Biological Actions of Carotenoid Metabolites

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Despite the fact that clinical intervention trials conducted to determine the chemoprotective effect of β-carotene as a potential chemopreventive agent on the incidence of lung cancer in smokers found either no protective effect or a harmful effect, supporting evidence for a protective role of fruits and vegetables rich in carotenoids in prevention of certain cancers (e.g., prostate, lung, breast, colorectal and stomach) and other chronic disease (e.g., atherosclerosis, diabetics, age-related macular degeneration, UV damage in skin) continues to be reported in human epidemiological studies and small intervention trials, as well as in mechanistic studies using cell culture and animal models. These findings have led to an increased effort to better understand the role of carotenoids and their derivatives in the process of these chronic diseases, with special attention to their metabolism and biological actions, dose effects, organ-specific effects and the oxidative environment, especially in smokers and alcohol drinkers (1). Within the last few years, we have gained greater knowledge of the biological effects of carotenoid derivatives and their potential benefits at small quantities or harmful effects at large quantities when produced as metabolic by-products (2). In particular, characterization and study of carotene 9',10'-oxygenase has demonstrated that this enzyme can catalyze the eccentric cleavage of both β-carotene and lycopene to form apo-10'-carotenoid and apo-10'-lycopenoid, respectively (3, 4). This finding raised an important question that remains unanswered and that is whether the effect of carotenoids, in particular lycopene, on various cellular functions and

signaling pathways is a result of the direct actions of intact carotenoids or theirs derivatives. While the initial impetus for studying the benefits of carotenoids in chronic disease prevention was their antioxidant capacity, significant advances have been made in understanding of the action of carotenoid cleavage products with regard to modulation of antioxidant/detoxifying phase II enzymes via nuclear factor E_2-related factor 2 (Nrf2) signaling. The first evidence was that an ethanolic extract containing lycopene and unidentified hydrophilic oxidative derivatives was shown to induce phase II enzymes and activate antioxidant response elements-driven reporter gene activity with a similar potency to lycopene (5), although those chemically produced oxidative derivatives have not been found in mammalian tissues. Evidence has been obtained recently to show that apo-10'-lycopenal, apo-10'-lycopenol and apo-10'-lycopenoic acid, were all effective in activating the Nrf2-mediated induction of hemo-oxygenase-1 (6). 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 several phase II enzymes, following apo-10'-lycopenoic acid treatment (6). In addition, pre-treatment of BEAS-2B cells with apo-10'-lycopenoic acid resulted in a dose-dependent inhibition of both endogenous ROS production and H_2O_2-induced oxidative damage, as measured by release of lactate dehydrogenase (6). These *in vitro* studies provided a mechanistic understanding for the chemopreventive effect of apo-10'-lycopenoic acid against carcinogen-induced cancer development in animal models *in vivo* (7,8). Since 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, which will

potentially provide invaluable insights into the mechanisms underlying the beneficial effects of carotenoids to humans especially in terms of chronic disease prevention.

References

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