Mechanistic understanding of β-cryptoxanthin and lycopene in cancer prevention in animal models

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Abstract

To better understand the potential function of carotenoids in the chemoprevention of cancers, mechanistic understanding of carotenoid action on genetic and epigenetic signaling pathways is critically needed for human studies. The use of appropriate animal models are the most justifiable approaches to resolve mechanistic issues regarding protective effects of carotenoids at specific organs and tissue sites. While the initial impetus for studying the benefits of carotenoids in cancer prevention was their antioxidant capacity and pro-vitamin A activity, significant advances have been made in the understanding of the action of carotenoids with regards to other mechanisms. This review will focus on two common carotenoids, provitamin A carotenoid β-cryptoxanthin and non-provitamin A carotenoid lycopene, as promising chemopreventive agents or chemotherapeutic compounds against cancer development and progression. We reviewed animal studies demonstrating that β-cryptoxanthin and lycopene effectively prevent the development or progression of various cancers and the potential mechanisms involved. We highlight recent research that the biological functions of β-cryptoxanthin and lycopene are mediated, partially via their oxidative metabolites, through their effects on key molecular targeting events, such as NF-κB signaling pathway, RAR/PPARs signaling, SIRT1 signaling pathway, and p53 tumor suppressor pathways. The molecular targets by β-cryptoxanthin and lycopene, offer new opportunities to further our understanding of common and distinct mechanisms that involve carotenoids in cancer prevention.

Keywords

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Conflict of Interest

The authors declare no conflict of interest

Introduction

Dietary intervention is one of the main strategies for preventing cancer development and increasing cancer survival rates. Despite the earlier unexpected findings of the human intervention trials conducted to determine the chemoprotective effect of high doses of β-carotene on the incidences of lung cancer in smokers, which found no protective effects or even harmful effects, supporting evidence indicates that the protective roles of fruits and vegetables rich in carotenoids in cancer prevention continues to be reported in human epidemiological studies and in mechanistic studies using cell culture and animal models. There are three provitamin A carotenoids (β-carotene, α-carotene, and β-cryptoxanthin) and three non-provitamin A carotenoid (lycopene, lutein and zeaxanthin) that can be found routinely in human plasma and tissues. These carotenoids have been studied for their potential beneficial roles against cancer development (e.g., lung, liver, prostate, breast, colorectal and stomach). The reader is referred to accompanying review article for both preclinical and epidemiological data on carotenoids in cancer prevention in this special issue [1]). Carotenoids are lipophilic plant pigments with polyisoprenoid structure, typically containing a series of conjugated double bonds in the central chain of the molecule, which makes them susceptible to oxidative and enzymatic cleavage and formation of potentially bioactive metabolites. Within the past years, we have gained greater knowledge of the biological effects of carotenoids, particularly the impact of oxidation on these carotenoids and the potential for beneficial effects of small quantities or harmful effects of large quantities of the resulting metabolic products. In particular, it is important to understand the protective roles of carotenoids and their derivatives in the process of chronic disease development, with special attention to their metabolism and biological actions, molecular targets, dose effects, and organ-specific effects. In this review, we focus on recent animal studies for potential underlying mechanisms for chemopreventive effects of β-cryptoxanthin and lycopene in tumorigenesis, dependent and independent of the carotenoid cleavage enzymes, in particularly, in the lung and liver. The reader is referred also to recent review articles regarding other common carotenoids, such as β-carotene [2], lutein [2–4], and zeaxanthin [2–4]. These studies help us understand the common and distinct molecular mechanisms by which carotenoids and their metabolites protect against the development of cancers in different tissues.

1.   Chemistry and metabolism of β-cryptoxanthin and lycopene and the role of BCO1 and BCO2 beyond carotenoid cleavage activity

1.1.   Chemistry and metabolism of β-cryptoxanthin and lycopene

β-Cryptoxanthin is a pro-vitamin A carotenoid primarily found in citrus fruits such as tangerines, oranges, mandarins, and papaya, and vegetables, such as sweet red peppers and butternut squash [5, 6]. Lycopene is the pigment principally responsible for the characteristic deep-red color of ripe tomato and tomato products, and watermelon. β-Cryptoxanthin and lycopene are two of the six most abundant carotenoids in human plasma and tissues [7]. Indeed, epidemiological studies provided evidence that β-cryptoxanthin and lycopene may act as anti-carcinogenic agents against certain types of cancers, including those of the lung, colon and prostate [1].

In mammalians, two carotenoid cleavage enzymes are involved in apocarotenoid biosynthesis and include beta-carotene-15,15'-oxygenase (BCO1) for retinoid [8, 9], and beta-carotene-9',10'-oxygenase (BCO2) for apo-10'-carotenoids [10, 11]. The reader is referred to accompanying review article in this special issue that discuss carotenoid metabolism for details [12]. BCO1 cleaves β-cryptoxanthin at the 15,15′ double bond, which is critical for vitamin A production [13], while BCO2 cleaves β-cryptoxanthin at the 9',10' double bond to generate apo-10'-carotenoids [9, 14] (Fig. 1). Lycopene [15], lutein and zeaxanthin [14] can be preferentially cleaved by BCO2 to form their metabolite, apo-10'-carotenoids, also referred to as apo-10'-lycopenoid from lycopene cleavage (Fig. 2). When BCO2 was ablated in mice, the levels of lycopene were significantly elevated in hepatic and adipose tissues, as compared to wild-type mice, providing further evidence that lycopene is preferentially cleaved by BCO2 [16]. Both BCO1 and BCO2 are highly expressed in the liver and other peripheral tissues. β-Cryptoxanthin feeding resulted in a significant yellow coloration of the liver and adipose tissue due to accumulation of β-cryptoxanthin in the absence of either BCO1 [12] or both BCO1 and BCO2 [17].

1.2. Genetic variants of *BCO1/BCO2* in animals and humans

Single nucleotide polymorphisms (SNPs) of the *BCO1/BCO2* genes related to a variety of conditions have been reported in humans. Previous studies have reported that *BCO1* gene SNPs are common in humans and related to impaired catalytic activity in the bioconversion of β-carotene to vitamin A [18], although no significant association has been observed between *BCO1* SNPs and the risk of various cancers such as breast [19], prostate [19], and lung cancer [20]. A recent study has shown that *BCO1* SNPs are associated with plasma lycopene in response to the consumption of tomato juice in prostate cancer patients [21]. The Age-Related Eye Disease Study demonstrated that the *BCO2* rs2250417 SNP is strongly related to age-related eye disease [22]. *BCO2* SNPs have also been associated with alterations in the status of human and animal carotenoid levels, pro-inflammatory cytokine IL-18 expression [23], and susceptibility to ischemic stroke [24]. Higher serum levels of carotenoids have been reported to be associated with decreased risk of several cancers [25, 26]. However, whether the conflicting clinical trial results regarding the chemo-preventive effects of carotenoids might be due to the existence *BCO1/BCO2* polymorphisms and the potential function of BCO1/BCO2 in cancers in humans need further investigation.

1.3. The role of BCO1 and BCO2 other than carotenoid cleavage activity

Recent studies using BCO1 and BCO2 knockout (KO) mice indicate that BCO1/BCO2 play diverse roles in many physiological processes [27, 28] beyond their carotenoid cleavage activities; BCO1 is involved in regulating lipid accumulation [29], insulin [16], steroid metabolism [30], and heart function [31], while BCO2 is involved in modulating mitochondria [8, 27], and anemia [28]. BCO2 also regulates nutrient metabolism, hypothalamic mitochondrial function, and local oxidative stress and inflammation [32]. We have showed that BCO1/BCO2 double knockout (BCO1/BCO2 DKO) mice exhibited mild liver steatosis and had significantly higher levels of hepatic cholesterol and triglycerides compared to wild-type (WT) animals [33]. Interestingly, microRNAs (miR-34a, miR-33, and miR-122) related to lipid and cholesterol metabolism were altered in BCO1/BCO2 DKO mice [33]. Moreover, hepatic oxidative stress markers, including HO-1, SOD1, SOD2, GPX,

and catalase, were significantly altered in BCO1/BCO2 DKO mice [33]. The mRNA levels of sirtuin 1 (SIRT1) and farnesoid X receptor protein were impaired in BCO1/BCO2 DKO mice [33], indicating that BCO1/BCO2 could play an important role in maintaining normal hepatic lipid and cholesterol homeostasis, potentially through the activation of the miR-34a/SIRT1 pathway.

In terms of tumorigenesis, emerging cell culture studies and a xenograft study have indicated that the BCO1 and BCO2 enzymes might serve as tumor suppressor genes [34–36]. The authors observed that the inhibition of BCO1 in colon cancer cells increased certain characteristics of colon cancer including cell migration and invasion by up-regulating metalloproteinase 7 and 28 [34]. BCO1 overexpression in human neuroblastoma cells led to the suppression of cancer stemness and metastasis in human neuroblastoma cells [36]. BCO2 overexpression in prostate cancer cells also inhibited colony formation and proliferation [35]. However, there were no significant associations between *BCO1* SNPs and various cancers risk such as breast [19], prostate cancer [19], and lung cancer have been observed in clinical data [20]. The ablation of BCO2 significantly attenuated the anti-prostate cancer effect in lycopene or tomato-fed groups, but the absence of BCO2 did not contribute to prostate tumorigenesis in control diet-fed group [37]. We have recently demonstrated that there were no significant differences in diethylnitrosamine (DEN)-initiated and a high-refined carbohydrate-diet-promoted hepatocellular carcinoma (HCC) development between WT and BCO1/BCO2 double KO mice [38]. Although this finding may not be universally applicable to other different cancer models, we provide the in vivo evidence that BCO1 and BCO2 do not play a major role as tumor promoters or tumor suppressors [38]. More relevant evidence involving use of a murine knockout model is necessary for better understanding the roles of BCO1 and BCO2 in cancer development at different organs.

2.   The effects of β-cryptoxanthin and lycopene in cancer prevention

2.1.   β-Cryptoxanthin and lycopene in cancer prevention

Recent data from the National Health and Nutrition Examination Survey III [39] and other epidemiological studies [40, 41], including seven large well-implemented cohorts [42], have shown that a high serum level of β-cryptoxanthin is associated with a lower risk of lung cancer death in current smokers. Importantly, the protective effect of β-cryptoxanthin was independent of the consumption of other nutrients found in fruits and vegetables, such as vitamin C, folate, and other carotenoids including α-carotene, lycopene, lutein, and zeaxanthin [39, 42]. These data support the concept that the beneficial effects anti-lung cancer effects of β-cryptoxanthin are unique and that β-cryptoxanthin, rather than β-carotene, is an effective preventive agent. The protective role of β-cryptoxanthin-rich fruits and vegetables in the prevention of cancer development has been demonstrated in human epidemiological studies, indicating that higher levels of serum β-cryptoxanthin are associated with a lowered risk of several cancers including lung cancer [42], squamous cell carcinoma of the esophagus [43], and bladder cancer [44]. A recent clinical intervention study has shown that consumption of β-cryptoxanthin-enriched juice with a carotenoid mixture capsule for 2.5 years led to a lowered risk of liver cancer among hepatitis patients

with cirrhosis [45]. Animal studies have shown that β-cryptoxanthin exerts protective effects against the development of several cancers including lung cancer [46–48], colon cancer [49], gastric cancer [50], urinary bladder carcinogenesis [51], and liver cancer [38] by targeting multiple molecular mechanisms. These studies raise an important question whether the protective effect of β-cryptoxanthin against cancer development is due to intact β-cryptoxanthin or its metabolites such as vitamin A or apo-carotenoids. In the molecular mechanism section below, we highlight the major targets of β-cryptoxanthin that can lead to the suppression of the development or progression of various cancers. There are multiple avenues of evidence from both in vitro and in vivo experiments, indicating that the preventive effects of β-cryptoxanthin were likely due to biological activities of their intact molecules and metabolites produced by BCO1 and BCO2 against cancer development.

Although studies are inconsistent, epidemiologic studies suggested that higher intake of tomato products and lycopene are associated with lowered risk of prostate cancer [52, 53]. Animal studies using ferrets and mice have suggested that lycopene or the metabolites of lycopene supplementation may be therapeutic agents that can prevent the development of cancers such as lung cancer [54–56], liver cancer [57, 58], skin tumorigenesis [59], and prostate cancer [60] via multiple molecular pathways. There were several animal studies using whole foods intervention approach, such as using tomato powder or tomato paste which enriched in lycopene, to investigate the role of tomato consumption in the development of liver [61] and prostate cancer [62, 63]. Numerous oxidative metabolites of lycopene have been identified in both in vitro and in vivo systems, raising the possibility that the chemopreventive effect of lycopene could be, at least in part, due to its metabolites [64]. Indeed, apolycopenoids exist in tomatoes and tomato products, and a series of apolycopenoids including apo-10'-lycopenal have been identified in human plasmas of individuals who consumed tomato juice [65]. In mammalian tissues, lycopene can be cleaved by BCO2, producing apo-10'-lycopenal that can be oxidized into apo-10'-lycopenoic acid [11]. Recent study demonstrated that lycopene feeding inhibited hepatic tumorigenesis via differential mechanisms depending on BCO2 in mice [58]. This suggests that lycopene and the metabolites of lycopene may activate different molecular pathways, which may lead to the same preferable results in tumor outcomes. Here, we reviewed most recent studies and summarized the molecular mechanisms by which tomato consumption, lycopene, and metabolites of lycopene prevents the development of cancers.

2.2. Molecular mechanisms underlying β-cryptoxanthin and lycopene suppression of tumorigenesis

2.2.1. The NF-κB signaling pathway—Nuclear factor-κB (NF-κB) is a ubiquitous nuclear transcription factor that plays a pivotal role in various pathological processes such as inflammation, cell growth and survival, immune response, and development [66, 67]. NF-κB has been shown to activate the expression of genes involved in cell proliferation and cell survival [68]. It has been shown that tumor samples from lung cancer patients had significantly high levels of NF-κB in both non-small lung cancer and small cell lung cancer [69], which was correlated with cancer progression and poor prognosis [70]. Emerging pre-clinical evidence has demonstrated the tumor promoting role of NF-κB activation in lung inflammation, and tumorigenesis [71, 72]. Several factors can activate the NF-κB signaling

pathway including tobacco-specific N-nitrosamine, cigarette smoke condensate, tumor necrosis factor (TNF)-α, and oxidative stress [73, 74]. Additionally, certain therapies for lung cancer, including systemic chemotherapy or radiation, which have been shown to induce NF-κB activation, decreased the efficacy of these treatments. [75]. Thus, it is important to identify dietary components targeting the NF-κB signaling pathway.

It has been showed that male ferrets exposed to tobacco smoke induced significantly higher levels of inflammation, oxidative stress DNA damage, and squamous metaplasia in the lung tissues, which were significantly improved by β-cryptoxanthin supplementation ((10 mg/kg diet and 20 mg/kg diet) in a dose-dependent manner [47]. Using immunohistochemistry analysis, the protein expression levels of inflammation markers including TNF-α, NF-κB, and activator protein-1 (AP-1) were significantly reduced by β-cryptoxanthin supplementation compared with the cigarette smoke alone ferrets [47]. Indeed, β-cryptoxanthin supplementation increased lung and plasma β-cryptoxanthin levels in a dose-dependent manner, suggesting that β-cryptoxanthin itself may have protective effects against lung lesions potentially by regulating the NF-κB pathway [47]. β-Cryptoxanthin supplementation also inhibited tobacco carcinogen (NNK)- and nicotine-induced IL-6 expression, emphysema and lung cancer development in AJ mice [46]. These results suggest that β-cryptoxanthin can serve as an effective dietary component against smoke-induced lung cancer by suppressing the NF-κB and inflammation pathway (Fig. 3).

Lycopene treatment inhibits NF-κB activation in cells and animal models by down-regulating the binding ability of NF-κB [76–78]. The study by Kolberg et al. used the nude mice bearing human prostate cancer cells to investigate the effects of a 10% tomato paste diet on the development of prostate cancer and its underlying mechanisms. Although there were no significant differences in tumor size between vehicle control-fed mice and tomato diet-fed mice, tomato paste feeding effectively suppressed TNF-α-induced NF-κB activity [62]. Interestingly, lycopene supplementation (100 mg/kg diet) for 24 weeks activated different protective mechanisms in liver tumorigenesis depending on the presence or absence of BCO2 [58]. In WT mice, but not in BCO2 KO mice, the protective effects of lycopene supplementation against hepatic tumorigenesis were associated with lycopene-mediated inhibition of NF-κB phosphorylation in WT mice [58]. Furthermore, lycopene metabolite, apo-10'-lycopenoic acid supplementation (10 mg/kg diet) significantly inhibited hepatic inflammation and liver cancer based on the protein expression levels of pro-inflammatory markers, including NF-κB, compared with high-fat diet-fed mice without supplementation [57]. The inhibitory effect of apo-10'-lycopenoic acid in NF-κB protein expression was correlated with a reduction in IL-6 protein levels and liver tumor volume [57]. In this in vivo study, the levels of apo-10'-lycopenoic acid in the liver tissues were in the picomolar range, which is significantly lower than the levels of lycopene in the liver in rats (7.5–17.6 nmol/g liver) [79] or in humans (0.1–20.7 nmol/g liver) [80]. These data indicate that metabolites of lycopene may play potential roles in regulating NF-κB mediated hepatic inflammation and liver tumorigenesis. However, the regulation of NF-κB by lycopene and its metabolites remains unclear and should be further investigated in future studies.

2.2.2.   Retinoic acid signaling pathway—Retinoic acid (RA) is a critical bioactive metabolite of vitamin A [81]. Importantly, RA and its derivatives has been regarded as

potential chemopreventive agents owing to their ability to inhibit proliferation and induce apoptosis, differentiation, and anti-oxidant effects in cancers [82]. RA activity is mostly mediated via RA receptors (RARs) and retinoid X receptors (RXRs), which are members of the nuclear receptor superfamily but differ in their amino-and carboxyl-terminal domain sequence and retinoid-binding specificity [83, 84]. Downregulation of RA signaling has been observed in several cancer cell types including head and neck [85, 86], breast [87, 88], esophagus [89], prostate [90], lung [91–93], and cirrhosis and liver cancer [94]. It has been reported that cigarette smoke reduces RAR-β2 expression with morphological changes in the lung tissues of animals [95] and that the combination of cigarette smoke and (4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) treatment leads to aberrant methylation of RARs in murine lung tumors [96]. Activation of the RAR signaling pathway is considered a potential therapeutic strategy for cancer prevention [97]. As the bioavailability of various natural RAR ligands (such as all-trans RA) are affected by various factors, such as retinoid binding proteins involved in transport, uptake, storage, and sequestration of retinoid metabolic enzymes [98], it is important to identify natural RAR ligands other than RA to treat various chronic diseases [99]. β-Cryptoxanthin has been reported to be a novel natural RAR ligand [46, 100]. It has been demonstrated that β-cryptoxanthin treatment (1–20 μmol/L) suppressed the growth of lung cancer cells by up-regulating RARβ expression in a dose-dependent manner [101]. The doses of β-cryptoxanthin treatment used in this study were above the β-cryptoxanthin levels in serum collected from fasting subjects (0.05–0.52 μmol/L) [102]. However, the estimated intracellular β-cryptoxanthin levels (0.04–7.4 μmol/L) in cells treated with 1–20 μmol/L of β-cryptoxanthin were much lower than the β-cryptoxanthin levels in the cell culture medium [101]. This effect was similar to the physiological effects achieved with dietary sources in animal studies. For example, serum β-cryptoxanthin levels (~17.38 nmol/g tissue) were much higher than lung β-cryptoxanthin levels (~0.16 nmol/g tissue) in lung cancer murine model [48]. β-Cryptoxanthin treatment (1–20 μmol/L) also activated retinoic acid response elements (RARE)-driven transcription activity, suggesting that the activation of the retinoid signaling pathway by β-cryptoxanthin could be due to β-cryptoxanthin or its metabolites [101] (Fig. 3). Matsumoto *et al.* demonstrated that β-cryptoxanthin had high binding activity against RAR in an *in vitro* CoA-BAP system, indicating that β-cryptoxanthin itself might be a natural RAR ligand [99]. Interestingly, β-cryptoxanthin supplementation (10 and 20 mg/kg diet), which are equivalent to daily consumption of 3–5 raw tangerines daily in human, which are equivalent to daily consumption of 3–5 raw tangerines daily in human, restored the down-regulated RARβ by tobacco carcinogen (NNK) and nicotine exposure to normal, without significant changes of retinoid levels in A/J lung cancer mouse model [46]. Similarly, Quesada-Gómez *et al.* demonstrated that β-cryptoxanthin treatment (0.5 mM) reduced vessel formation by potentially up-regulating RAR levels in mice [103].

One of the important aspects is that the beneficial and adverse effects of carotenoids may be due to their metabolites or decomposition products [104]. In addition to RA, carotenoid metabolites can activate RARE-driven transcription activity. Previous studies demonstrated that acycloretinoic acid (Fig. 2) activates the transcription of RARβ and inhibit cancer cell proliferation in vitro [105, 106]. Due to the similarity in chemical structures between apo-10'-lycopenoic acid and acycloretinoic acid, we have demonstrated that apo-10'-

lycopenoic acid can transactivate RARβ using a reporter vector containing the RARβ promoter fragment in the promoter region of luciferase gene [55]. When the RARE in RARβ promoter was mutated, the ability of apo-10'-lycopenoic acid to transactivate RARβ promoter was abolished [55]. These results suggest that activation of RARs may account for the growth inhibitory effect of apo-10'-lycopenoic acid. Indeed, apo-10'-lycopenoic acid (Fig. 2) supplementation (1 to 120 mg/kg diet) inhibited the number of NNK-induced lung tumors in mice in a dose-dependent manner, suppressed the growth of lung cancer cell lines, and decreased cell cycle progression in the G1 phase by decreasing cyclin E [55]. Importantly, apo-10'-lycopenoic acid increased RARβ mRNA expression in a dose-dependent manner, and plasma apo-10'-lycopenoic acid levels were correlated with apo-10'-lycopenoic acid dose in the diet [55]. It is possible that anti-proliferation effects of lycopene or metabolites of lycopene in cancer may be achieved via nuclear receptors other than RAR/RXR. For example, apo-10'-lycopenoic acid (2.5 to 40 μM) inhibited cancer cell motility and angiogenesis by upregulating peroxisome proliferator-activated receptor γ (PPARγ) [107] (Fig. 4), which is involved in controlling angiogenesis, tumor progression, and metastasis [108]. In terms of apo-carotenoids, the combination treatment of β-carotene (30 μmol/L) and its metabolite, apo-14'-carotenoic acid (1 to 10 μmol/L), increased RARβ expression levels in human bronchial epithelial cells with or without benzopyrene, a primary lung carcinogen from cigarette smoke [109]. A recent study showed that apo-14′-carotenoic acid is present endogenously in the human plasma and increased after carrot juice rich in β-carotene supplementation in human subjects [110]. Apo-14′-carotenoic acid is a moderate activator of RAR-transactivation in reporter cell lines and apo-14′-carotenoic acid can potently activate retinoid signaling in DR5/RARE-reporter mice [110]. The authors concluded that apo-14′-carotenoic acid alone or in combination with its metabolite, all-trans-13,14-dihydroretinoic acid, could be an alternative pathway for potent RAR-mediated signaling [110]. Taken together, these results indicate that activation of RARs by carotenoids themselves or their metabolites can contribute to the suppression the cancer development, especially lung cancer.

2.2.3.   SIRT1 signaling pathway—SIRT1, a nicotine adenosine dinucleotide (NAD$^+$)-dependent protein-deacetylase, plays important biological roles in several processes including circadian rhythms, inflammation, lipid/glucose metabolism, and immune function [111–113]. SIRT1 can be activated in response to various conditions including calorie restriction, fasting, changes in NAD$^+$ levels, and resveratrol [114]. Nicotinamide phosphoribosyltransferase (NAMPT), the rate limiting NAD biosynthetic enzyme, and NAD$^+$ display circadian oscillation, as they are regulated by the circadian machinery in peripheral tissues such as lung, liver and adipose tissues [115]. NAMPT-mediated NAD$^+$ synthesis has been shown to be significantly decreased in peripheral metabolic organs by high fat diet [116]. Smoke exposure can decrease SIRT1 levels in the nucleus, thereby contributing to the increased acetylation of nuclear RelA/p65 and IL-18 secretion [117]. Recent study reported that tobacco carcinogen (NNK)- and nicotine-induced lung cancer and emphysema were ameliorated with β-cryptoxanthin supplementation (10 mg/kg diet and 20 mg/kg diet) in AJ mice [46]. Moreover, NNK and nicotine treatment significantly reduced the protein levels of SIRT1 in lung tissues, which recovered to normal levels following β-cryptoxanthin supplementation in AJ mice [46]. It has been reported that SIRT1 directly controls lung

inflammation [118]; SIRT1$^{-/-}$ mice showed higher levels of inflammation after ambient particulate matter exposure, which is intimately related to increased NF-κB acetylation [118]. The reduction in SIRT1 protein levels by NNK and nicotine treatment was accompanied by elevated IL-6, which was decreased by β-cryptoxanthin supplementation [46]. β-Cryptoxanthin supplementation suppressed the development of NAFLD by potentially up-regulating SIRT1 protein levels in the liver and inhibiting pro-inflammatory cytokine IL-6 mRNA expression along with up-regulation of SIRT1 mRNA expression in the mesenteric adipose tissues of BCO1/BCO2 DKO mice [119]. Collectively, these results suggest that β-cryptoxanthin is a potential dietary factor that plays an important role in restoring SIRT1 protein levels, thereby contributing to the amelioration of inflammation and carcinogenesis (Fig. 5).

Emerging studies have demonstrated the importance of circadian rhythms and oncogenic processes [120]. Oncogenic processes can inhibit the balance maintained by the circadian clock machinery, thus facilitating uncontrolled proliferation and promoting an inflammatory tumor microenvironment [121]. SIRT1 is intimately linked to circadian rhythms, as it regulates the transcription of clock genes including Bmal1, Per2, and Cry [122] (Fig. 5). Thus, it is important to identify dietary factors that can induce NAMPT and SIRT1 activity and restore circadian rhythmicity, thereby preventing inflammation and tumorigenesis (Fig. 5). Recent study showed that tomato powder containing substantial lycopene inhibits high-fat diet-induced hepatic steatosis, inflammation, and hepatic tumorigenesis [61]. This is associated with increased SIRT1 activity, NAMPT expression, and AMPK phosphorylation, as well as restored high-fat diet-reduced circadian clock genes (CLOCK, PER2, and CRY2) to the normal levels of the control group [61]. Moreover, the protective effects of tomato powder feeding were associated with decreased hepatic inflammatory foci and pro-inflammatory biomarkers (IL-6, IL-12a, MCP-1, and inducible NO synthase (iNOS)). Since metabolic modulations by SIRT1 have been shown to protect against inflammation by reducing IL-6 and TNF-α expression, potentially via NF-kB signaling [123], the study indicates that tomato powder feeding can inhibit hepatic inflammatory responses by the SIRT1 signaling pathway. It is also possible that the beneficial effects of tomato powder on liver tumorigenesis in the BCO1/BCO2 DKO mice are due to apo-lycopenoids that are produced by other unidentified carotenoid cleavage enzymes in tomatoes or gut bacteria. In plants, the production of apocarotenoids from carotenoids is catalyzed by a family of carotenoid cleavage dioxygenases which cleave the 9',10' double bonds of carotenoids including lycopene (57). A series of apolycopenoids including apo-10'-lycopenal have been identified in human plasmas of humans who consumed tomato juice for 8 weeks (4 to 8 ounces delivering 21.9 mg of lycopene/day) (58). This notion was supported by the previous report that the anti-carcinogenesis effects of apo-10'-lycopenoic acid in liver cancer are intimately related to up-regulation of hepatic SIRT1 and modulation of SIRT1 target genes [57]. Apo-10'-lycopenoic acid supplementation significantly decreased hepatic inflammation markers (inflammatory foci, IL-6, TNF-α, and NF-κB) and the proliferation marker, cyclin D1, while cleaved-PARP protein levels increased following apo-10'-lycopenoic acid supplementation [57]. These data suggest that anti-proliferation and pro-apoptotic effects of apo-10'-lycopenoic acid can be mediated by SIRT1 pathway.

However, SIRT1 has been reported to have dual effects on carcinogenesis depending on cancer cell lines and animal models [124]; For example, SIRT1 has been suggested as a potential tumor suppressor in human skin tumors [125], whereas it has been suggested as a potential tumor promoter in the ovary, breast, stomach, and pancreas cancer [126–129]. The role of SIRT1 in liver cancer alsoremains controversial [130–133]. Therefore, whether SIRT1 acts as a tumor suppressor or tumor promoter in tumorigenesis and furthermore, how carotenoids and their metabolites differently regulates SIRT1 levels in tumors vs. non-tumor tissues as well as potential mechanisms involved need further investigation.

2.2.4. Nicotinic Acetylcholine Receptor (nAChR) α7 signaling pathway—

Nicotine is the major component in cigarette smoke that can interact with nAChR [134–136]. Ionotropic nicotinic acetylcholine receptors (AChR) are expressed in both neuronal and non-neuronal cells. α7-nAChR is a major subtype of AChR, which is associated with chronic obstructive pulmonary disease and lung cancer development [134, 136, 137]; it can react with NNK and nicotine and is a proposed molecular target [135, 138–141]. Indeed, recent studies utilizing the ferrets, an animal model that closely mimic human lung cancer, have demonstrated that ferrets develop pulmonary preneoplastic and plastic lesions, and upregulate α7-nAChR expression in the bronchial epithelial cells and pulmonary carcinogenesis following NNK exposure [142]. Antagonizing α7-nAChR has been reported to inhibit lung tumor growth and tumor cell migration [139, 143].

Recent study demonstrated that carotenoids can inhibit α7-nAChR signaling pathway as a promising strategy to prevent development of smoke-related carcinogenesis [48, 144]. β-Cryptoxanthin inhibited cell migration and invasion of α7-nAChR positive cancer cells by inhibiting the α7-nAChR/PI3K/AKT signaling pathway, but not in α7-nAChR nagative cancer cells *in vitro* [48] (Fig. 6). Moreover, β-cryptoxanthin supplementation effectively reduced nicotine-promoted emphysema and NNK-induced adenocarcinoma multiplicity without significant changes in vitamin A (retinol and retinyl palmitate) levels in both mouse lungs and serums [48, 145]. In this study, β-cryptoxanthin supplementation in mice 2 weeks prior to NNK injection effectively reduced lung tumor multiplicity by 52 – 63%, suggesting that β-cryptoxanthin was effective in suppressing tumor promotion [48]. Collectively, β-cryptoxanthin suppress cancer cell motility and lung tumorigenesis via down-regulation of α7-nAChR/PI3K/AKT signaling (Fig. 6).

Lycopene also has been shown to suppress the α7-nAChR signaling pathway. Lycopene supplementation significantly decreased NNK-induced α7-nAChR and its downstream target proteins, including metalloproteinase (MMP)-2, cyclin D1, and NF-κB, in ferrets and decreased the NNK-induced mortality and pathological changes in lung tissues [144], indicating that lycopene could prevent the angiogenesis, proliferation, and inflammation by regulating pulmonary α7-nAChR. These results suggest that β-cryptoxanthin and lycopene can provide beneficial effects against smoke carcinogen-induced lung injury by inhibiting the α7-nAChR signaling pathway. The exactly mechanism(s) how carotenoids regulate α7-nAChR signaling pathway is unclear.

2.2.5. Tumor suppressor proteins p53 and p73—

p53 is a tumor suppressor gene that plays important roles in senescence, cell-cycle arrest, and apoptosis under various

cellular stress conditions [146]. Many cancers exhibit loss of p53, which contributes to chemotherapy resistance [147]; thus, re-activation of p53 is a potent strategy for treating cancer. p73, a member of the p53 transcription factor family, regulates similar target genes [148]. Several small molecules that activate p73 have been reported to have anti-tumorigenic effects [149, 150]. p73 undergoes mRNA splicing to produce Np73, an oncogenic truncated p73 that negatively regulates p53 and p73 and is responsible for chemo-resistance [151].

Anti-carcinogenic effects of β-cryptoxanthin were proved to regulate the levels of Np73 [49]. San *et al.* showed that the lymphocytes of healthy volunteers who were administered a juice containing 0.75 mg of β-cryptoxanthin for one month exhibited downregulation of Np73 in their lymphocytes [49]. β-cryptoxanthin treatment enhanced the anti-carcinogenic effects of oxaliplatin in colon cancer cell lines (HCT116, SW480) by decreasing the expression of Np73 [49]. Moreover, β-cryptoxanthin alone or the combination treatment of β-cryptoxanthin and oxaliplatin significantly suppressed tumor development along with significant inhibition of Np73 levels in the kidneys, normal colonic mucosa, and xenograft tumors compared to the control group [49]. These results suggest that β-cryptoxanthin affords protective effects against colon cancer growth by regulating the oncogenic p73 truncated isoform and might have broader effects on different tissues.

Post-translational modification of p53 has been gaining extensive interest; acetylation and phosphorylation of p53 have been reported to stabilize and activate p53 [152]. Recently, we found that β-cryptoxanthin supplementation significantly increased the protein levels of acetylated-p53, an active form of p53, in liver tumor tissues, thereby inhibiting the development of liver cancer in both WT and BCO1/BCO2 DKO mice [38]. It has been well established that p53 regulates apoptosis and cell proliferation; we found that the protein levels of cyclinD1 and anti-apoptosis marker, Bcl-xl, were significantly reduced in hepatic tumors by β-cryptoxanthin supplementation in both WT and BCO1/BCO2 DKO mice [38]. Gao *et al.* have shown that β-cryptoxanthin supplementation inhibited gastric carcinogenesis by inducing G0/G1 arrest and suppressing cyclinD, E, cyclin-dependent kinases, potentially by increasing p53 protein levels [50]. Miyazawa *et al.* investigated that β-cryptoxanthin feeding decreased the multiplicity and incidence of preneoplastic and neoplastic region of bladder cancer was reduced, in conjunction with inhibition of cyclin-D-positive cells [51]. Coral *et al.* also found that β-cryptoxanthin treatment inhibited the number of colon cancer cells in the S-phase largely due to the anti-proliferative activity of β-cryptoxanthin rather than apoptosis [49]. Anti-proliferative effects of β-cryptoxanthin treatment have been reported in both normal and tumor cells [101, 153]. Collectively, these results suggest that β-cryptoxanthin might be a potential natural bioactive component that can be used in combination with conventional chemotherapeutic agents; it negatively regulates Np73, but activates p53 potentially by regulating post-translational modification in cancer. However, further studies are required to unravel the mechanisms underlying β-cryptoxanthin regulation of p53 post-translational modification.

It is well accepted that the loss of function of p53 by mutation results in enhanced proliferative activity and tumor progression. Mutation of p53 can lead to increased mutant p53 proteins, which have a longer half-life than wild-type p53 protein, thereby accumulating

in cancer cells [154]. Furthermore, increased p53 protein may serve as a useful indicator for poor prognosis of several cancers, including lung cancer [155–157]. Moreover, p53 plays critical roles in cellular responses to various cellular stresses such as genotoxic and oncogenic stress [158]. In response to different genotoxic stresses, various protein kinases, such as p38 MAPK and JNKs, phosphorylate p53, especially at serine 15, leading to its activation [159]. Previous study has shown that p53 gene expression in the lung was significantly increased in smoke-exposed ferrets, while low dose of β-carotene restored p53 expression to normal levels compared to the control group [56]. Increased total p53 and phosphorylated-p53 protein levels were significantly induced by cigarette smoke in the gastric mucosa of ferrets, which were significantly decreased by lycopene supplementation in a dose-dependent manner, compared with the cigarette smoke alone group [160]. These data further indicate that either low- or high-dose lycopene supplementation may play a critical role in the prevention of cigarette smoke exposure-related alteration in p53 and its target genes involved in apoptosis and proliferation.

2.2.6.   Carotenoid metabolites and the insulin-like growth factor-1 (IGF-1) pathway—The insulin-like growth factors (IGFs) are mitogens involved in regulating cell proliferation, differentiation, and apoptosis [161]. The downstream pathway of the IGF-1R signaling involves the activation of both phosphatidylinositol 3'-kinase (PI3K)/Akt/protein kinase B and Ras/Raf/MAPK pathways. Disruptions of normal IGF-1 system components lead to hyperproliferation and survival signals and have been implicated in the development of various tumor types. Several lines of evidence implicate IGF-1 and its receptor, IGF-1R in lung cancer and other malignancies [161, 162]. Epidemiological evidence indicates that increased levels of IGF-1, reduced levels of IGF binding protein-3, or an increased ratio of IGF-1 to IGF binding protein-3 in circulation are associated with an increased risk for the development of several common cancers, including those of the breast, prostate, colon, and lung [162].

It has been reported that the IGF-1 stimulated cell growth was reduced by physiological concentrations of lycopene in endometrial, mammary (MCF-7) and lung (NCI-H226) cancer cells [163, 164]. Lycopene treatment was also associated with an increase in membrane-associated IGF binding proteins [164]. Two studies in humans have also shown that higher intake of cooked tomatoes or lycopene was significantly associated with lower circulating levels of IGF-1 and higher levels of IGF binding protein-3 [165]. In an animal study, lycopene supplementation reduced local prostatic IGF-1 expression in the Dunning prostate cancer model [166]. Lycopene supplementation in smoke-exposed ferrets inhibits lung squamous metaplasia by up-regulating IGF-binding protein 3 [167], which is a potent inhibitor of both PI3K/Akt/PKB and MAPK signaling pathways [168] and regulates the bioactivity of IGF-I by sequestering it away from its receptor in the extracellular milieu, thereby inhibiting the mitogenic and anti-apoptotic action of IGF-I (Figure 3). Furthermore, the changes of IGF-I binding protein-3 by lycopene supplementation in the plasma of the ferrets were associated the increased apoptosis and diseased cell proliferation in the lungs of smoke-exposed ferrets. Although the mechanism by which lycopene increases the level of IGF binding protein-3 remains to be elucidated, these results demonstrate the importance of IGF binding protein-3 in the regulation of smoke-induced lung lesion, proliferation and

apoptosis, suggesting that IGF binding protein-3 is a molecular target of lycopene for the prevention of lung cancer. These studies support the notion that the lycopene may exert biological functions in cancer prevention potentially by regulating IGF signaling pathway. However, the molecular properties of lycopene and its metabolites need more investigation and knowledge of their metabolic pathway, dose effects, and tissue specificity.

2.2.7.   Regulation of energy metabolism in tumors—Cancer cells tend to have altered energy metabolism, known as the Warburg effect, which is characterized by higher glucose uptake and glycolysis rather than oxidative phosphorylation [169]. The Warburg effect has been widely examined in human cancers, including hepatocellular carcinoma (HCC) [170], and is closely associated with the aggressiveness and high proliferation of the cancer [171, 172]. Gupta et al. demonstrated that the N-Nitrosodiethylamine alone treatment led to poorly differentiated HCC, which was inhibited following lycopene treatment in mice [173]. Additionally, the lycopene-mediated improvement of histopathology and ultrastructure was associated with inhibition of the activities of glycolytic enzymes, including hexokinase and phosphoglucose isomerase, compared with the N-Nitrosodiethylamine-induced HCC group [173]. These findings suggest that lycopene has the potential to inhibit HCC development by targeting glucose metabolism in the liver. The protein levels of lactate dehydrogenase is an important enzyme regulating glycolysis and HCC proliferation [174]. The enhancing gluconeogenesis in malignant HCC has been reported to suppress glycolysis and HCC progression [175]. Very recently, we found that β-cryptoxanthin concentrate feeding (10 mg/kg diet) significantly reduced HCC numbers, average tumor size, and total tumor volume in both WT and BCO1/BCO2 DKO mice [38]. The dose of β-cryptoxanthin used in this study was within a physiological range based on the levels of β-cryptoxanthin in WT-HRCD+β-cryptoxanthin mice. The mean β-cryptoxanthin levels (0.14 nmol/g tissue) in the liver tissues of WT-HRCD+β-cryptoxanthin mice were comparable to the β-cryptoxanthin levels in human livers (0.1–3.5 nmol/g tissue) [80]. The chemopreventive effects of β-cryptoxanthin were associated with increased gluconeogenesis markers (phosphoenolpyruvate carboxykinase, glucose 6-phosphatase) and decreased protein levels of a glycolysis marker (lactate dehydrogenase) and of the hypoxia-inducible factor-1α and its downstream targets, matrix metalloproteinase 2/9 in tumors [38]. Additionally, the β-cryptoxanthin-mediated alteration in glucose metabolism was associated with up-regulation of p53 acetylation [38]. It has been shown that p53 suppresses lactate dehydrogenase expression [176] and up-regulates phosphoenolpyruvate carboxykinase 1 and glucose 6-phosphatase [177]. Thus, it is plausible that β-cryptoxanthin feeding increases p53 acetylation and leads to modulation of glucose metabolism, which may contribute to the inhibition of HCC progression inhibition in both WT and BCO1/BCO2 DKO mice. There is a great need for experimental studies to further clarify the underlying mechanistic actions of β-cryptoxanthin.

2.2.8.   Modulation of the Reverse Cholesterol Transport mechanism—The role of cholesterol in cancer has received increasing attention recently [178]. A growing number of studies have demonstrated that cancer cells exhibit abnormal cholesterol accumulation, affecting various oncogenic cellular signaling pathways [179, 180]. *In vitro* studies have demonstrated that lycopene treatment inhibits cholesterol synthesis in macrophage cell lines

[181], as well as in prostate PC-3, lung BEN, and colon HCT-116 and HT-29 cancer cell lines by inhibiting the mevalonate pathway [180].

Lycopene treatment significantly reduced cancer growth in these cancer cell lines by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase expression [180]. A recent study using a ferret model showed that lycopene-mediated beneficial effects against smoke-induced chronic bronchitis, emphysema, and preneoplastic lesions, are attributed to the improvement of cholesterol homeostasis through reverse cholesterol transport [54]. Additionally, the changes in reverse cholesterol transport markers following lycopene supplementation were associated with the regulation of nuclear hormone receptors, such as PPARα and LXR [54]. Similarly, Yang et al. showed that lycopene treatment significantly inhibited human prostate cancer cells and reduced cellular cholesterol levels by activating PPAR-LXR-ABCA1 [182]. Taken together, these results suggest that lycopene plays a potential role in cholesterol metabolism in cancer, which may contribute to the inhibition of cancer development.

2.2.9.   Regulation of microbiome and cancer—Emerging studies indicate that the human gut microbiota plays a role in regulating inflammation, immune response, various metabolism, and cancer [183]. The liver is directly exposed to metabolites produced by the gut microbiota through portal circulation [184]. In the HCC mouse model, the intestinal microbiota has been shown to induce Toll-like receptors and inflammation, which may contribute to the HCC progression [185]. Moreover, alteration of gut microbiota composition induced by genetic or dietary obesity significantly increased deoxycholic acid, a metabolite of the gut microbiota, which may cause DNA damage [186]. The enterohepatic circulation of deoxycholic acid affects the senescence-associated secretory phenotype, thereby inducing inflammation and the carcinogenesis process in the liver [186]. Interestingly, inhibition of deoxycholic acid or gut microbiota prevented the development of HCC in obese mice [186], indicating that components and metabolites produced by the gut microbiota play an important role in the development of obesity-induced HCC. A recent clinical study showed that parcitipants who were administered different dose of lycopene (7 mg/day and 30 mg/day) for one month exhibited a dose-dependent increase in gut microbiota composition [187], suggesting that lycopene has prebiotic potential. A recent study using BCO1/BCO2 DKO mice that were fed either high-fat diet alone or high-fat diet with dietary tomato powder for 24 weeks revealed that tomato powder supplementation significantly decreased hepatic inflammatory foci, hepatic steatosis, and hepatic tumorigenesis, as compared with the high-fat diet alone-fed mice [61] (Fig. 7). In addition, tomato powder supplementation increased gut microbiota richness and diversity, but decreased *Clostridium* species, which are known to increase deoxycholic acid and decrease natural killer T cells [188, 189]. These studies suggest that carotenoids prevent inflammation with potential modulating gut microbiota and inhibits HCC development. The reader is referred to a recent review article regarding the effects of other common carotenoids, astaxanthin and β-carotene on gut microbiota dysbiosis [190]. Future studies are needed to investigate the role of lycopene in the gut microbiome, immune function, and cancer prevention.

2.2.10. Cancer stem cell and cancer cell niche in tumorigenesis—Cancer stem cells are a subset of cells that have stem-like characteristics in tumors that are responsible for self-renewal, tumor relapse, and drug resistance [191]. β-Carotene, a pro-vitamin A carotenoid, has been shown to inhibit neuroblastoma tumorigenesis by modulating cancer stem cell markers including Oct3/4 and delta-like 1 homologue and hypoxic tumor microenvironment marker, hypoxia-inducible factor-1α, in neuroblastoma tumors [192]. Our preliminary data showed that β-cryptoxanthin can suppress cancer stem cell marker CD133 in the liver tumors of WT and BCO1/BCO2 DKO mice (unpublished), suggesting that β-cryptoxanthin itself plays a role in inhibiting cancer stemness in HCC. Animal studies investigating the effects of β-cryptoxanthin or lycopene on cancer stem cell characteristics are still lacking and thus pre-clinical studies are highly encouraged to explore this.

Cancer cell niche, including nutrient supply and hypoxic tumor microenvironment, play important roles in obesity-driven carcinogenesis. Accumulating evidence in recent years has drawn attention in the role of lipid droplets in cancer development [193–195]; lipid-rich cancer cells exhibit more aggressive behavior and chemotherapy resistance in animal and human studies [193–195]. Lipid droplets are intimately related to inflammation and hypoxic tumor cells, which can lead to the development and progression of neoplastic regions [196, 197]. Hypoxic tumor microenvironment triggers cancer cells to uptake fatty acids from the outside [198]. Moreover, cancer cells can uptake lipids secreted by extra-vesicles secreted from nearby hypoxic cells [199]. Recently, we found that the average liver tumor size was significantly correlated with hepatic steatosis assessed in the non-tumor region, and importantly, hepatic steatosis scores were significantly decreased in the livers of WT and BCO1/BCO2 DKO mice treated with β-cryptoxanthin supplementation compared with the high-refined carbohydrate diet littermates [119]. The protein levels of hypoxia-inducible factor-1α and its downstream targets, metalloproteinase (MMP)-2 and 9, were significantly suppressed by β-cryptoxanthin feeding in the hepatic tumors of both WT and BCO1/BCO2 DKO mice [38]. It is unclear whether the inhibition of lipid accumulation by β-cryptoxanthin in the surrounding tissue of hepatic tumor affects the development of hepatic tumor growth.

Inflammatory tumor microenvironment is also important in tumor growth. Natural killer cells are the primary innate immune cells with a major role in directing tumor killing. Emerging evidence have been focusing on natural killer cell-based cancer immunotherapy [200]. Further, natural killer cells are a major target in immunotherapy owing to their ability to detect and remove cancer stem cells [201, 202]. Previously, it has been demonstrated that β-cryptoxanthin oral administration (1.5 μg/kg for one week) significantly reversed a stress-induced decrease in the cytotoxic activity of natural killer cells in mice, demonstrating a potential effect of β-cryptoxanthin on natural killer cells [203]. More recently, lycopene feeding significantly increased inflammatory cells including natural killer cells in tumor tissues and reduced prostate cancer tumor burden [60], indicating that lycopene may promote the immune system in cancer. These data suggest that β-cryptoxanthin and lycopene may have potential roles in immune system in tumor microenvironment in mice. Taken together, β-cryptoxanthin and lycopene might constitute good chemopreventive agent candidates that can regulate tumor microenvironment, thereby affecting cancer development.

3. Conclusions and future perspectives

Epidemiologic studies have shown that dietary intake patterns with increased consumption of fruits and vegetables rich in carotenoids and, thus, increased serum levels of carotenoids have been associated with a decreased development of cancers. We reviewed the animal experimental evidence which has shown that dietary β-cryptoxanthin and lycopene exert comprehensive chemopreventive and therapeutic effects. This review opens several new research questions around the effects of β-cryptoxanthin and lycopene in carcinogenesis research. Future research should include mechanistic and translational pre-clinical experimental studies with both male and female animal models. The anticancer effects of β-cryptoxanthin and lycopene are associated with multiple signaling pathways, including p53, NF-κB, SIRT1, α7-nAChR, IGF-1, and retinoid signaling pathway. Recent studies indicated that the anti-cancer effects of lycopene are related to regulating gut microbiome, cholesterol metabolism, and energy metabolism in tumors in animal models. Emerging studies revealed that β-cryptoxanthin and lycopene are good candidates to regulate tumor microenvironment. Cross-talk between cancer cells and surrounding tumor microenvironment is very important in cancer initiation and progression; thus, animal studies investigating whether β-cryptoxanthin or lycopene feeding differentially regulate these aforementioned pathways in cancer cells and non-cancerous cells are necessary in the future. Further investigation, using animal cancer models, into the effect of β-cryptoxanthin and lycopene on immune function should be conducted. Unraveling these questions will be helpful when considering β-cryptoxanthin and lycopene as potential dietary bioactive treatment and immunotherapy aid for cancers. Further investigations elucidating how β-cryptoxanthin and lycopene or the combination prevent tumorigenesis in animal models are needed to provide insight into the future usage of β-cryptoxanthin and lycopene as a potential bioactive component either by itself or together with cancer treatment medications.

Acknowledgements

Abbreviations:

BCO1	β-Carotene-15,15′-oxygenase
BCO2	β-carotene-9′,10′-oxygenase
SNP	single nucleotide polymorphism
BCO1/BCO2 DKO	BCO1$^{-/-}$/BCO2$^{-/-}$ double knockout
WT	wild-type
SIRT1	sirtuin 1
DEN	diethylnitrosamine

IGF-1	insulin-like growth factor-1
RA	retinoic acid
RARs	RA receptors
RXRs	RA X receptors
NNK	nicotine-derived nitrosamine ketone
RARE	retinoic acid response element
NF-κB	nuclear factor-κB
TNF-α	tumor necrosis factor α
AP-1	activator protein 1
NAD	nicotine adenosine dinucleotide
NAFLD	non-alcoholic fatty liver disease
HCC	hepatocellular carcinoma
nAChR	nicotinic acetylcholine receptor
PPAR	peroxisome proliferator-activated receptor
NAMPT	nicotinamide phosphoribosyltransferase
PI3K	phosphatidylinositol 3'-kinase

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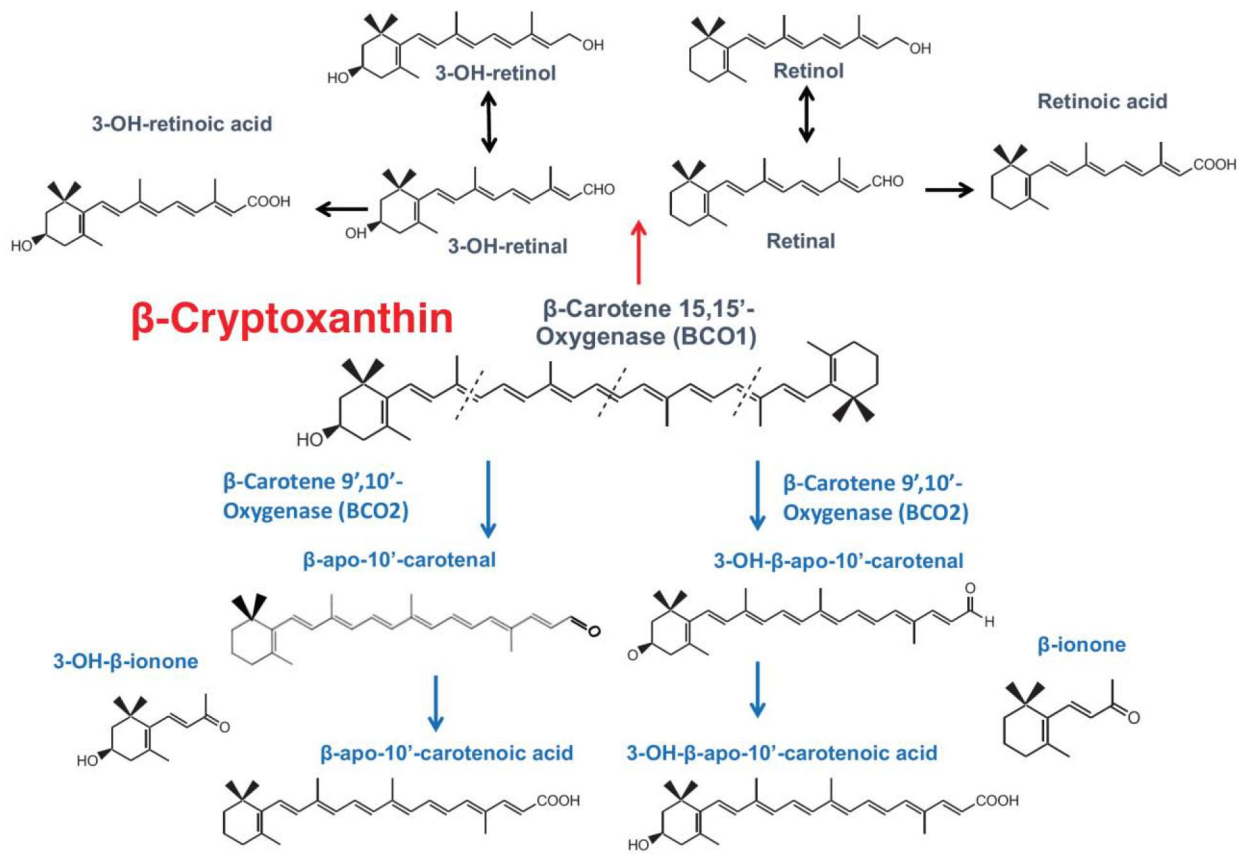
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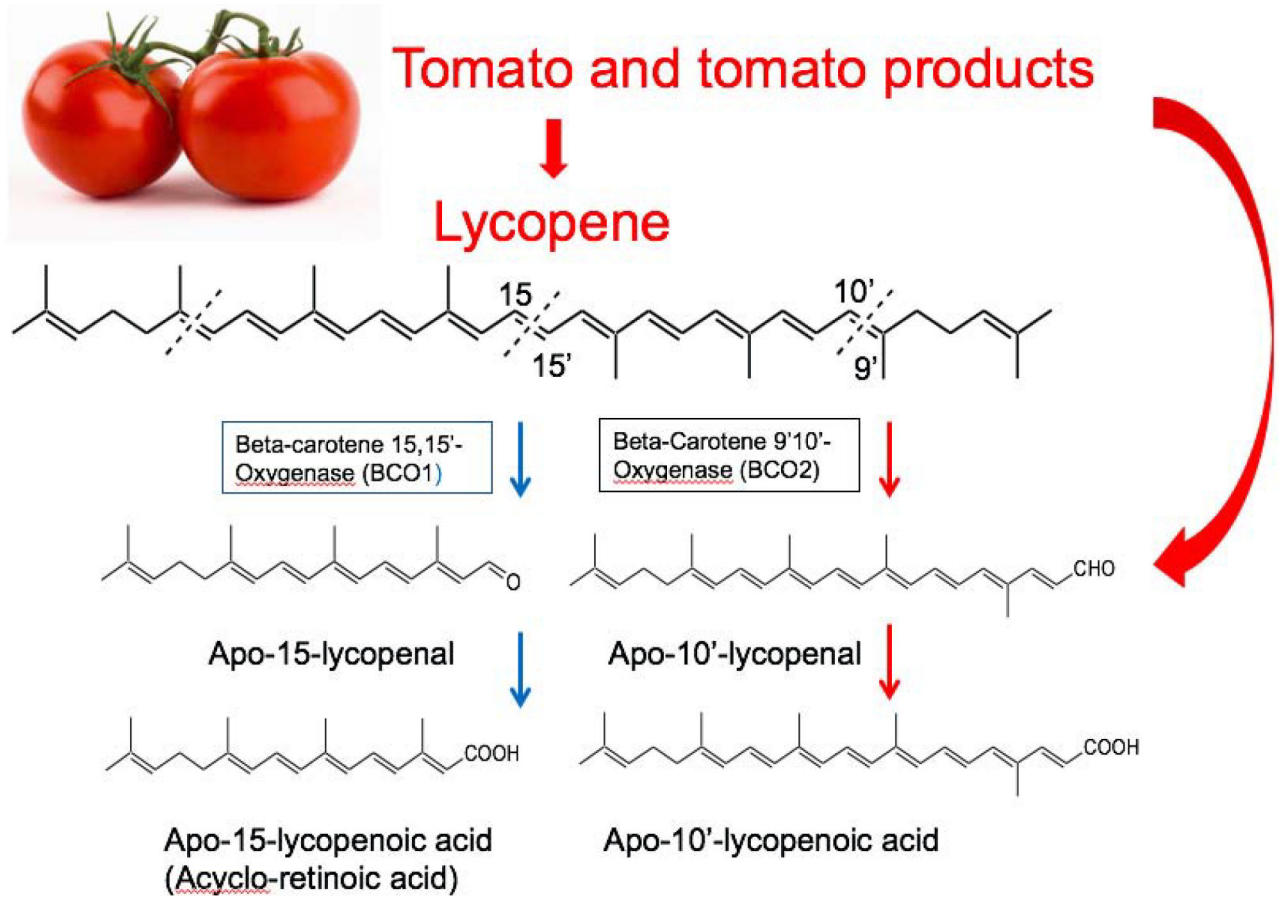
Figure 1.
Metabolism of β-cryptoxanthin.

Figure 2.
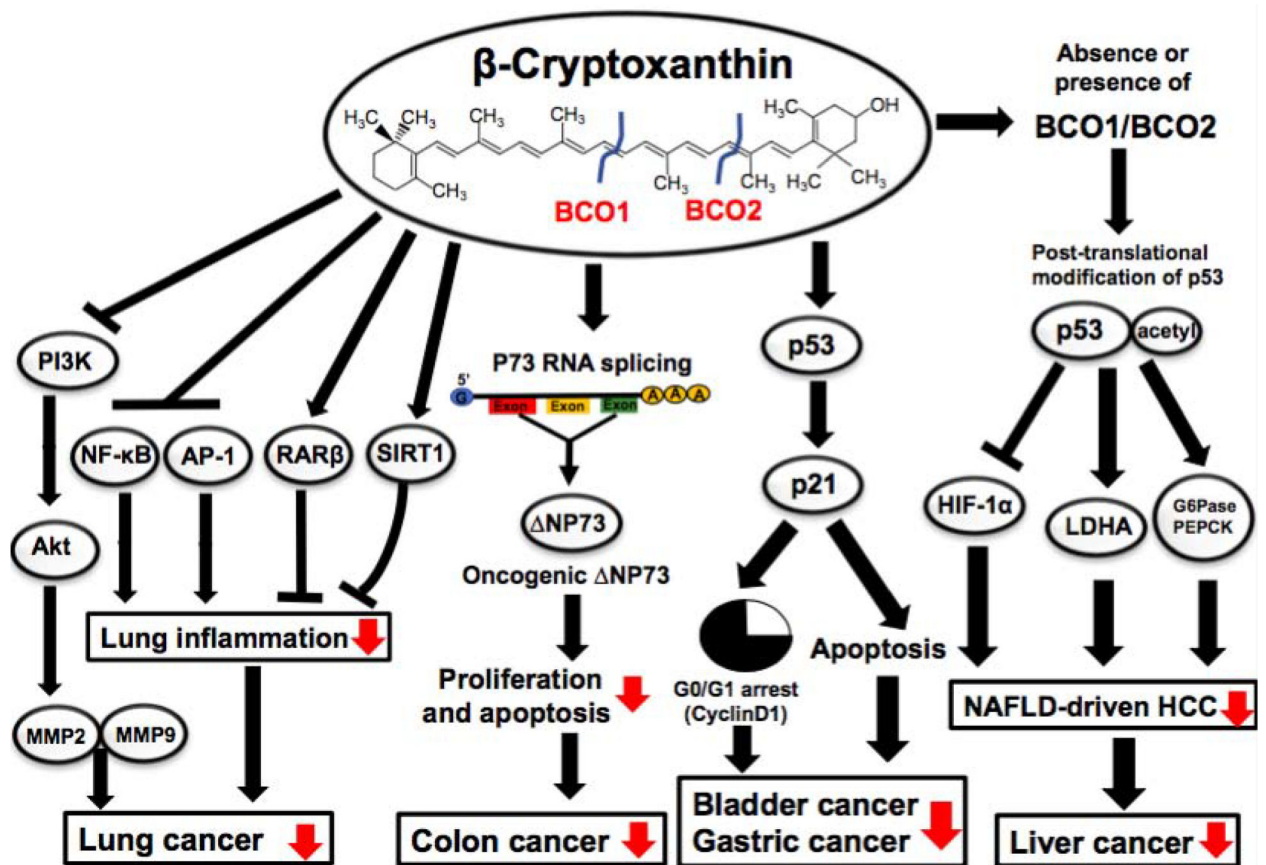Metabolism of lycopene (modified from [204])

Figure 3. Potential molecular mechanisms underlying β-cryptoxanthin prevention of cancer development/progression.

β-Cryptoxanthin supplementation inhibits lung inflammation by reducing nuclear NF-κB and AP-1 and also suppresses lung cancer development by restoring RARβ, SIRT1, and NAChRs/PI3K/Akt pathway in lung cancer murine models; β-cryptoxanthin treatment regulates p73 RNA splicing, producing less oncogenic truncated ΔNP73, thereby suppressing proliferation and contributing to the inhibition of colon cancer in mice; β-cryptoxanthin increases acetylated-p53, an active form of p53, thereby inhibiting HIF-1α, LDHA, and increasing G6Pase and PEPCK in hepatic tumors and leading to the suppression of HCC in WT and BCO1/BCO2 DKO mice; β-cryptoxanthin upregulates p53 and induces G0/G1 cell cycle arrest and apoptosis in gastric and bladder cancer in mice. AP-1, activator protein 1; G6Pase, glucose-6 phosphatase; HIF-1α, hypoxia-inducible factor 1α; LDHA, lactate dehydrogenase; MMP, matrix metallopeptidase; PEPCK, phosphoenolpyruvate carboxykinase; RAR, retinoic acid receptor; SIRT1, sirtuin1.
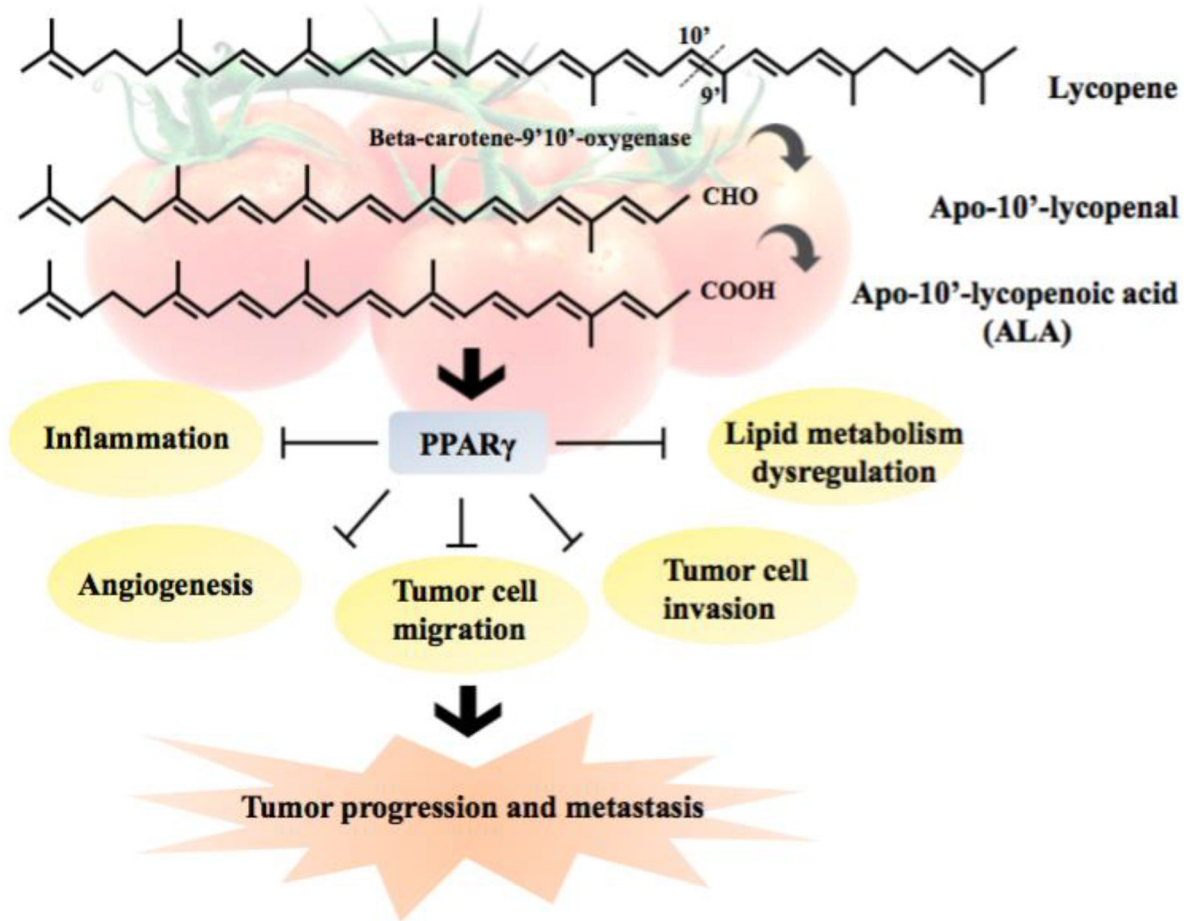
Figure 4.
Molecular mechanisms by which apo-10'-lycopenoic acid up-regulates PPARγ signaling pathway and inhibits tumor progression and metastasis (modified from [107])
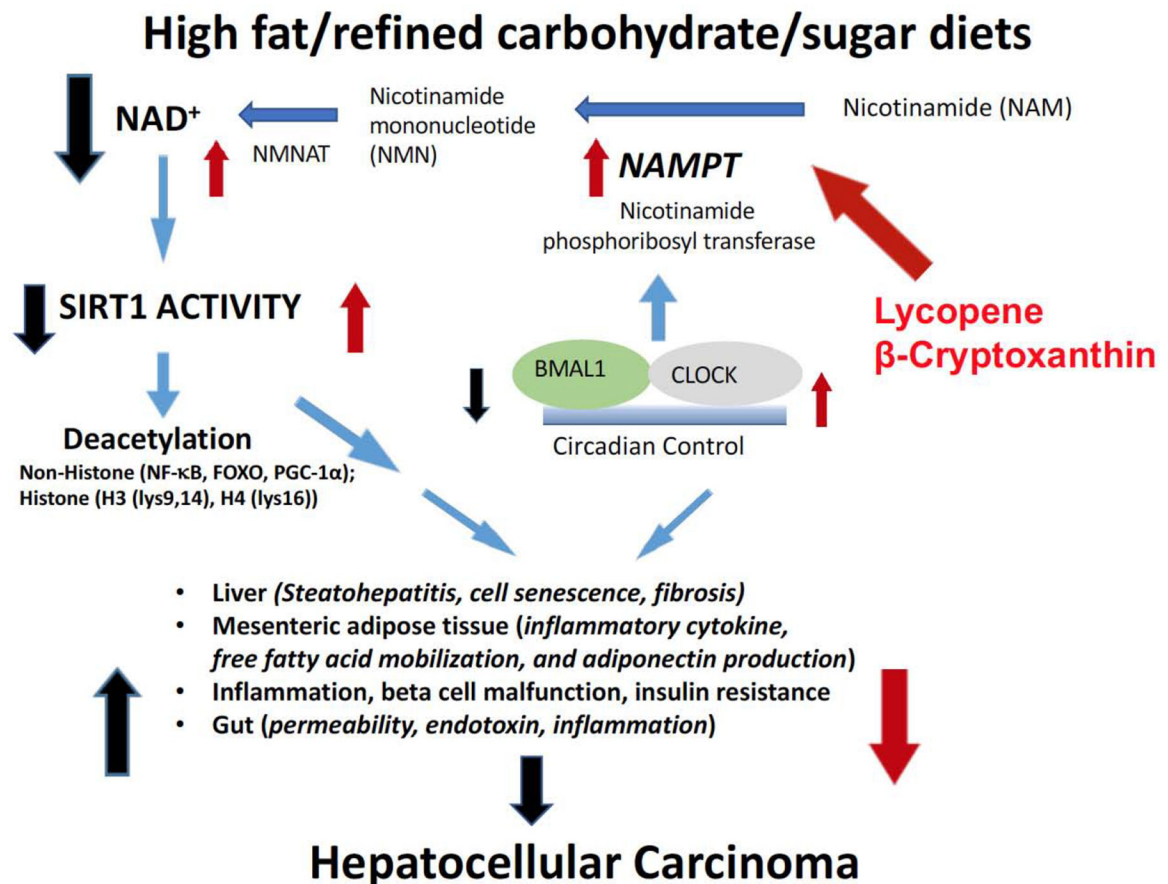
Figure 5. Molecular mechanisms underlying β-cryptoxanthin and lycopene regulates SIRT1, a nicotine adenosine dinucleotide (NAD$^+$)-dependent protein-deacetylase, thereby inhibiting western diet (high fat/refined carbohydrate/excessive sugar)-promoted inflammation and carcinogenesis.

High fat/refined carbohydrate/sugar diets impaired SIRT1 activity, thereby increasing susceptibility of many diseases, including non-alcoholic steatohepatitis and HCC, by targeting multiple organs. Carotenoids may restore western diet-reduced SIRT1 deacetylase activity and NAD$^+$ levels by up-regulating nicotinamide phosphoribosyltransferase (NAMPT). NAD$^+$, nicotine adenosine dinucleotide; NMN, nicotinamide mononucleotide; NMNAT, nicotinamide mononucleotide adenylyltransferase; NAMPT, nicotinamide phosphoribosyltransferase; HCC, hepatocellular carcinoma; SIRT1, sirtuin1.
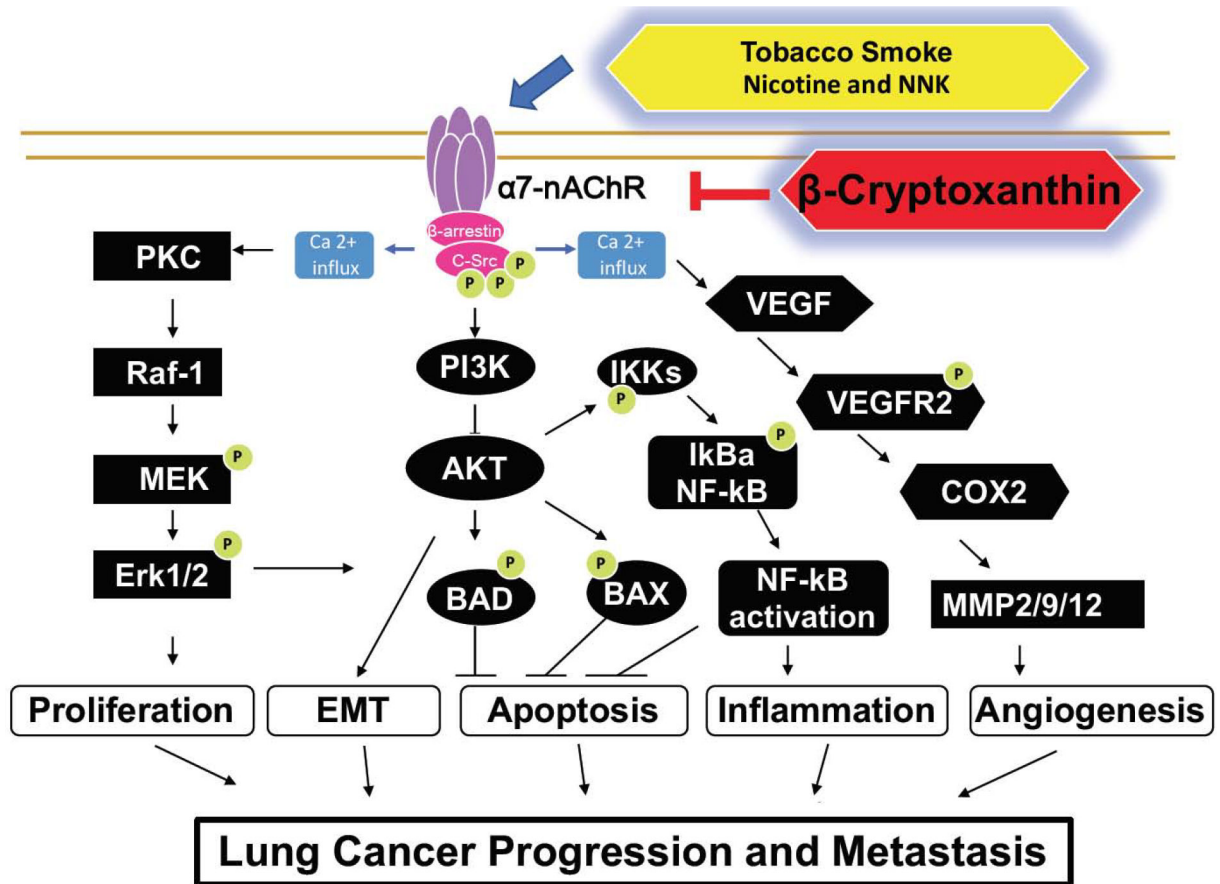
Figure 6. Molecular mechanisms underlying β-cryptoxanthin inhibits α7-nAChR, thereby leading to the inhibition of lung cancer progression and metastasis.
The binding of nicotine and NNK, a tobacco carcinogen derived from nictine to α7-nAChR might induce the formation of an oligomeric complex, including Src, β-arrestin, and α7-nAChR. This can lead to the elevation of cytosolic calcium influx and activation of the MEK/ERK signaling pathway, thereby promoting lung cancer proliferation. Nicotine also phosphorylates VEGFR2, which in turn increases COX and induces MMPs, which can cause cancer cell invasion. Nicotine can activate NF-κB by activation of the PI3K/Akt pathway, which may increase inflammation, survival, and proliferation. β-Cryptoxanthin inhibits lung cancer progression and metastasis by inhibiting α7-nAChR in mice. α7-nAChR, α7 nicotinic acetylcholine receptor; BCO1, β-carotene 15,15'-dioxygenase; BCO2, β-carotene 9',10'-oxygenase; COX2, cyclooxygenase2; MMP, matrix metallopeptidase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
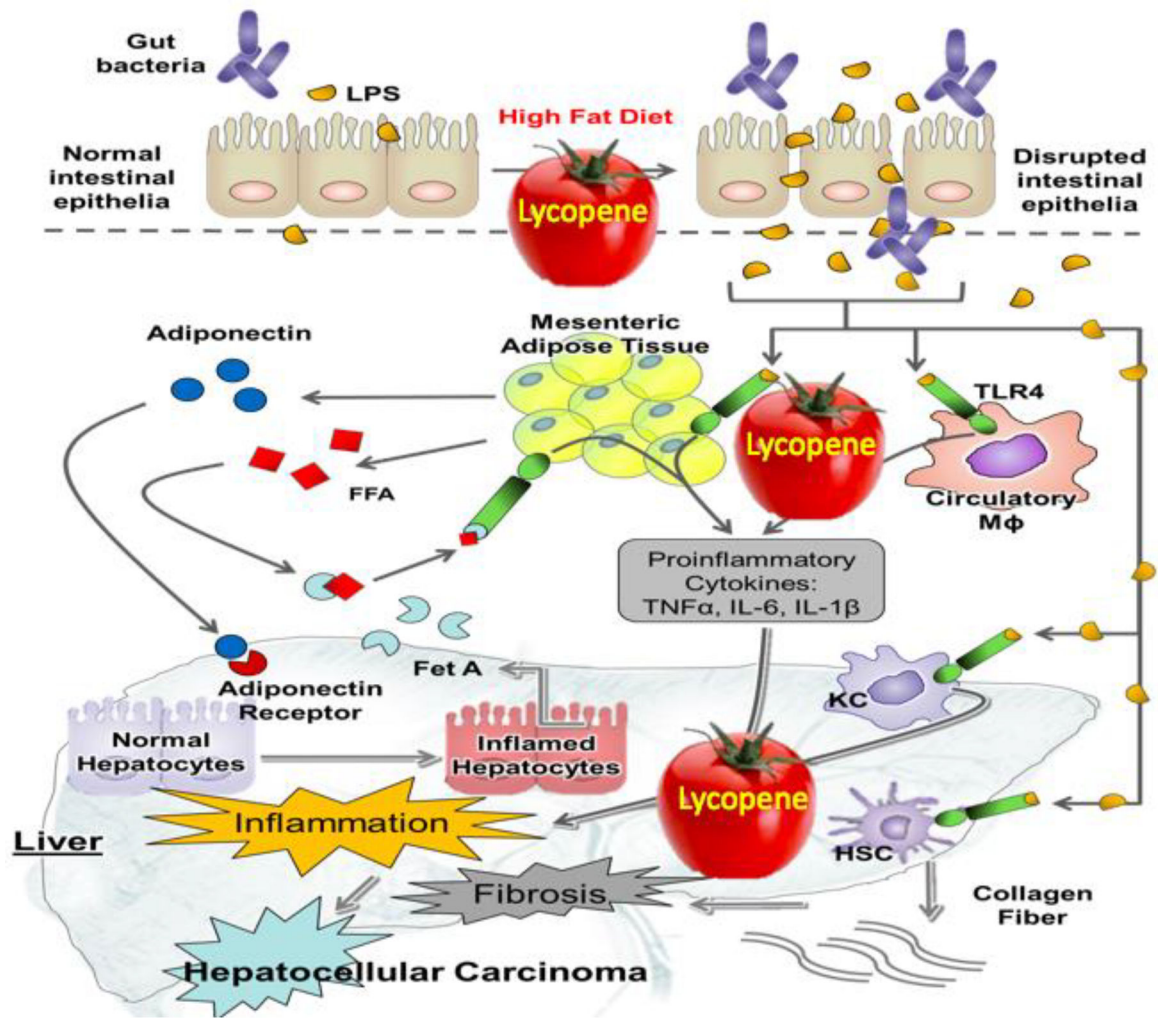
Figure 7. The proposed mechanisms of how tomato powder containing lycopene regulates microbiome and inhibits the development of hepatic inflammation and hepatocellular carcinoma (modified from [205]).

A high-fat diet can impair the intestinal epithelium, which may lead to hepatic inflammation and HCC by increasing lipopolysaccharides (LPS). Obesity can induce adipocyte hypertrophy, which may facilitate releasing free fatty acids (FFA) into the circulation. Circulatory FFA can activate Toll-like receptor 4 (TLR4)-mediated inflammatory signaling pathways in macrophages and adipocyte. Tomato powder supplementation reverses these reactions, thereby attenuating hepatic inflammation, hepatic steatosis, and HCC. FFA, free fatty acids; HCC, hepatocellular carcinoma; LPS, lipopolysaccharides; TLR4, toll-like receptor 4.