

Targeting Apoptosis Pathways in Cancer—Letter

Stephen Safe

The review article entitled "Targeting Apoptosis Pathways in Cancer and Perspectives with Natural Compounds from Mother Nature" (1) provides a comprehensive listing of the effects of natural products on genes/pathways that result in induction of apoptosis in cancer cells and tumors. Despite the multiple cancer cell context-dependent effects of natural products, the lack of underlying mechanisms of action for many compounds has limited their clinical applications and use in combined therapies. However, there are relevant mechanistic studies for some classes of natural products that were not covered in this review. For example, the authors have summarized the effects of various proapoptotic agents that act through two interrelated pathways, namely "mitochondrial-mediated" and "reactive oxygen species (ROS)-mediated" apoptosis because drugs targeting mitochondria often induce ROS. Previous studies in this laboratory have demonstrated that natural products such as curcumin, betulinic acid, phenethyl isothiocyanate (PEITC), piperlongumine, and celastrol, which induce ROS and apoptosis, also downregulate specificity protein (Sp) transcription factors Sp1, Sp3, and Sp4, which are highly expressed in cancer cells (2–6). For most of these studies, compound-induced apoptosis and compound-induced downregulation of Sp transcription factors were reversed in cancer cells after cotreatment with antioxidants. The importance of Sp transcription factors as targets for proapoptotic natural products is

due to Sp-regulated prosurvival genes such as *survivin* and *bcl-2*, which are also downregulated by ROS-inducing anticancer agents (2–6).

The high expression of Sp transcription factors in cancer cells is due, in part, to suppression of the transcriptional (Sp) repressors ZBTB10/ZBTB34 and ZBTB4 by microRNA-27a (miR-27a) and miR-20a/miR-17-5p, respectively (6–8). These microRNAs are members of the miR-23a~27a~24-2 and miR-17-92 clusters, which are overexpressed in multiple cancer cells and tumors. The key mechanistic linkage between induction of ROS and modulation of the miR:ZBTB:Sp axis was initially reported in studies showing that, in colon cancer cells, hydrogen peroxide induced genome-wide shifts of repressor complexes from non-GC-rich to GC-rich promoters, and this downregulated expression of the oncogene *cMyc*. Our recent studies showed that PEITC also decreased expression of *Myc* in pancreatic cancer cells (ROS-dependent), resulting in decreased expression of *Myc*-regulated miR-27a and miR-20a/miR-17-5p, induction of ZBTBs, and downregulation of Sp transcription factors and prosurvival Sp-regulated genes (8). Further evidence that ROS targets Sp transcription factors and Sp-regulated survival genes has been observed in other studies using hydrogen peroxide, pharmacologic concentrations of ascorbic acid that induce hydrogen peroxide, *t*-butyl hydroperoxide, and other ROS-inducing anticancer agents. These studies provide some understanding of the underlying mechanisms of action that contribute to the proapoptotic effects of ROS-inducing natural products reviewed by Millimouno and colleagues in *Cancer Prevention Research* (1).

Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, Texas.

Corresponding Author: Stephen Safe, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX 77843-4466. Phone: 979-845-5988; Fax: 979-862-4929; E-mail: ssafe@cvm.tamu.edu

doi: 10.1158/1940-6207.CAPR-14-0405

©2015 American Association for Cancer Research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received November 12, 2014; accepted January 22, 2015; published OnlineFirst January 27, 2015.

References

1. Millimouno FM, Dong J, Yang L, Li J, Li X. Targeting apoptosis pathways in cancer and perspectives with natural compounds from Mother Nature. *Cancer Prev Res* 2014;7:1081–107.
2. Chadalapaka G, Jutooru I, Safe S. Celastrol decreases specificity proteins (Sp) and fibroblast growth factor receptor-3 (FGFR3) in bladder cancer cells. *Carcinogenesis* 2012;33:886–94.
3. Chintharlapalli S, Papineni S, Lei P, Pathi S, Safe S. Betulinic acid inhibits colon cancer cell and tumor growth and induces proteasome-dependent and -independent downregulation of specificity proteins (Sp) transcription factors. *BMC Cancer* 2011;11:371.
4. Jutooru I, Chadalapaka G, Lei P, Safe S. Inhibition of NFkappaB and pancreatic cancer cell and tumor growth by curcumin is dependent on specificity protein down-regulation. *J Biol Chem* 2010;285:25332–44.
5. Gandhi SU, Kim K, Larsen L, Rosengren RJ, Safe S. Curcumin and synthetic analogs induce reactive oxygen species and decreases specificity protein (Sp) transcription factors by targeting microRNAs. *BMC Cancer* 2012;12:564.
6. Jutooru I, Guthrie AS, Chadalapaka G, Pathi S, Kim K, Burghardt R, et al. Mechanism of action of phenethylisothiocyanate and other reactive oxygen species-inducing anticancer agents. *Mol Cell Biol* 2014;34:2382–95.
7. Mertens-Talcott SU, Chintharlapalli S, Li X, Safe S. The oncogenic microRNA-27a targets genes that regulate specificity protein transcription factors and the G2-M checkpoint in MDA-MB-231 breast cancer cells. *Cancer Res* 2007;67:11001–11.
8. Kim K, Chadalapaka G, Lee SO, Yamada D, Sastre-Garau X, Defossez PA, et al. Identification of oncogenic microRNA-17-92/ZBTB4/specificity protein axis in breast cancer. *Oncogene* 2012;31:1034–44.

Cancer Prevention Research

Targeting Apoptosis Pathways in Cancer—Letter

Stephen Safe

Cancer Prev Res 2015;8:338. Published OnlineFirst January 27, 2015.

Updated version Access the most recent version of this article at:
doi:[10.1158/1940-6207.CAPR-14-0405](https://doi.org/10.1158/1940-6207.CAPR-14-0405)

Cited articles This article cites 8 articles, 4 of which you can access for free at:
<http://cancerpreventionresearch.aacrjournals.org/content/8/4/338.full#ref-list-1>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cancerpreventionresearch.aacrjournals.org/content/8/4/338>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.