Published OnlineFirst June 17, 2013; DOI: 10.1158/1940-6207.CAPR-13-0202

Cancer Prevention Research

Perspective

See related article by Derry et al., p. 625

Targeting Epigenetics for Cancer Prevention By Dietary Cancer Preventive Compounds—The Case of miRNA

Ah-Ng Tony Kong[1,2], Chengyue Zhang[1,2], and Zheng-Yuan Su[1,2]

Abstract

In cancer, genetic mutations have long been considered to be the only driver of neoplasia. However, there is increasing evidence that epigenetic alterations could also play a major role in carcinogenesis and cancer. A number of experimental and epidemiologic studies have shown that many classes of dietary phytochemicals possess cancer-preventive and epigenetic-modifying properties. The report by Derry and colleagues in this issue of the journal shows that grape seed extract (GSE) prevents azoxymethane (AOM)-induced colon colitis via epigenetic microRNA (miRNA) regulation. Although the precise mechanism underlying the control of miRNA expression is not well understood currently, epigenetic changes could play a major role. This report, along with increasing evidence showing the impact of dietary phytochemicals on epigenetic activities, offers new perspectives on miRNA and epigenetic regulation in cancer prevention. *Cancer Prev Res; 6(7); 622–4. ©2013 AACR.*

In cancer, genetic mutations have long been considered to be the only driver of neoplasia (1). However, there is increasing evidence that epigenetic alterations, defined as changes in the regulation of the expression of gene activity without alteration of genetic structure, could also play a major role in carcinogenesis and cancer (2). Unlike genetic alterations, for instance, chemicals or drugs could reverse a decrease in gene expression due to epigenetic silencing via aberrant promoter hypermethylation. Therefore, small molecules targeting enzymes responsible for DNA methylation and histone modifications could potentially be important for cancer prevention and therapy. In this context, inhibitors of DNA methyltransferases (DNMT) and histone deacetylases (HDAC) have been approved for cancer treatment by the U.S. Food and Drug Administration and proven to have therapeutic potency against a number of malignancies (3). Many classes of dietary phytochemicals have been shown to possess cancer-preventive properties through studies in *in vitro* and *in vivo* animal models and findings from numerous epidemiologic studies (4, 5). Surprisingly, these dietary cancer-preventive agents have also been found to regulate epigenetic activities (6–8). For instance, green tea polyphenol (−)-epigallocatechin-3-gallate inhibits DNMT and reactivates methylation-silenced genes in cancer cell lines (9), whereas sulforaphane and 3, 3′-diindolylmethane from cruciferous vegetables have been reported to inhibit HDACs activities (10). Curcumin from turmeric and resveratrol from red grapes have also been reported to elicit epigenetic-modifying activities, among others (11, 12). Hence, epigenetic modifications seem to play an important role in cancer prevention such that they can be inhibited by dietary cancer-preventive phytochemicals.

Grape seed extract (GSE) has been extensively investigated for the prevention and treatment of cancers in *in vitro* and *in vivo* preclinical models (13–15). In this issue of the journal, Derry and colleagues report the efficacy of GSE against azoxymethane (AOM)-induced colon tumorigenesis in A/J mice (16). Results from their study show that dietary supplement of GSE dramatically decreases colon tumor incidence and overall tumor size. Biomarker examination shows antiproliferation and proapoptosis effects of GSE on colon tumor tissues. Interestingly, GSE strongly modulates microRNA (miRNA) expression profiles and miRNA-processing machinery associated with alterations in NF-κB, β-catenin, and mitogen-activated protein kinase signaling. Immunohistochemistry analyses show downregulation of inflammatory signaling pathways including NF-κB activation and its downstream targets COX-2, iNOS, and VEGF, decreased β-catenin signaling and its target gene C-myc, and a reduction in phosphorylated extracellular signal-regulated kinase 1/2 levels corroborating miRNA expression profiles. Derry and colleagues suggest that GSE exerts its efficacy against colon tumorigenesis by targeting inflammation, proliferation, and apoptosis possibly via modulation of miRNA expression.

miRNAs are endogenous small noncoding RNA molecules that can control gene expression at both transcriptional and posttranscriptional level. miRNAs bind to their target mRNA in either complete or incomplete

Authors' Affiliations: [1]Center for Cancer Prevention Research and [2]Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, the State University of New Jersey, Piscataway, New Jersey

Corresponding Author: Ah-Ng Tony Kong, Center for Cancer Prevention Research, Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, 160 Frelinghuysen Road, Piscataway, NJ 08854. Phone: 732-455-3831; Fax: 732-455-3134; E-mail: KongT@pharmacy.rutgers.edu

doi: 10.1158/1940-6207.CAPR-13-0202

complementary fashion, thus they downregulate the stability and/or translation of their target mRNAs (17). miRNAs have been shown to be involved not only in normal tissue differentiation and development (18) but also in carcinogenesis. For instance, Iorio and colleagues reported that miR-21 is aberrantly upregulated in human breast cancers, serving as an antiapoptosis factor (19). Attenuated expression of miR-let7 was reported in human lung cancers, and forced expression of let-7 in A549 lung adenocarcinoma cell line inhibited cell growth (20). More recently, cellular and molecular studies show that miRNAs affect inflammation and cytokine signaling (21, 22), and relatedly, alteration of miRNAs expression by dietary compounds has been shown to be associated with their cancer-preventive and therapeutic benefits (23, 24). Before the report by Derry and colleagues in this issue, regulation of miRNA expression by GSE has been reported in human hepatocellular carcinoma HepG2 cell line (25). Meanwhile, Gao and colleagues reported dysregulation of immune/inflammation-related miRNAs in AOM–dextran sulfate sodium (DSS)–induced colitis-associated colorectal cancer model (26). The current work of Derry and colleagues links the alteration of miRNA expression and those previously identified molecular targets, indicating that a potential epigenetic/miRNA mechanism could exist for the cancer chemopreventive efficacy of GSE.

Although increasing evidence shows the importance of miRNA in cancer initiation and development, the mechanism of miRNA regulation and targeting is still not well understood. Many miRNAs are located in the introns of protein-coding genes (27). As reviewed by You and Jones (2), epigenetic mechanisms including DNA methylation and histone modifications can control the expression of many protein-coding genes, and it is possible that epigenetics could play a critical role in miRNA expression control. A recent study by Wilting and colleagues (28) shows an increase in CpG methylation of miR-149, -203, and -375 during cervical carcinogenesis, whereas expression of these epigenetically silenced miRNAs was restored upon treatment with a potent DNMT inhibitor 5-aza-2′-deoxycytidine. Similarly, inhibition of HDACs leads to a rapid change in miRNA expression profile in human breast cancer cell line SKBr3 (29), while recent studies show the importance of histone methyltransferases and acetyl-histone recognition proteins in miRNA regulation in aggressive B-cell lymphomas (30, 31). As discussed above, many dietary cancer chemopreventive phytochemicals from our daily-consumed fruits and vegetables have been reported to exhibit epigenetic modification activities. With respect to GSE, Vaid and colleagues reported that GSE treatment decreased the expression and activity of DNMT, caused downregulation of global DNA methylation level, and resulted in reactivation of silenced tumor suppressor genes, such as *RASSF1A*, *p16*^{INK4a}*(CDKN2A)*, and *Cip1/p21 (CDKN1A)* in human squamous cell carcinoma A431 and SCC13 cell lines (32). Together, these findings may provide some insights into the epigenetic regulatory mechanism by GSE from 2 possible scenarios: GSE may turn on the tumor suppressor genes that are aberrantly silenced by epigenetic mechanism via CpG demethylation and histone modifications, and on the other side of the coin, GSE may reactivate miRNAs controlling tumor suppressor genes resulting in downregulation of target oncogenic mRNAs. Further studies would be needed to interrogate the connectivity between epigenetic changes and alteration of miRNA expression profiles by GSE and other cancer-preventive dietary phytochemicals in *in vitro* and *in vivo* cancer models.

In conclusion, the findings of Derry and colleagues and others, epigenetic modifications by dietary phytochemicals in cancer prevention, provide new potential insights into cancer-preventive mechanisms of GSE and other dietary phytochemicals. It is highly conceivable that epigenetically controlled chromatin remodeling such as CpG methylation, histone modifications as well as miRNA that drive various stages of carcinogenesis could be intervened or interrupted by dietary cancer-preventive phytochemicals (33). Uncovering these potential epigenetic molecular targets by phytochemicals will certainly advance our basic understanding of carcinogenesis and phytochemical–cancer relationships that can ultimately translate to chemopreventive or therapeutic strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A.-N.T. Kong, Z.-Y. Su
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.-N.T. Kong
Writing, review, and/or revision of the manuscript: A.-N.T. Kong, C. Zhang, Z.-Y. Su
Study supervision: A.-N.T. Kong

Received June 1, 2013; accepted June 5, 2013; published OnlineFirst June 17, 2013.

References

1. Floor SL, Dumont JE, Maenhaut C, Raspe E. Hallmarks of cancer: of all cancer cells, all the time? Trends Mol Med 2012;18:509–15.
2. You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? Cancer Cell 2012;22:9–20.
3. Kelly TK, De Carvalho DD, Jones PA. Epigenetic modifications as therapeutic targets. Nat Biotechnol 2010;28:1069–78.
4. Kaur M, Agarwal C, Agarwal R. Anticancer and cancer chemopreventive potential of grape seed extract and other grape-based products. J Nutr 2009;139:1806S–12S.
5. Lee KW, Bode AM, Dong Z. Molecular targets of phytochemicals for cancer prevention. Nat Rev Cancer 2011;11:211–8.
6. Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. J Nutr 2007;137:223S–8S.
7. Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. Epigenomics 2011;3:503–18.
8. Ho E, Beaver LM, Williams DE, Dashwood RH. Dietary factors and epigenetic regulation for prostate cancer prevention. Adv Nutr 2011; 2:497–510.

Published OnlineFirst June 17, 2013; DOI: 10.1158/1940-6207.CAPR-13-0202

9. Fang MZ, Wang Y, Ai N, Hou Z, Sun Y, Lu H, et al. Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Res 2003;63:7563–70.
10. Ho E, Clarke JD, Dashwood RH. Dietary sulforaphane, a histone deacetylase inhibitor for cancer prevention. J Nutr 2009;139: 2393–6.
11. Khor TO, Huang Y, Wu TY, Shu L, Lee J, Kong AN. Pharmacodynamics of curcumin as DNA hypomethylation agent in restoring the expression of Nrf2 via promoter CpGs demethylation. Biochem Pharmacol 2011;82:1073–8.
12. Papoutsis AJ, Lamore SD, Wondrak GT, Selmin OI, Romagnolo DF. Resveratrol prevents epigenetic silencing of BRCA-1 by the aromatic hydrocarbon receptor in human breast cancer cells. J Nutr 2010;140: 1607–14.
13. Mittal A, Elmets CA, Katiyar SK. Dietary feeding of proanthocyanidins from grape seeds prevents photocarcinogenesis in SKH-1 hairless mice: relationship to decreased fat and lipid peroxidation. Carcinogenesis 2003;24:1379–88.
14. Raina K, Singh RP, Agarwal R, Agarwal C. Oral grape seed extract inhibits prostate tumor growth and progression in TRAMP mice. Cancer Res 2007;67:5976–82.
15. Engelbrecht AM, Mattheyse M, Ellis B, Loos B, Thomas M, Smith R, et al. Proanthocyanidin from grape seeds inactivates the PI3-kinase/PKB pathway and induces apoptosis in a colon cancer cell line. Cancer Lett 2007;258:144–53.
16. Derry M, Raina K, Balaiya V, Jain A, Shrotriya S, Huber K, et al. Grape seed extract efficacy against azoxymethane-induced colon tumorigenesis in A/J mice: interlinking miRNA with cytokine signaling and inflammation. Cancer Prev Res 2013;6: 625–33.
17. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer 2006;6:259–69.
18. Alvarez-Garcia I, Miska EA. MicroRNA functions in animal development and human disease. Development 2005;132:4653–62.
19. Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Res 2005;65:7065–70.
20. Takamizawa J, Konishi H, Yanagisawa K, Tomida S, Osada H, Endoh H, et al. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. Cancer Res 2004;64:3753–6.
21. Gantier MP, Stunden HJ, McCoy CE, Behlke MA, Wang D, Kaparakis-Liaskos M, et al. A miR-19 regulon that controls NF-κB signaling. Nucleic Acids Res 2012;40:8048–58.
22. Rossato M, Curtale G, Tamassia N, Castellucci M, Mori L, Gasperini S, et al. IL-10-induced microRNA-187 negatively regulates TNF-α, IL-6, and IL-12p40 production in TLR4-stimulated monocytes. Proc Natl Acad Sci USA 2012;109:E3101–10.
23. Link A, Balaguer F, Goel A. Cancer chemoprevention by dietary polyphenols: promising role for epigenetics. Biochem Pharmacol 2010;80:1771–92.
24. Tsang WP, Kwok TT. Epigallocatechin gallate up-regulation of miR-16 and induction of apoptosis in human cancer cells. J Nutr Biochem 2010;21:140–6.
25. Arola-Arnal A, Blade C. Proanthocyanidins modulate microRNA expression in human HepG2 cells. PLoS ONE 2011;6:e25982.
26. Gao Y, Li X, Yang M, Zhao Q, Liu X, Wang G, et al. Colitis-accelerated colorectal cancer and metabolic dysregulation in a mouse model. Carcinogenesis 2013 April 24. [Epub ahead of print].
27. Kim VN, Nam JW. Genomics of microRNA. Trends Genet 2006;22: 165–73.
28. Wilting SM, Verlaat W, Jaspers A, Makazaji NA, Agami R, Meijer CJ, et al. Methylation-mediated transcriptional repression of microRNAs during cervical carcinogenesis. Epigenetics 2013;8:220–8.
29. Scott GK, Mattie MD, Berger CE, Benz SC, Benz CC. Rapid alteration of microRNA levels by histone deacetylase inhibition. Cancer Res 2006;66:1277–81.
30. Zhang X, Zhao X, Fiskus W, Lin J, Lwin T, Rao R, et al. Coordinated silencing of MYC-mediated miR-29 by HDAC3 and EZH2 as a therapeutic target of histone modification in aggressive B-Cell lymphomas. Cancer Cell 2012;22:506–23.
31. Zhao X, Lwin T, Zhang X, Huang A, Wang J, Marquez VE, et al. Disruption of the MYC-miRNA-EZH2 loop to suppress aggressive B-cell lymphoma survival and clonogenicity. Leukemia 2013 Mar 29. [Epub ahead of print].
32. Vaid M, Prasad R, Singh T, Jones V, Katiyar SK. Grape seed proanthocyanidins reactivate silenced tumor suppressor genes in human skin cancer cells by targeting epigenetic regulators. Toxicol Appl Pharmacol 2012;263:122–30.
33. Lee JH, Khor TO, Shu L, Su ZY, Fuentes F, Kong AN. Dietary phytochemicals and cancer prevention: Nrf2 signaling, epigenetics, and cell death mechanisms in blocking cancer initiation and progression. Pharmacol Ther 2013;137:153–71.

Published OnlineFirst June 17, 2013; DOI: 10.1158/1940-6207.CAPR-13-0202

American Association for Cancer Research

Cancer Prevention Research

Targeting Epigenetics for Cancer Prevention By Dietary Cancer Preventive Compounds−−The Case of miRNA

Ah-Ng Tony Kong, Chengyue Zhang and Zheng-Yuan Su

Cancer Prev Res 2013;6:622-624. Published OnlineFirst June 17, 2013.