Carotenoids Research Interaction Group (CARIG) 2015 Conference

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CESSIAM, Guatemala City, Guatemala

Earl Harrison delivering the James Allen Olson Perspectives in Carotenes Memorial Lecture.

The 2015 CARIG Conference was held in Boston on the eve of the Experimental Biology meeting. Sherry Tanumihardjo was the moderator, and the annual James Allen Olson Perspectives in Carotenes Memorial Lecture – presented elsewhere in this issue – was delivered by Earl Harrison of Ohio State University. It was titled "Conversion of Dietary Carotenoids and Vitamin A into Bioactive Retinoids: Exploring Trails Blazed by Jim Olson."

The unifying theme of the conference was Carotenoids, Retinoids and Cancer. Four complementary presentations provided a comprehensive and congruent focus on the role of carotenoids and their derivative metabolites in the processes of protection from, induction of, and progression of, malignancy.

Retinoic acid biosynthesis defects in cancer

In the first presentation of the series, Maureen Kane (Baltimore School of Pharmacy at the University of Maryland, USA) spoke on the topic of "Retinoic Acid Biosynthesis Defects in Cancer." The protagonist of the presentation was cellular retinol-binding protein 1 (CRBP-1), a critical element of the retinoid regulatory pathway. Kane covered aspects of the changes in CRBP-1 phenotypes and the associated retinoid metabolites and their roles in cellular hyperplasia and cancer. Her findings were based on a unique analytical capacity for quantifying retinoid species that exists in her laboratory in Baltimore: this uses fast liquid chromatography-tandem mass spectrometry with backflush technology. Kane's pivotal observation was about levels of retinoic acid (RA), the retinoid metabolite that acts in the complex system of regulation of transcription in the nucleus for protein synthesis. Evidence suggests that the underlying substrate for RA in the cellular retinyl-esters pool is not limited in cells in either normal or hyperplastic conditions. The research group then reasoned that a downstream action – such as chaperoning that retinoid into the metabolic conversion – would be the regulatory step. CRBP-1 comprises that chaperone.

Kane detailed evidence for reduced RA biosynthesis in cancer, and explained how demonstrations with genetic manipulation (knock-out mice) and external stressors (hypoxia), among other factors, indicate that the CRBP-1 process of chaperoning of retinoids within the cell is likely the sensitive step in this mechanism. As a final speculation, Kane linked these findings with the conjecture that measures to restore CRBP-1 with the object of increasing RA availability in proliferative or malignant disorders (such as by epigenetic reprogramming or pharmacological induction) might offer therapeutic promise.

The antioxidant conundrum

Next in the series was the presentation by Harold Seifried (National Cancer Institute of the NIH in Bethesda, Maryland, USA) entitled "The Antioxidant Conundrum: Just Do It???" Seifried began by relating an old theory of tumor biology, which proposes that if cancer therapy generates excessive levels of oxidative

Harold Seifried, NationalCancer Institute of the NIH in Bethesda, Maryland, USA.

free radicals, then oxidants will be protective against neoplasia. To set the stage for the "conundrum," Seifried then cited the classic paper by Gladys Block and colleagues.[1] The authors of that paper comment: "A statistically significant protective effect of fruit and vegetable consumption was found in 128 of 156 dietary studies in which results were expressed in terms of relative risk." This constitutes 85% of the evidence extant two decades ago.

> "Measures to restore CRBP-1 might offer therapeutic promise"

The question to resolve, then, was whether dietary antioxidants were promoting of, or rather protective against, the occurrence of cancer.

The best-known β-carotene (BC) intervention trials in smokers – in which average daily doses ranged from 20 to 30 mg, and in which the prevention of lung cancer was the objective – were illustrative. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study in Finnish smokers and the Beta-Carotene and Retinol Efficacy Trial (CARET) in North American smokers and men exposed to asbestos, the paradoxical finding was that of increased mortality from lung malignancies in the treatment arms. Seifried speculated that tobacco metabolites may interact to make BC into a pro-oxidant. The long-term follow-up of the ATBC study has found substantial reduction of colon cancer (-22%), prostate cancer (-32%) and chronic mortality (-25%). Similarly, in a sub-study from CARET among men who gave up smoking, various protective effects have been found in the follow-up monitoring.

In France, the SU.VI.MAX trial (abbreviated from its French title of *Supplementation en Vitamines et Mineraux Antioxydants*) was a double-blind, randomized, placebo-controlled trial testing, for 7.5 years, the effect of a combination of antioxidant vitamins and minerals (120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 µg selenium and 20 mg zinc) at doses considered to be nutritional. Follow-up of SU.VI.MAX participants has identified a 58% reduction in prostate cancer, and a 31% decline for all cancers.

The high doses of BC in the trials, associated with high serum levels in the subjects, do not reflect physiological exposures. Nonetheless, reflecting on the data, BC may have been safe – and often protective – in the non-smokers within the trials. Combined with the early epidemiologic findings, antioxidants in the homeostatic range seem to exert a protective role, and high doses turn pro-oxidant.

> "Antioxidants in the homeostatic range seem to exert a protective role, and high doses turn pro-oxidant"

Tomato carotenoids and fatty liver disease and liver cancer

Next, Xiang-Dong Wang of the Human Nutrition Research Center on Aging in Boston, MA, USA spoke on "Tomato Carotenoids and Fatty Liver Disease." A number of nutritional factors have been implicated in liver cancer. Overweight and consumption of alcoholic beverages are causative factors for liver cancers, whereas coffee-drinking decreases liver cancer in both sexes. In animal models, the dietary combination of alcohol and high-fat diet induces fatty liver. This can progress in both humans and animals through a sequence that leads from simple steatosis through fibrosis to cirrhosis, and finally to hepatocellular carcinoma.

Wang related this background to the topic of interest with a focus on lycopene and tomato extract treatments. In rats on a high-fat diet, supplementation with both treatments abolishes the carcinogenic effect. Tomato extract reduces peroxidation and reduces alcohol-induced hepatic inflammation. Lycopene induces an anti-inflammatory mechanism. The lycopene attenuation depends on the carotenoid cleavage enzyme. A metabolite derivative of lycopene via the eccentric oxidative cleavage, α-10'-lycopenoic acid (ALA), decreases fat accumulation in the Ob/Ob (obese) mouse model.

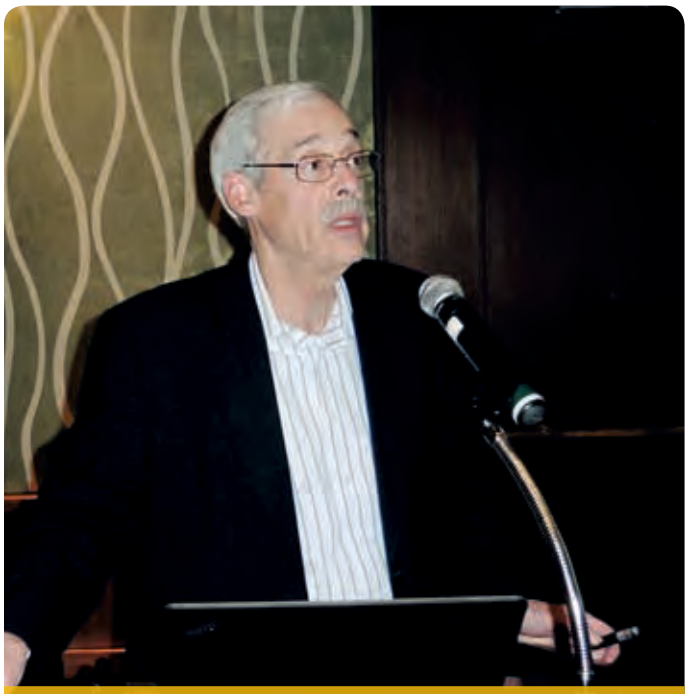
Finally, on the mechanistic side, a deacetylase enzyme known as Sirtuin 1 may be instrumental in the hepatic cancer context. Sirtuin 1 is a mediator, via the transcription factor NFκB, of reduced inflammation. It is induced by several well-known factors such as nicotinamide adenine dinucleotide (NAD), resveratrol, and caloric restriction. A final established Sirtuin 1 inducer is the carotenoid family, and this represents a feasible linkage of lycopene to a suppression of the pathway to hepatic tumorigenesis.

"Lycopene can be linked to a suppression of the pathway to hepatic tumorigenesis"

Tomato carotenoids and risk of prostate cancer

Concluding the conference was a paper by John W Erdman, Jr (University of Illinois, USA) with the theme of "Tomato Carotenoids and Risk of Prostate Cancer." Erdman covered five aspects of the topic: Incidence; epidemiology; animal trials; mechanisms; and conclusion. With respect to relative incidence, prostate cancer comprises 28% of malignancies in men, accounting for 9% of cancer deaths. In the Health Professional Health Study in the United States, among other observational studies, consumption of pizza, tomatoes and tomato sauce was inversely related to the total incidence of prostate cancer and deaths from the illness.

Xiang-Dong Wang: "A number of nutritional factors have been implicated in liver cancer."



John W Erdman, Jr; "Prostate cancer accounts for 9% of all cancer deaths."

Animal trials have been instrumental regarding the dietary specifics. In one mouse model for prostate cancer, the combination of broccoli and tomatoes reduced the tumor growth more than pure, isolated lycopene. TRAMP is the acronym for an aggressive cancer of the mouse prostate. In dietary studies, soy germ, tomato paste and the combination of the two had significant protective effects in the TRAMP model, with roughly equivalent efficacy. Further animal experimentation reveals insights into the mechanisms. In a knock-out (null) mouse, with absence of the carotene oxidase (BCO2) enzyme for eccentric cleavage, the protective effects of both pure lycopene and tomato against prostate cancer were reduced, suggesting a dependence on cleavage-products. Prostate growth is dependent upon male (androgen) hormones, and protective diets produced inhibition of the enzymes that up-regulate androgens in gene-array studies across the mouse genome. Erdman concluded that lycopene inhibits prostate cancer, most likely through a derivative metabolite originating as a carotenal.

"Lycopene inhibits prostate cancer"

VARIG-CARIG poster competition

In the evening, students and professionals gathered for the VARIG-CARIG Reception.

The prize-winning presentations in the VARIG-CARIG poster competition for graduate and post-doctoral students were as follows:

- **Emily Mohn,** E Johnson. "Distribution of Lutein Membranes of Rhesus Macaque Brain." Tufts University, Boston, Massachusetts, USA.
- **Joshua R Smith,** X Gong and LP Rubin. "Selective Carotenoid Growth Inhibition in Breast Cancer: Independence of Hormonal Sensitivity. University of Texas El Paso and Texas Tech Health Sciences Center El Paso, Texas, USA.
- **Michael R La Frano,** B Gannon, SA Tanumihardjo, JW Newman. "Targeted Metabolomic Profiling of Lipid Mediators and Bile Acids Influenced by Vitamin A Status in a Rodent Model." University of California Davis and University of Wisconsin-Madison, Madison, Wisconsin, USA.

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