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Letter to the Editor

Cancer Prevention Research

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 c*Myc*. 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).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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