Lycopene metabolism and its biological significance1–5

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ABSTRACT
The beneficial effects of a high intake of tomatoes and tomato products on the risk of certain chronic diseases have been presented in many epidemiologic studies, with the suggestion that lycopene (a major carotenoid in tomatoes) is a micronutrient with important health benefits. Within the past few years, we have gained greater knowledge of the metabolism of lycopene and the biological effects of lycopene derivatives. In particular, the characterization and study of β-carotene 9’,10’-oxygenase has shown that this enzyme can catalyze the excentric cleavage of both provitamin and non–provitamin A carotenoids to form apo-10’-carotenoids, including apo-10’-lycopenoids from lycopene. This raised an important question of whether the effect of lycopene on various cellular functions and signaling pathways is a result of the direct actions of intact lycopene or its derivatives. Several reports, including our own, support the notion that the biological activities of lycopene can be mediated by apo-10’-lycopenoids. More research is clearly needed to identify and characterize additional lycopene metabolites and their biological activities, which will potentially provide invaluable insights into the mechanisms underlying the effects of lycopene in humans.

INTRODUCTION
The most abundant carotenoids in human plasma include β-carotene, α-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene. These 6 major carotenoids account for ~70% of all carotenoids identified in human plasma and tissues. Carotenoids are divided into 2 major groups: xanthophylls, which are oxygenated carotenoids that include lutein, zeaxanthin, and β-cryptoxanthin, and carotenes, which are hydrogen-carbon carotenoids that are either cyclized, such as α-carotene and β-carotene, or linear, such as lycopene (1). More recently, lycopene has attracted considerable attention because of its association with a decreased risk of certain chronic diseases, including cardiovascular diseases and cancers (2). Considerable efforts have been expended to identify its biological and physiochemical properties. Relative to β-carotene, lycopene has the same molecular mass and chemical formula, yet lycopene is an open-polyene chain lacking the β-ionone ring structure. Whereas the metabolism of β-carotene has been extensively studied, the absorption, transport, metabolism, and biological activities of lycopene remain undefined. Within the past few years we have gained greater knowledge of the biological effects of lycopene and its derivatives (3, 4); apo-lycopenoids, which are lycopene derivatives (5), are formed when the carbon skeleton is shortened by the removal of fragments from one or both ends of the lycopene with the position of the point of cleavage indicated, e.g., apo-10’-lycopenal from lycopene. The cleavage of lycopene with a long-chain of conjugated double bonds by autooxidation, radical-mediated oxidation, and singlet oxygen has been documented; however, the importance of such products remains poorly understood (6). Recently, the characterization and study of β-carotene 9’,10’-oxygenase (BCO2)6 have shown that this enzyme can catalyze the excentric cleavage of both provitamin and non–provitamin A carotenoids to form apo-10’-carotenoids including apo-10’-lycopenoids from lycopene (7, 8). Importantly, these metabolites possess specific and nonspecific biological activities in both in vitro and in vivo systems (9). In this review, the metabolic pathway of lycopene and the potential biological actions of lycopene metabolites will be highlighted.

LYCOPENE ABSORPTION AND TRANSPORT
Humans absorb a significant portion of intact lycopene directly, and it circulates through and accumulates in their plasma, liver, and peripheral tissues. The half-life of plasma carotenoids ranges from ≤12 d for β-carotene, α-carotene, and cryptoxanthin to 12–33 d for lycopene and 33–61 d for zeaxanthin and lutein (10). In terms of absorption, β-carotene, not lycopene and other carotenoids, has been the most extensively studied. Although further investigation of the absorption of individual carotenoids and their cis isomers is needed, the factors that influence the absorption of β-carotene may affect lycopene similarly (Figure 1). Similar to other carotenoids, tomato carotenoids, including lycopene, phytoene, and phytofluene, are embedded in their food matrix and cannot be absorbed efficiently. Food processing and

1 From the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA.
2 Presented at the conference “New Developments in Carotenoids Research,” held in Boston, MA, March 11–12, 2011.
3 Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of NIH and the USDA.
4 Supported by NIH grant R01CA104932 and USDA grant 1950-51000-064S.
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6 Abbreviations used: ARE, antioxidant response element; BCO1, β-carotene 15,15’-oxygenase; BCO2, β-carotene-9’,10’-oxygenase; HO-1, heme oxygenase-1; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; ISX, intestine-specific homeobox; Nrf2, nuclear factor E2–related factor 2; RAR, retinoic acid receptor; RARE, retinoic acid response element; SR-B1, scavenger receptor class B type 1.

First published online October 10, 2012; doi: 10.3945/ajcn.111.032359.
and secreted into the lymphatic system for transport to the liver. Vitamin A and other metabolites or packaged into chylomicrons in the intestine, they are either cleaved by BCO1 and/or BCO2 into adipose tissue (16).

Has shown that CD36 is involved in lycopene and lutein uptake by the role in the movement of carotenoids into cells. A recent study of long-chain fatty acids and oxidized LDLs, might also play a role in the inactivation of carotenoids into cells.

Another protein, CD36, a surface membrane glycoprotein in the duodenum and jejunum involved in the uptake of long-chain fatty acids and oxidized LDLs, might also play a role in the movement of carotenoids into cells. A recent study has shown that CD36 is involved in lycopene and lutein uptake by adipose tissue (16).

After carotenoids are taken up by the mucosa of the small intestine, they are either cleaved by BCO1 and/or BCO2 into vitamin A and other metabolites or packaged into chylomicrons and secreted into the lymphatic system for transport to the liver and other peripheral tissues (Figure 1). Some polar metabolites can be directly transported into the liver via the portal blood system (17). It seems that the differential absorption of carotenoids and their metabolites into lymph or portal blood is dependent on the polarity of the metabolites involved. Chylomicrons in the bloodstream are partially degraded by lipoprotein lipase, which leaves chylomycin remnants that are quickly taken up by the liver (Figure 1). Some carotenoids may be released from these lipoproteins and taken up directly by extracellular tissues. In the fed state, the liver stores or secretes the carotenoids in VLDL and LDL. In the fasting state, plasma carotenes are found mainly in LDL. Xanthophylls (lutein, zeaxanthin, and β-cryptoxanthin) are located mainly in both LDL and HDL, with small amounts located in VLDL. LDL transport accounts for ~55%, HDL for 31%, and VLDL for 14% of total blood carotenoids. Specific factors that regulate tissue uptake, recycling of carotenoids back to the liver, and excretion are not yet understood (18).

LYCOPENE METABOLISM

Carotenoids such as β-carotene, α-carotene, and β-cryptoxanthin are cleaved symmetrically at their central double bond by BCO1 (19–21) and are present in several mouse and human tissues (eg, liver, kidney, intestinal tract, and testis) (22, 23).

Purified recombinant human BCO1 enzyme cleaves β-carotene in vitro with a Michaelis constant (Km) and Vmax of 7 μmol/L and 10 nmol retinal/mg × min, respectively (24). Retinal formed from β-carotene can be subsequently reduced to retinol or oxidized further to form retinoic acid (Figure 1). Non–provitamin A carotenoids, such as lycopene, were cleaved by purified recombinant murine and ferret BCO1 with much lower or no activity (22, 25, 26). Four conserved histidines and one conserved glutamate residue are essential for the catalytic mechanism of BCO1, presumably for the coordination of the iron cofactor required for catalytic activity (27).

Chicken BCO1 showed substrate specificity toward a broad array of carotenoid substrates, including α-carotene, β-carotene, γ-carotene, β-cryptoxanthin,
apo-4'-carotenal, and apo-8'-carotenal (26). In light of this evidence, it appears that the presence of at least one unsubstituted \( \beta \)-ionone ring is sufficient for catalytic cleavage of the central carbon 15,15\# double bond.

Building on evidence that the excentric cleavage of \( \beta \)-carotene leads to a series of homologous carbonyl cleavage products (28–30), the existence of this pathway was confirmed by the molecular identification of BCO2 in mice, humans, zebra fish, and ferrets (7, 8). BCO2 shares overall sequence homology with BCO1 and the same conserved pattern of histidine residues and glutamate residues presumably involved in binding the iron cofactor in both proteins (7, 27). BCO2, a mitochondrial enzyme (31), is highly expressed in the liver and testis, and at lower amounts in the kidney, lung, heart, spleen, prostate, intestine, stomach, colon, and brain (7, 8). Recombinant ferret BCO2 cleaves all-trans \( \beta \)-carotene to form \( \beta \)-apo-10'-carotenal in a pH- and time-dependent linear manner with a pH optimum of between 8.0 and 8.5. The reaction exhibited Michaelis-Menton kinetics, with an estimated \( K_m \) of 3.5 \pm 1.1 \mu mol/L for \( \beta \)-carotene and a \( V_{max} \) of 32.2 \pm 2.9 pmol \( \beta \)-apo-10'-carotenal \( \cdot \) mg\(^{-1}\) \( \cdot \) h\(^{-1}\). \( \beta \)-Apo-carotenals can be cleaved further by BCO1 to produce retinol and retinoic acid (32, 33) or oxidized to their corresponding apo-\( \beta \)-carotenoic acids (Figure 1). Apo-\( \beta \)-carotenoic acids may then undergo a process similar to \( \beta \)-oxidation of fatty acids, until the further oxidation is blocked by the methyl group at the C13 position (34). This shortening produces retinoic acid from \( \beta \)-carotene (34). \( \beta \)-Apo-12'-carotenal and \( \beta \)-apo-10'-carotenal were isolated from ferret intestinal mucosa after perfusion of \( \beta \)-carotene in vivo (35, 36) and \( \beta \)-apo-8'-carotenal was detected in humans given an oral dose of all-trans [10,10',11,11'-\( ^{14} \)C]-\( \beta \)-carotene (37). More recently, underlycopenoids, including apo-6-, apo-8'-, apo-10'-, apo-12', and apo-14'-lycopenal, were detected in the plasma of humans who had consumed tomato juice (38) Although the exact contribution of BCO2 in vitamin A biosynthesis remains unknown (39), recent data show that the mutation in the bovine \( BCO2 \) gene results in increased adipose, serum, and milk \( \beta \)-carotene concentrations and decreased liver retinol (40, 41).

Whereas BCO1 catalyzes the cleavage of provitamin A carotenoids with much greater activity than non–provitamin A carotenoids, the activity of BCO2 is higher toward non–provitamin A carotenoids, such as \( cis \)-lycopene isomers, lutein, and zeaxanthin, than toward \( \beta \)-carotene as a substrate (8, 42). Interestingly, the recombinant ferret BCO2 catalyzes the excentric cleavage of \( cis \)-lycopene isomers effectively but not all-trans lycopene at the 9',10' double bond (Figure 2) (8). In addition, \( cis \)-lycopene may act as a better substrate than all-trans \( \beta \)-carotene.
for the ferret BC02 (8, 43). The mechanism whereby ferret BC02 preferentially cleaves the 5-cis and 13-cis isomers of lycopene into apo-10'-lycopenal but not all-trans lycopene is currently unknown. One possible explanation is that the chemical structure of cis isomers of lycopene could mimic the ring structure of the β-carotene molecule and fit into the substrate-enzyme binding pocket. Although this hypothesis warrants further investigation, the observation that supplementation of all-trans lycopene results in a significant increase in cis-lycopene tissue concentration in ferrets underlines the significance of this observation (44, 45). Recently, it has been shown that the non–provitamin A carotenoids including lutein and zeaxanthin are preferentially cleaved over provitamin A carotenoids, indicating a key role of BC02 in non–provitamin A carotenoid metabolism (8, 42). This provides strong biochemical evidence supporting the recent genetic evidence that accumulation of the xanthophylls lutein and zeaxanthin in adipose tissue and skin are due to mutations in the BC02 gene (46, 47). Recent animal genetic reports have provided evidence of broad substrate specificity of BC02. Bovine BC02 was shown to contain a single nucleotide polymorphism resulting in a truncated and presumably non-functional BC02 protein (40, 41). In Norwegian white sheep (Ovis aries), a nonsense mutation in the BC02 gene was significantly associated with a yellow adipose phenotype (46). In chickens, a yellow skin phenotype is associated with a single nucleotide polymorphism in the BC02 gene (47). The decrease in skin BC02 leads to the yellow skin pigmentation of domestic chickens, suggesting a decreased ability to cleave the xanthophylls lutein and zeaxanthin, which are the major accumulated carotenoids in chicken skin (48). Considering the possible beneficial effects of lycopene, lutein, and zeaxanthin in human health, enzymatic cleavage of non–provitamin A carotenoids by BC02 represents a new avenue of research regarding vertebrate carotenoid metabolism and biological function.

However, the identification of enzymatic metabolites of lycopene in vivo is challenging. Previously, Khachik et al (49) identified a group of lycopene oxidative products, 2,6-cyclolycopene-1,5-diol A and B, in human serum and many other tissues, including prostate, lung, and colon. Recently, a series of apo-lycopenals, including apo-10'-lycopenal, have been identified in human plasma (38), although it is unknown whether these metabolites are enzymatic cleavage products or the products of chemical oxidative cleavage of lycopene. In animal studies, among several metabolites detected in lung tissue of these lycopene-supplemented ferrets, one was identified as apo-10'-lycopenol, with a concentration of 8 ± 3 pmol/g wet-weight lung tissue (8). However, no apo-10'-lycopenol was detected, which suggested that apo-10'-lycopenal, the primary cleavage product, might be an intermediate compound and could be either reduced to apo-10'-lycopene or oxidized to apo-10'-lycopenoic acid. This was supported by the conversion of apo-10'-lycopene into apo-10'-lycenoic acid in the presence of NAD+, and to both apo-10'-lycenoic acid and apo-10'-lycopenol in the presence of NADH (8) (Figure 2). Gajic et al (50) reported the detection of apo-8'- and apo-12'-lycopenal as well as other unidentified polar metabolites of lycopene in the liver of rats given lycopene-enriched food. Interestingly, a recent study indicated that apo-10'- and apo-14'-lycenoic acid have a remarkable ability to upregulate BC02 expression (51). In addition, the expression of BC02 mRNA in ferret lung was upregulated 4-fold by lycopene supplementation compared with animals not receiving lycopene supplementation (8). These results show that lycopene can be converted to apo-10'-lycopenoids, which can regulate BC02 function in mammalian tissues both in vitro and in vivo. These observations also raise the question of whether apo-10'-lycopenoids have important biological functions related to human health (see below).

**BILOGICAL FUNCTIONS OF LYCOPENE AND ITS METABOLITES**

Because plasma values of carotenoids are biomarkers for the consumption of diets rich in fruit and vegetables, which contain other potentially bioactive nutrients, an association does not necessarily prove that lycopene is the active compound. To show these molecular effects in human systems, which involve multiple genetic and epigenetic events, is even more challenging. On the other hand, although it has not been confirmed whether or not lycopene is an important food component with health benefits, many human epidemiologic, cell culture, and animal model studies provide strong evidence that lycopene and its metabolites are active in several biological activities (Figure 3). Because there are several recent reviews on lycopene metabolism and biological function (12, 52, 53), recent studies on the biological activities of lycopene metabolites will briefly be reviewed.

**INDUCTION OF ANTIOXIDANT/PHASE II DETOXIFYING ENZYMES**

Free radicals can cause cellular damage by reacting with proteins, lipids, carbohydrates, and DNA and may be involved in the etiology of human diseases including cancer, cardiovascular disease, and age-related diseases. Whereas the initial impetus for studying the benefits of lycopene in chronic disease prevention was its antioxidant capacity, significant advances have been made in the understanding of the action of lycopene cleavage products with regard to modulation of antioxidant/detoxifying phase II enzymes via nuclear factor E2–related factor 2 (Nrf2) signaling. The transcription factor Nrf2, a key regulator of the cellular response to oxidative stress in multiple tissue and cell types, is a primary factor in the induction of antioxidant/phase II detoxifying enzymes (54, 55). Phase II enzymes have important detoxifying and antioxidant properties in combating reactive oxygen species and foreign substances (xenobiotics), including potential carcinogens. Induction of phase II detoxify/antioxidant enzymes is mediated through cis-regulatory DNA sequences known as antioxidant response elements (AREs), which are located in the promoter or enhancer region of the gene. The major ARE transcription factor Nrf2 is a primary agent in the induction of antioxidant and detoxifying enzymes, such as heme oxygenase-1 (HO-1), glutathione S-transferases, and NAD(P)H: quinone oxidoreductase. Under normal conditions, most of the Nrf2 is sequestered in the cytoplasm by Kelch-like erythroid Cap’n’Collar homolog-associated protein 1, and only residual nuclear Nrf2 binds to the ARE to drive basal activities. Exposure to certain carotenoids leads to the dissociation of the Nrf2–Kelch-like erythroid Cap’n’Collar homolog-associated protein 1 complex in the cytoplasm and the translocation of Nrf2 into the nucleus (56, 57). The nuclear accumulation of Nrf2 subsequently activates target genes of phase II/antioxidant enzymes.
Non–provitamin A carotenoids including lycopene, lutein, canthaxanthin, and astaxanthin are shown to induce several phase II enzymes both in vivo and in vitro (58, 59). Because of its critical roles in the detoxification and antioxidant process during carcinogenesis, Nrf2 has been recognized as a potential molecular target for cancer prevention.

The first evidence was that an ethanolic extract containing lycopene and unidentified hydrophilic oxidative derivatives was shown to induce phase II enzymes and activate ARE-driven reporter gene activity with a similar potency to lycopene (56), although those chemically produced oxidative derivatives have not been found in mammalian tissues. Further evidence has been obtained recently to show that apo-10\(^{-2}\)-lycopenoic acid, apo-10\(^{-1}\)-lycopenoic acid, and apo-10\(^{-3}\)-lycopenoic acid were all effective in activating the Nrf2-mediated induction of HO-1 (60). HO-1, one of the major targets of Nrf2 regulation, is a rate-limiting enzyme in the degradation of heme to produce biliverdin (and its break-down product bilirubin), which behaves as a potent antioxidant by scavenging free radicals and plays an important antiinflammatory role in a number of chronic inflammatory diseases including alcohol-related inflammation (61, 62). Carbon monoxide, another break-down product of heme by HO-1, has strong antiinflammatory effects (61, 62). Work with BEAS-2B human bronchial epithelial cells has shown a dose-dependent and time-dependent increase in the accumulation of nuclear Nrf2 protein, as well as induced mRNA expression of HO-1, after apo-10\(^{-1}\)-lycopenoic acid treatment (60). In addition, pretreatment of BEAS-2B cells with apo-10\(^{-3}\)-lycopenoic acid resulted in a dose-dependent inhibition of both endogenous reactive oxygen species production and H\(_2\)O\(_2\)-induced oxidative damage, as measured by release of lactate dehydrogenase (60). These in vitro studies provide a mechanistic understanding for the chemopreventive effect of lycopene metabolites against carcinogen-induced cancer development in animal models in vivo (57). However, lycopene supplementation at a higher dose significantly induced hepatic phase I enzyme cytochrome P4502E1 protein and the incidence of inflammatory foci in alcohol-fed rats (63). These data indicate an interaction between chronic alcohol ingestion and lycopene supplementation and suggest a need for caution among individuals consuming high amounts of both alcohol and lycopene. Because induction of phase II detoxifying or antioxidant genes by dietary carotenoids represents an important cellular defense in response to oxidative and electrophilic insults, more research is clearly needed to identify and characterize additional carotenoid metabolites and their biological activities.

**INTERACTION WITH RETINOID RECEPTORS**

Provitamin A carotenoids can serve as direct precursors for all-\textit{trans} and 9-\textit{cis} retinoic acid (64, 65), which are ligands for RAR and retinoid X receptor. \(\beta\)-Carotene was able to maintain normal tissue levels of retinoic acid and inhibit the activation of mitogen-activated protein kinase pathways, cell proliferation, and phosphorylation of p53 (66). Certain excentric cleavage metabolites, such as \(\beta\)-apo-carotenoid acid, but not \(\beta\)-apo-13-carotenone, can also induce RAR\(\beta\) expression and transactivate the RAR\(\beta\) promoter via primary metabolism to the potent RAR ligand, all-\textit{trans} retinoic acid (67). Therefore, the molecular mode of the action of provitamin A carotenoids is likely to be mediated by retinoic acid through transcriptional activation of a series of genes (68).

Discovery of the excentric cleavage of carotenoids heightens interest in carotenoid cleavage products and their possible biological interaction with nuclear receptors. The production of apo-carotenoids and apo-lycopenals is shown in several studies (37, 42, 69, 70). Without being converted into retinoids, the nonvolatile apo-carotenoids and apo-lycopenals can inhibit cell growth (57, 71–73), stimulate differentiation (74), transactivate nuclear receptors (57), or antagonize nuclear receptor activation.

![FIGURE 3. Schematic illustration of potential biological effects, both beneficial and harmful, attributed to carotenoids and their metabolites to human health. Although small quantities of carotenoid metabolites may offer protection against chronic diseases and certain cancers, larger amounts maybe harmful, especially when coupled with a highly oxidative environment (eg, the lungs of cigarette smokers or liver of excessive alcohol drinkers). Adapted with permission from reference 3. PPAR, peroxisome proliferator–activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor.](https://example.com/figure3.png)
FACTORS MODULATION OF HORMONES AND GROWTH

The volatile apo-carotenoid β-ionone is also shown to inhibit cell proliferation and induce apoptosis both in vitro (76–78) and in vivo (79). Interestingly, β-cryptoxanthin dose-dependently increases retinoic acid response element (RARE)–dependent promoter activity of retinoic acid receptor β in cells cotransfected with an RAR expression vector (80), and this transactivation activity of β-cryptoxanthin is shown to be due to its binding and activating RAR receptors directly without its conversion into retinoids (81). It is possible that beyond participating in known retinoid signaling pathways, carotenoids and their metabolites are able to interact directly with transcription factors without their conversion into retinoids.

Among identified lycopene metabolites, acycloretinoic acid has been shown to inhibit cell proliferation (82–84), induce apoptosis (85), and enhance gap junction communication (86). As an analog of retinoic acid, the ability of acycloretinoic acid to activate RAR was first examined by Ben-Dor et al (83) and Stahl et al (86). Although acycloretinoic acid is able to activate RARE-driven luciferase gene transcription, the required concentration is much higher than that of all-trans retinoic acid, which suggests that acycloretinoic acid is a weak activator of RARs (83, 86). Because of the similarity in chemical structures among apo-10'-lycopenoic acid, acycloretinoic acid, and all-trans retinoic acid (Figure 2), we questioned whether apo-10'-lycopenoic acid is an activator of RARs. We showed that treatment with 3–5 µmol apo-10'-lycopenoic acid/L significantly increased the mRNA level of RARβ, which is a transcriptional target of RARs (87), in lung cells (normal human bronchial epithelial, BEAS-2B, and A549 cells) (57). We then constructed a reporter vector containing the RARβ promoter fragment in the promoter region of luciferase gene. We showed that apo-10'-lycopenoic acid treatment increased the luciferase activity of HeLa cells transfected with this reporter vector. When the RARE in RARβ promoter was mutated, the ability of apo-10'-lycopenoic acid to transactivate RARβ promoter was abolished. These results suggest that apo-10'-lycopenoic acid can transactivate RARs and that activation of RARs may account for the growth inhibitory effect of apo-10'-lycopenoic acid (57).

MODULATION OF HORMONES AND GROWTH FACTORS

Steroid hormones (such as androgens and estrogen) and insulin-like growth factor (IGF) signaling systems may play a role in the biological action of carotenoids, in particular lycopene (88). Lycopene reduced the expression of 5α-reductase-1 in rat prostate tumors (89). Lycopene, phytotoxene, and phytofluene inhibited the estrogen-induced transactivation of the estrogen response element bound by the nuclear estrogen receptors ERα and ERβ (90). The IGF signaling system may also play a role in the biological action of lycopene (91). It has been suggested that the IGF signaling system may play a critical role in the biological action of lycopene (91, 92). By binding to membrane IGF-1 receptor, IGFBPs activate intracellular phosphatidylinositol 3’-kinase/Akt/protein kinase B and Ras/Raf/mitogen-activated protein kinase pathways, which regulate various biological processes such as cell-cycle progression, survival, and transformation (93). Lycopene treatment was shown to inhibit IGF-1–stimulated insulin receptor substrate 1 phosphorylation and cyclin D1 expression, block IGF-1–stimulated cell-cycle progression (91, 94), and increase membrane-associated IGF binding proteins (IGFBPs) in MCF-7 breast cancer cells (91), suggesting that lycopene may inhibit cell proliferation by acting on IGF-1 signaling pathway.

In circulation, IGFBPs are sequestered by a family of binding proteins (IGFBP-1–IGFBP-6), which regulate the availability of IGFBPs to bind to the IGF receptors (93). Consistent with in vitro studies that showed lycopene as a modulator of IGF signaling (91, 92), higher dietary intake of lycopene has been associated with lower circulating concentrations of IGF-1 (95) and higher concentrations of IGFBP-3 (96) in epidemiologic studies. In addition, the modulation of IGF-1 signaling is suggested to play an important role in lung carcinogenesis (97–99). Ferrets (Mustella putorius furo) offer an excellent model for mimicking the conditions of carotenoid intervention studies in humans because ferrets and humans are similar in terms of lycopene absorption, tissue distribution and concentrations, and metabolism (100). By using the ferret as a model, we found that plasma concentrations of IGF-1 were not affected by either lycopene supplementation or cigarette smoke exposure (44). Interestingly, cigarette smoke exposure decreased ferret plasma concentrations of IGFBP-3, whereas ferrets supplemented with both doses of lycopene had higher concentrations of IGFBP-3, regardless of cigarette smoke exposure. Furthermore, the ratio of IGF-1 to IGFBP-3 was significantly decreased in ferrets supplemented with lycopene and exposed to smoke than in those exposed to smoke alone (44). The increased plasma IGFBP-3 by lycopene supplementation was associated with the inhibition of cigarette smoke–induced lung squamous metaplasia, decreased proliferating cellular nuclear antigen and phosphorylated BAD protein concentrations and the restoration of cleaved caspase-3 concentrations in lung tissue (44), which suggested the inhibition of proliferation and induction of apoptosis. Recently, we observed that apo-10'-lycopenoic acid treatment significantly induced hepatic sirtuin 1 (101) and IGFBP-3 expression in several cancer cell lines including lung BEAS-2B cells, liver THLE-2 cells, and prostate PC-3 cells (F Lian, KQ Hu, CA Peach, XD Wang, unpublished data, 2011). These results support the notion that lycopene metabolites may affect IGF signaling by the modulation of IGFBP-3 expression and play a role in the prevention of lung tumor development.

CHEMOPREVENTIVE EFFECTS

Previously, it has been shown that a mixture of lycopene oxidative products were able to inhibit the growth of HL-60 human promyelocytic leukemia cells (82) and induce ARE-dependent transcription of phase II xenobiotic-metabolizing enzymes (56), suggesting that lycopene metabolites may be biologically active components against initiation, promotion, or progression stages of carcinogenesis. In addition to acycloretinoic acid as mentioned above, the biological activities of other lycopene metabolites have also been investigated. For example, Aust et al (102) showed that 2,7,11-trimethyl-tetradecahexaene-1,14-dial, a metabolite of lycopene formed by a fragmentation at the 5,6 and 12,13 positions, is able to enhance gap-junction communication, whereas Zhang et al (103) showed that (E,E,E)-4-methyl-8-oxo-2,4,6-nonatrienal, the product of oxidative cleavages at the 5,6- and 13,14 double bonds of lycopene induced apoptosis, downregulated Bcl-2 and Bcl-XL, and activated caspase cascades in HL-60 cells. However,
the physiologic roles of these lycopene products remain unknown because none of these metabolites have been detected in biological systems. Because we have detected apo-10'-lycopenol, a derivative of BCO2 cleavage of lycopene, in ferret lungs after lycopene supplementation (8, 42), we investigated the biological activity of apo-10'-lycopenoic acid, as well as its potential chemopreventive effect on lung carcinogenesis (57). We have shown that apo-10'-lycopenoic acid significantly decreased lung cancer cells in the S phase and increased cells in the G1 phase and was associated with decreased cyclin E and increased p21 and p27 expression. In addition, the lower sensitivity of A549 cells to apo-10'-lycopenoic acid treatment, as compared with NHBE and BEAS-2B cells, suggests that apo-10'-lycopenoic acid may be a better agent for cancer prevention than cancer therapy (57). This was further confirmed by an in vivo study to determine whether apo-10'-lycopenoic acid could inhibit lung tumor development in the A/J mouse model of lung cancer. Supplementation with apo-10'-lycopenoic acid decreased tumor number in a dose-dependent manner from an average of 16 tumors/mouse in the 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butane injection-alone group, to an average of 10, 7, and 5 tumors/mouse in groups injected with 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butane and supplemented with apo-10'-lycopenoic acid at doses of 10, 40, and 120 mg/kg, respectively, which represents declines of 32.7%, 53.6%, and 65.4% in tumor number compared with the non-supplemented group (57). A recent study showed that apo-12'-lycopenal reduced the proliferation of androgen-independent DU145 prostate cancer cells, in part by inhibiting normal cell-cycle progression (104). In summary, both in vitro and in vitro studies have shown that apo-10'-lycopenoic acid, an enzymatic metabolite of lycopene, is a potential chemopreventive agent against lung cancer. It will be interesting to investigate if lycopene metabolites may, at least in part, mediate the chemopreventive effect of lycopene on other cancers.

CONCLUSIONS

There is evidence from both epidemiologic studies and animal and cell culture studies that lycopene has multifaceted biological actions. These data have led to an increased effort to better understand the role of lycopene and its derivatives in the process of chronic diseases. In particular, the characterization and study of BCO2 has shown that this enzyme can catalyze the excentric cleavage of both provitamin and non–provitamin A carotenoids to form apo-10'-carotenoids, including apo-10'-lycopenoids from lycopene. Enzymatic kinetic analysis indicates that the non–provitamin A carotenoids including lycopene are preferentially cleaved over provitamin A carotenoids, indicating a key role of BCO2 in non–provitamin A carotenoid metabolism. Several in vivo and in vitro reports suggested that the biological activities of lycopene can be mediated, in part, by lycopene metabolites. More research is clearly needed to identify and characterize additional lycopene metabolites and their biological activities, which will potentially provide invaluable insight into the mechanisms underlying the beneficial effects of lycopene in humans, particularly in terms of chronic disease prevention. As our understanding of carotenoid metabolism, molecular biological properties, and their interaction with genetic and epigenetic factors improves, greater insight will be achieved into the role and application of carotenoids and their metabolites in human health and disease.

The author had no conflicts of interest.

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