk factors and associated signal pathways inobesity-associated colon cancer. It reduces leptin and insulin/IGF-1 levels and inhibits PI3K/Akt, MAPK, bcl-2 and NF-κB. Abbreviation: EGCG, (-)-epigallocatechin-3 gallate; IL6, interleukin 6; IGF-1, insulin-like growth factor-1; PI3K/Akt, phosphoinositide 3-kinase/ protein kinase B; MAPK, mitogen activated protein kinase; bcl-2, B-cell lymphoma 2; NF-κB, nuclear factor-kappaB

are important in obesity-associated colon cancer. EGCG also interacts directly with the PI3K downsteam target bcl-2, an anti-apoptotic protein (53,54). EGCG can inhibit NF-κB, a transcriptional factor, also a downstream target of the PI3K/Akt pathway (55). Therefore, EGCG can cause cell cycle arrest (56). The effects of EGCG on cancer risk factors increased in obesity include increasing serum level of IGFBP-3, decreasing the serum levels of IGF-I, insulin and leptin. Therefore, EGCG can inhibit activated signal pathways of obesity-associated colon cancer at multiple points (50).

Curcumin

Tumeric, derived from the plant *Curcuma longa L* of the Zingiberaceae family, has been used as a medicinal agent for thousands of years in Asian countries (57,58). Curcumin is a major component of the spice turmeric which has similar chemical structure of aspirin, a well known chemical that can prevent carcinogenesis (59).

In vitro studies, curcumin has been shown to decrease proliferation and increase apoptosis in several colon cancer cell lines. Addition of curcumin at the concentration of 50 μM to cultured colon cancer cell line HT29 induced apoptosis (60-62). Curcumin was also shown to effectively inhibit the growth of HCT116 cells that survived through fluorouracil and oxaliplatin treatment (63,64). Wei *et al.* tested the effect of curcumin on 5 cell lines SW480, HCT116, LoVo, SW48, HCT15 and demonstrated it caused apoptosis in all these cells (65). The preventive effect of curcumin on colon cancer has been confirmed in animal models of colon cancer (66).

It has been demonstrated that curcumin can inhibit tumour initiation in obese animal models. Pettan-Brewer *et al.* showed that diet containing 35% of fat increase polyp number by 23% and 0.5% curcumin reversed the high-fat accelerated polyp formation in an $Apc^{min/-}$ mouse model (67). Curcumin increased apoptosis and DNA repair. It also reduced high-fat induced weight gain in the model. The anti-obesity property of curcumin (57,68) could also mediate its preventive effect on obesity-associated colon cancer. Kubota investigated the effect of curcumin in C57BL/KsJ-db/db obese mice in AOM model and found that 0.2% and 2% curcumin feeding reduced polyp formation markedly (69-71).

The mechanisms for the protective effect of curcumin on carcinogensis in obesity-associated colon cancer are multiple. Curcumin can inhibit MAPK and Akt pathways (63) (*Figure 2*). It has been shown to reduce TNF-alpha-induced NF-κB. Curcumin reduced levels of TNF-alpha, IL-6, IGF-1 receptor and cyclooxygenase-2 (COX2) mRNA (63). Cox-2 was considered to be a good target for the prevention of colon cancer (72). Indeed, increased Cox-2 is also involved in obesity-associated colon cancer (73). In addition, curcumin reduces inflammation in obesity (74).

Curcumin is not well dissolved in water and this limits its bioavailability. Nanotechnology has been used to increase its bioavailability and a polymeric nanocarrier-curcumin (PNCC) has been used for colon cancer prevention in AOM-induced tumours in rats (75). PNCC markedly reduced tumour number and size with decreased cell proliferation and increased apoptosis. The study showed that beta-catennin and Bcl-2 proteins were decreased and Bax protein was increased. Several curcumin analogues have

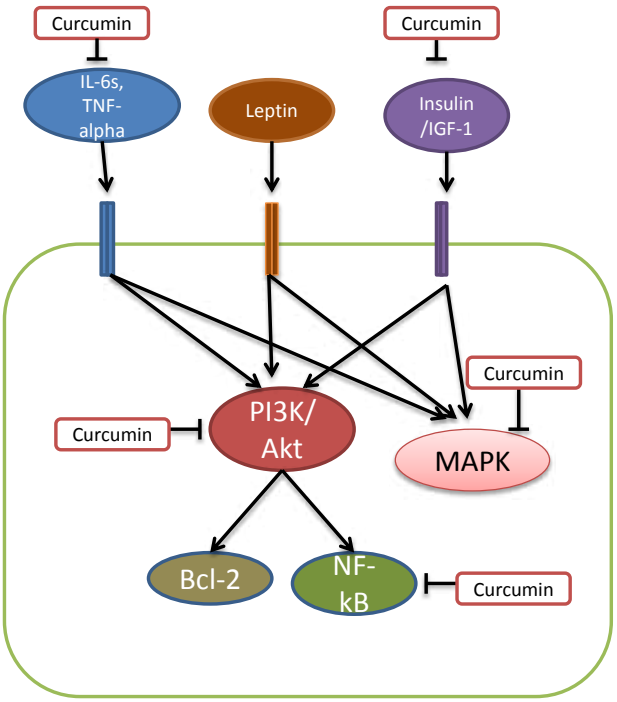

Figure 2 The effect of curcumin on signal pathways in obesity-associated colon cancer. The figure shows that curcumin reduces IL-6, TNF-alpha leptin and insulin/IGF-1 levels and inhibits PI3K/Akt, MAPK and NF-κB. Abbreviation: EGCG, (-)-epigallocatechin-3 gallate; IL6, interleukin 6; IGF-1, insulin-like growth factor-1; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; MAPK, mitogen activated protein kinase; bcl-2, B-cell lymphoma 2; NF-κB, nuclear factor-kappaB

also been developed to increase its effectiveness (76-79).

Combinatorial implications of EGCG and curcumin

As both EGCG and curcumin have preventive effects on obesity-associated colon cancer, it is interesting to investigate whether combination of both agents has synergistic effect. Indeed, two studies have revealed the synergistic effect of EGCG and curcumin. Manikandan showed that EGCG and curcumin produced highest levels of inhibitory effect on HCT15 and HCT116 cells in combination although EGCG and curcumin can cause apoptosis individually (38). Kondo *et al.* also showed that EGCG significantly lowed the dose needed for curcumin to inhibit pAkt/mTOR pathway (80). Further studies are needed to characterise the effect of combinatorial use of EGCG and curcumin on obesity-associated colon cancer and on the key signalling molecules.

Conclusions

Both EGCG and curcumin have been demonstrated to have preventive effects on obesity-associated colon cancer. The mechanisms are their properties to inhibit multiple signalling pathway components especially that in PI3K/Akt and MAPK pathways. These components are activated in obesity and responsible for increased incidence of colon cancer. Combinational use of EGCG and curcumin produced synergistic effect on colon cancer cells. Further studies are warrant for such as effect in the obesity-associated colon cancer model and to characterise the inhibition of signalling molecules.

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