Beta-cryptoxanthin, a carotenoid, inhibits nicotine-linked lung cancer development in mice

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Beta-cryptoxanthin (BCX), a carotenoid pigment compound found primarily in plants, reduces the number and invasiveness of tumors in mouse and cell models of lung cancer, report scientists from the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University (USDA HNRCA). The findings were published in the November issue of *Cancer Prevention Research*.

A team led by Xiang-Dong Wang, M.D., Ph.D., senior scientist and director of the Nutrition and Cancer Biology Laboratory at the USDA HNRCA, studied the effect of BCX using a mouse strain that develops lung tumors when exposed to NNK—a nicotine-derived carcinogen found in tobacco products and some electronic-cigarette liquids. For two weeks prior to a single high dose of NNK and for 16 weeks after, mice were given BCX in their normal daily diet, at concentrations of either one or 10 milligrams per kilogram of food. The team calculated that these doses are equivalent to approximately 0.087 and 0.87 milligrams of daily BCX intake in humans (eating a tangerine or cup of sweet red peppers per day, for example).

At the end of the experimental period, mice fed BCX developed on average 50 to 60 percent fewer tumors than mice not fed BCX, with a slightly stronger reduction in the group that ate more BCX. No differences in tumor size or type were observed. In parallel laboratory experiments, cultured human lung cancer cells that were treated with

varying doses of BCX had significantly reduced migration and invasion capacity compared with non-treated cells.

The team's findings corroborate human epidemiological studies that have found an association between higher BCX intake and lower risk of lung cancer in current smokers from North America and Asian countries. In addition, prior work from Wang's laboratory demonstrated that BCX can decrease cigarette smoke-induced lung inflammation and nicotine-related emphysema in animal models.

"For smokers, tobacco product users or individuals at higher risk for tobacco smoke exposure, our results provide experimental evidence that eating foods high in BCX may have a beneficial effect on lung cancer risk, as suggested by previous epidemiological studies. We emphasize that the best way to get BCX is from food, which include other nutrients that can have additive or complementary effects," said Wang, who is also a professor at the Friedman School of Nutrition Science and Policy at Tufts. "The amounts of BCX used in our study were easily achieved by eating a modest amount of sweet red peppers, pumpkin, oranges, or other BCX-rich foods."

Wang and his colleagues found that BCX likely reduces tumor number and invasiveness by inhibiting the production of a specific nicotine receptor, alpha7 nAChR. Prior studies have suggested that exposure to nicotine and NNK triggers overproduction of these nicotine receptors in lung tissue, which can lead to increased cell growth, cell migration and risk for tumor formation. In the current study, the research team found that BCX-fed mice had roughly half the alpha7 nAChR levels in their lung tissue after NNK exposure compared to mice on a normal diet. Additional laboratory experiments revealed that BCX suppresses the expression of alpha7 nAChR and associated signaling pathways that promote cell growth and migration, and that BCX had no effect on cells lacking the alpha7 nicotine receptor.

"Our study is the first to demonstrate that BCX prevents overproduction of the alpha7 nicotine receptor, which represents a possible mechanism for how BCX inhibits the development of lung tumors," Wang said. "While we believe BCX has preventive or therapeutic potential against lung cancer, additional studies are required as human biology cannot be fully mimicked by cell and animal models. We are now further investigating the molecular interactions between BCX and lung cancer, and exploring the possibility for small-scale human clinical trials."

Along with alpha- and beta-carotene, BCX is a provitamin A carotenoid that the human body metabolizes into vitamin A. Previous clinical trials, as well as animal studies conducted by Wang's laboratory, have found that supplementation with extremely high levels of retinyl ester—a form of vitamin A found in animal products—and beta-carotene is associated with increased risk of lung cancer, and that supplementation with beta-carotene has no preventative effect. In the current study, Wang and his colleagues found that the unique preventative effects of BCX against lung cancer risk are likely due to BCX itself and are unrelated to biologically generated vitamin A. The team are further investigating the underlying mechanisms.

As a carotenoid, BCX is part of the family of pigment compounds responsible for red, orange and yellow colors in fruits and vegetables. According to the USDA Agricultural Research Service's Food Composition Databases, foods containing the highest amounts of BCX include sweet red peppers, paprika, butternut squash, persimmons, tangerines, papaya, peaches and oranges. The Recommended Dietary Allowances of vitamin A for individuals aged 14 or older are 900 micrograms per day for males, 700 micrograms per day for adult females, and 750 and 1,200 micrograms per day for pregnant and lactating females respectively, according to the Food and Nutrition Board at the Institute of Medicine of the National Academies. Excessive vitamin A intake can result in liver damage and birth defects.

More information: A. R. Iskandar et al, -Cryptoxanthin Reduced Lung Tumor Multiplicity and Inhibited Lung Cancer Cell Motility by Downregulating Nicotinic Acetylcholine Receptor 7 Signaling, *Cancer Prevention Research* (2016). DOI: 10.1158/1940-6207.CAPR-16-0161