

## Perspective

See related article by Qiu et al., p. 419

## Is Lycopene an Effective Agent for Preventing Prostate Cancer?

Michael B. Sporn and Karen T. Liby

## Abstract

The role of lycopene, an open-chain carotenoid found in tomatoes and devoid of retinoid activity, as an anticarcinogenic, chemopreventive agent, especially for use in prostate cancer, is still under active investigation. In this issue, Qui and colleagues show that lycopene induces responses in human prostate epithelial cells that are antiproliferative, antioxidative, and anti-inflammatory, as well as downregulating targets in the androgen receptor signaling pathway. In this perspective, we review aspects of the molecular and cellular biology of lycopene that support its use for prevention of prostate cancer. Whether lycopene itself or its metabolites induce most of its benefits is still uncertain. At present, meta-analysis of clinical studies of lycopene for prevention of prostate cancer in men does not yet support the definitive clinical use of this carotenoid in a preventive setting. *Cancer Prev Res*; 6(5); 384–6. ©2013 AACR.

Development of a safe and effective drug for clinical chemoprevention of prostate cancer remains an important goal. This is particularly significant for prostate cancer because of the long-standing controversy on the management of early lesions, namely the differences in opinion on surgery versus "watchful waiting." If there were a generally accepted potent and safe chemopreventive drug with essentially no side effects, much of the controversy would disappear. Although antagonism of the androgen receptor has yielded effective drugs for clinical chemoprevention of prostate cancer, this too remains a controversial area, and the use of such drugs is not universally accepted.

Thus, in this context the emergence of lycopene as a potential candidate for clinical chemoprevention has recently become a hot topic in prevention studies (1–3). There is a little question that lycopene, the red carotenoid pigment found in tomatoes and other red vegetables and fruits, is an exceptionally safe molecule for use in humans. Millions of people have been ingesting lycopene for centuries with apparently no detectable side effects. Structurally like  $\beta$ -carotene, lycopene is a 40-carbon polyisoprenoid molecule; its red color is the result of its large number of conjugated double bonds (see Fig. 1), which also make it a uniquely potent agent for quenching of reactive oxygen species, such as singlet oxygen (4). However, unlike  $\beta$ -carotene, lycopene is an open chain molecule without terminal  $\beta$ -ionone rings and thus cannot serve as a precursor for all-

*trans*-retinol, retinal, or retinoic acid—the active forms of "vitamin A."

The major questions that remain about lycopene and cancer are: (i) is it a potent enough agent for preventing human cancer, especially prostate cancer, and if so, (ii) what are the mechanisms and targets that are involved in its chemopreventive actions? As has happened in the development of many chemopreventive agents, the first indications of potential use have come from epidemiologic studies, which have suggested that consumption of large amounts of tomatoes and tomato products is associated with a lowered risk for developing prostate cancer (5, 6). Following these initial epidemiologic studies, there has been a flurry of activity to show that lycopene itself or its metabolites are the active agents in tomatoes for chemoprevention of prostate cancer in animals and to determine molecular mechanism of action and molecular targets.

In this context, the article by Qui and colleagues in this issue of *Cancer Prevention and Research* is a welcome contribution (7). The authors have shown that a range of proteins involved with anticarcinogenic and antioxidant responses, as well as cytoprotection, were upregulated in human prostate cells by lycopene treatment. These experiments were conducted at a physiologically relevant concentration of 2  $\mu$ mol/L in tissue culture. In contrast, relevant procarcinogenic signal transduction pathways, such as androgen receptor signaling and the Akt/mTOR pathway, were downregulated. However, all these effects, although statistically significant, were less than 2-fold.

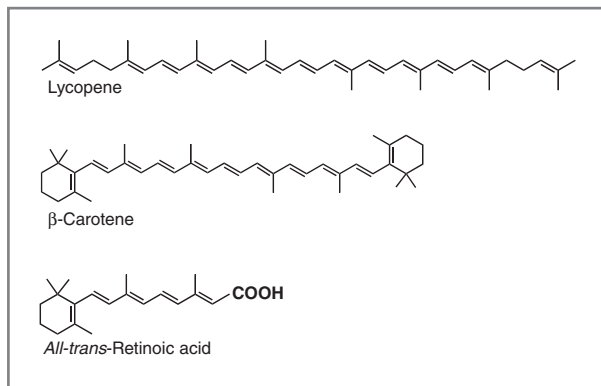
The results are notable in that they have been obtained by proteomic analysis, using new high-performance liquid chromatography-tandem mass spectrometry techniques, to identify specific proteins rather than by conventional gene array analysis; the latter method fails to measure protein expression. The results are also notable in that the authors have used highly relevant benign primary human prostate

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**Figure 1.** Structures of lycopene,  $\beta$ -carotene, and all-*trans*-retinoic acid.  $\beta$ -carotene (40 carbon atoms) can serve as a dietary precursor of retinoids (20 carbon atoms) by the process of enzymatic cleavage, but lycopene (40 carbon atoms), which does not have a  $\beta$ -ionone ring, is not a retinoid precursor. Lycopene seems to be a much safer drug for chronic human administration than  $\beta$ -carotene.

epithelial cells, which they have established in culture from surgical specimens, as the reader cells rather than less relevant malignant prostate cells such as LNCaP or PC-3. However, effects of lycopene on the various cells of the microenvironment, which can be so important for chemoprevention (8, 9) of cancer, were not evaluated in the present study. Overall, the present data suggest that lycopene is active in suppressing cancer initiation, promotion, and/or progression rather than at later stages of carcinogenesis; similar conclusions have previously been published.

There is no question that lycopene is indeed a multifunctional compound (1); in no way does it fit the current fashion for single-targeted drug therapy for either prevention or treatment of cancer. Not only is lycopene highly reactive toward oxygen and free radicals, it has a range of other mechanistic actions that are highly relevant to suppression of carcinogenesis. These include induction of apoptosis, antiproliferative, and antimetastatic activity, as well as the induction of cytoprotective "phase II" enzymes that inhibit the carcinogenic effects of many xenobiotics (1, 10). This latter effect is mediated by enhancement of the activity of the transcription factor, Nrf2, which results in increased transcription of cytoprotective genes regulated by the antioxidant response element on DNA. Lycopene was the most potent of a series of carotenoid molecules tested in this regard (10).

Moreover, it has been amply shown that lycopene itself is converted to a large number of metabolites. These conversions include isomerization of the *trans*-double bond system of the 40-carbon molecule, as well as cleavage and hydroxylation of many of the double bonds (11, 12). It has been suggested that, "there is limited experimental support for the (direct) antioxidant hypothesis as a major mechanism of lycopene's *in vivo* action" and that instead, "metabolic products of lycopene, the "lycopenoids", may be more active than the parent molecule" (12). Furthermore, in this analysis, the desirable effects of the lycopenoids are suggested to be the result of alterations in gene expression.

The ultimate use of this entire approach to prostate cancer rests on its effectiveness *in vivo*, particularly in human subjects. Attempts to show preclinical efficacy in animal models of chemoprevention of prostate cancer have thus far not been impressive. Although statistically significant, while chemopreventive results have been reported in transgenic (TRAMP) and chemically induced (nitrosomethylurea plus testosterone) mouse (13) and rat (14) models, the effects were not particularly striking. Indeed, in the latter model, tomato powder was more effective than lycopene itself.

Final clinical proof of efficacy has been difficult to obtain. Oral administration of lycopene extracts to men with prostate cancer or benign prostatic hyperplasia caused major increases in lycopene levels in both prostate biopsies and plasma. However, in the same patients, no beneficial effects on biomarkers of oxidative stress and lipid peroxidation, such as 8-oxo-deoxyguanosine or malondialdehyde, were observed in either prostate tissue or plasma (15).

Similarly, 2 major recent retrospective studies (2, 3), which have surveyed many clinical trials for the potential benefits of lycopene supplements for prevention and treatment of prostate cancer, have failed to support any true optimism that lycopene itself will be an effective clinical chemoprevention drug. Fortunately, however, there is no evidence that lycopene can increase human cancer incidence, as has sadly happened with  $\beta$ -carotene in clinical trials (16–18). Although lycopene did decrease plasma PSA levels in some trials, the ultimate conclusion of the latest systematic review is that, "given the limited number of randomized clinical trials published, and the varying quality of existing studies, it is not possible to support, or refute, the use of lycopene for prevention or treatment of benign prostatic hypertrophy or prostate cancer" (3).

Perhaps, like many other natural products that can be shown to prevent cancer in experimental animals, lycopene is simply not potent enough to be a clinically useful drug. Concentrations in excess of 1  $\mu$ mol/L are necessary to achieve biologically meaningful responses. Perhaps what is needed is to build upon what has already been shown, namely that lycopene does indeed have some chemopreventive activity but then to chemically modify this natural product scaffold to make more potent derivatives (19, 20). Such new semisynthetic derivatives hopefully will then be able to deliver the preventive results that are needed so urgently.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** M.B. Sporn

**Writing, review, and/or revision of the manuscript:** M.B. Sporn, K.T. Liby

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## References

1. van Breemen RB, Pajkovic N. Multitargeted therapy of cancer by lycopene. *Cancer Lett* 2008;269:339–51.
2. Haseen F, Cantwell MM, O'Sullivan JM, Murray LJ. Is there a benefit from lycopene supplementation in men with prostate cancer? A systematic review. *Prostate Cancer Prostatic Dis* 2009;12:325–32.
3. Ilic D, Misso M. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. *Maturitas* 2012;72:269–76.
4. DiMascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys* 1989; 274:532–8.
5. Clinton SK. Lycopene: chemistry, biology, and implications for human health and disease. *Nutr Rev* 1998;56:35–51.
6. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *J Natl Cancer Inst* 1999;91:317–31.
7. Qui X, Yuan Y, Vaishnav A, Tessel MA, Nonn L, van Breemen RB. Effects of lycopene on protein expression in human primary prostatic epithelial cells. *Cancer Prev Res* 2013;6:419–27.
8. Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. *Nat Rev Cancer* 2007;7:139–47.
9. Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. *Nat Med* 2011;17:320–9.
10. Ben-Dor A, Steiner M, Gheber L, Danilenko M, Dubi N, Linnewiel K, et al. Carotenoids activate the antioxidant response element transcription system. *Mol Cancer Ther* 2005;4:177–86.
11. Mein JR, Lian F, Wang XD. Biological activity of lycopene metabolites: implications for cancer prevention. *Nutr Rev* 2008;66:667–83.
12. Erdman JW Jr, Ford NA, Lindshield BL. Are the health attributes of lycopene related to its antioxidant function? *Arch Biochem Biophys* 2009;483:229–35.
13. Konijeti R, Henning S, Moro A, Sheikh A, Elashoff D, Shapiro A, et al. Chemoprevention of prostate cancer with lycopene in the TRAMP model. *Prostate* 2010;70:1547–54.
14. Boileau TW, Liao Z, Kim S, Lemeshow S, Erdman JW Jr, Clinton SK. Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. *J Natl Cancer Inst* 2003;95:1578–86.
15. van Breemen RB, Sharifi R, Viana M, Pajkovic N, Zhu D, Yuan L, et al. Antioxidant effects of lycopene in African American men with prostate cancer or benign prostate hyperplasia: a randomized, controlled trial. *Cancer Prev Res* 2011;4:711–8.
16. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–5.
17. Greenberg ER, Sporn MB. Antioxidant vitamins, cancer, and cardiovascular disease. *N Engl J Med* 1996;334:1189–90.
18. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029–35.
19. Sporn MB, Liby KT, Yore MM, Suh N, Albini A, Honda T, et al. Platforms and networks in triterpenoid pharmacology. *Drug Dev Res* 2007; 68:174–82.
20. Liby KT, Sporn MB. Synthetic oleanane triterpenoids: multifunctional drugs with a broad range of applications for prevention and treatment of chronic disease. *Pharmacol Rev* 2012;64:972–1003.

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