Asian Journal of Andrology (2011) 13, 357–358

www.nature.com/aja

RESEARCH HIGHLIGHT

Implications for chemoprevention of prostate cancer with intake of cruciferous vegetables

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Asian Journal of Andrology (2011) **13,** 357–358; doi:10.1038/aja.2011.28; published online 18 April 2011

Efforts on chemoprevention have been an attractive target of investigation for prostate cancer. Since prostate cancer is the most common non-cutaneous malignancy among American men, efforts for chemopreventative strategies make sense. However, such undertaking has been wrought with problems and wide-scale efforts to launch drug chemoprevention have been dampened by mixed results. One of the natural approaches to chemoprevention has been the intake of fruits and vegetables, with the long-held view that these harbor anticancer properties. One such group is the cruciferous vegetables, of which the *Brassica* genus forms one of the most commonly consumed vegetables; examples include broccolis, cabbage and cauliflowers. The anticancer effects of cruciferous vegetables have been investigated previously and chemicals that carry isothiocyanate as functional groups were believed to be the active compound contributing to its antitumor properties. Isothiocyanates are generated from glucosinolates through the hydrolytic action of an enzyme called myrosinase upon chewing or chopping vegetables.[1] In a recent paper by Powolny *et al.*,[2] the anticancer effect of phenethyl isothiocyanate (PEITC), an active constituent seen in many edible cruciferous vegetables, was investigated. They investigated the potential mechanisms in which PEITC can induce reduction of prostate tumors.

Many potential mechanisms have been described to explain the anticancer effect of these compounds which include apoptosis and autophagy, a process that involves cell destruction through lysosomal degradation. To illustrate further the mechanisms which might explain the cellular processes involved in chemoprevention with the use of these compounds, transgenic adenocarcinoma of mouse prostate (TRAMP) mice were given diets consisting of control diet (without PEITC) or diet supplemented with two varying doses of PEITC (1.5 or 3 μmol PEITC/g) in varying experiments. First of all, the results showed that administering PEITC in mice was safe. Second, the incidence of poorly differentiated tumors was less in mice fed with higher doses (3 μmol PEITC/g) compared to the control with a difference of 35.9% (P=0.04). Next, in order to determine whether PEITC inhibited cell proliferation, Powolny *et al.* performed immunohistochemical staining for a proliferation marker Ki-67. In addition, apoptotic marker terminal deoxynucleotidyl transferase dUTP nick end labeling-positive bodies and CD31 staining for angiogenesis were performed. However, no statistically significant differences were found between the two groups in these varying assays, indicating that effects on cell proliferation and neo-angiogenesis were not evident, although vessel normalization was apparent. PEITC though, affected the induction of autophagy as evidenced by an increase in autophagosomes and expression of LC3, an autophagy regulator, in the dorsolateral prostate of the TRAMP mice fed with PEITC, suggesting *in vivo* evidence that autophagy occurs as a potential mechanism. In addition, E-cadherin expression was also higher in the dorsolateral prostate of the TRAMP mice, effects of which are important since E-cadherin has been implicated in the suppression of invasion and growth in many epithelial cancers. The propensity for lung metastasis was also investigated and the PEITC fed mice showed a 38% less number of lung metastasis and a 60% reduction in the mean pulmonary metastasic area. In order to identify candidate biomarkers, plasma samples from TRAMP mice were obtained and a plasma proteomics approach was used to identify clusterin. Clusterin, a highly conserved protein involved in apoptosis, is of interest in prostate cancer and had been found to be associated with higher Gleason scores in prostate cancer patients,[3] though not related to prognosis. Clusterin was found to be statistically significantly decreased in the plasma of TRAMP mice fed with PEITC. It is important to note that secreted clusterin may have a prosurvival function, whereas nuclear and mitochondria-based clusterin appears to have pro-apoptotic effects. Although further experiments showed that clusterin inhibition may not be exclusively an effect of PEITC treatment, since suppression was also observed following treatment with diallyl trisulfide, it could be used as a biomarker for future clinical studies.

The implications of this study are varied. The potential mechanisms of action underlying intake of cruciferous vegetables may pave the way for future clinical trials testing the compound as a chemopreventive agent. Epidemiological studies looking at the relationship between intake of cruciferous vegetables and prostate cancer had previously been reported and had shown inverse correlation between cruciferous vegetable intake and prostate cancer risk.[4] However, a prospective study examining its relationship using the Health Professionals Follow-up Study cohort showed no considerable association between baseline intake and prostate cancer risk, although there was a slight inverse association in men with

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organ-confined prostate cancer,[5] suggesting that perhaps the cruciferous vegetables may have a protective role in early prostate carcinogenesis. Thus, efforts on chemoprevention may be a reasonable approach to utilizing this therapeutic strategy. Investigations have thereafter focused on the possible mechanisms of action resulting in anticancer properties of the cruciferous vegetables. One such mechanism for instance, for another active constituent alyll isothiocyanate, was shown to cause G_2/M arrest in certain prostate cancer cell lines.[6] Other studies examining the potential mechanism of action for PEITC also involves apoptosis related to caspase-like activity,[7] or blockade of tumor promoter.[8] The paper by Powolny *et al.* is a step towards identifying autophagy as a mechanism of action for induction of antitumor effect, although the authors did not demonstrate consistent inhibition of angiogenesis, apoptosis or cellular growth. Similarly, potential search for a biomarker to more accurately identify the antitumoral effects of PEITC requires more refinement.

The challenge inherent in all chemopreventive drug trials, especially in prostate cancer, includes the requirement of a large number of patients to identify the beneficial effects for a disease that has a potentially long natural history. Given that vegetables are ubiquitous in nature and the impact of such therapy is often welcomed by many, further efforts to identify unique properties of exerting antitumor effects and effectively translating these findings to the clinic would be the next anticipated step.

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