Biomarkers as Indicators of Cancer Risk Reduction Following Dietary Manipulation

Xenobiotic Metabolism Relevance to Cancer

Roderick H. Dashwood

Linus Pauling Institute, Oregon State University, Corvallis OR 97331-6512

Expanded Abstract

Xenobiotic metabolism—the double-edged sword

It has been two decades since Wattenberg's seminal review on the chemoprevention of cancer, cited over 900 times according to the ISI Web of Knowledge, subdivided cancer inhibitory agents into 3 broad categories (1). The classification scheme included 1) inhibitors of carcinogen formation from precursors, 2) agents that alter xenobiotic metabolism and protect against DNA damage, so-called “blocking” agents, and 3) “suppressing” agents that act postinitiation to prevent initiated cells from progressing to neoplasia. The review was important and timely and gave impetus to many subsequent studies on natural and synthetic chemopreventive agents. For example, >150 such agents have been tested against 1 chemical class alone, the cooked meat heterocyclic amines (2).

From the outset, however, there were aspects of Wattenberg's scheme that were viewed as a possible double-edged sword. Blocking agents that acted on a specific class of cytochrome P450 could, in principle, protect against certain carcinogens but enhance the metabolic activation of others. Phase 2 conjugations that were broadly viewed as “detoxification” reactions were known, in certain cases, to augment the activation and DNA reactivity of some chemical carcinogens. “Anticarcinogens” such as indole-3-carbinol also could act as promoters or tumor-enhancing agents, depending on the testing protocols used in vivo (3). Ito et al. (4) referred to “stage dependent paradoxical effects” of agents that inhibited during the initiation phase but promoted postinitiation.

Wattenberg believed that the most promising cancer chemopreventive agents were likely to be those in the suppressor agent category, because presumably most of us harbor initiated cells from an early age. However, he was quick to acknowledge that we lacked insight into the specific mechanisms that operated postinitiation, and as a result, few such agents had been identified, although the review article cited, among other compounds, retinoids and isothiocyanates as having some merit as later-stage preventive agents (1). This is noteworthy because of the knowledge that has accrued during the intervening 20 y, indicating that both classes of compounds affect gene expression, at least in part, via chromatin remodeling.

Chromatin remodeling: response to xenobiotic agents

The “histone code” refers to a range of posttranslational modifications that can affect access of transcription factors to DNA, thereby silencing and/or unsilencing gene expression. For example, reversible acetylation and methylation of lysine residues in histones occurs during chromatin remodeling, and global loss of monoacetylation and trimethylation of histone H4 is a common hallmark of human tumor cells (5). Cell cycle mediators, such as p53, can affect chromatin remodeling on a global scale via transcriptional mechanisms that recruit or displace histone deacetylases (HDACs) (6). Direct HDAC inhibitors also can affect changes in gene expression and impact on key regulators of apoptosis and the cell cycle (7), including retinoic acid receptors (RARs).

RARs are targets of retinoids, such as retinoic acid, which can exhibit both pro and con activities for cancer prevention (8). Interestingly, certain cases of acute promyelocytic leukemia that are resistance to retinoic acid treatment respond to compounds that interact directly with HDAC as competitive inhibitors (9). HDAC inhibitors influence cell cycle arrest and apoptosis through derepression of genes such as P21 and BAX, and cancer cells appear to be more sensitive than nontransformed cells to the actions of HDAC inhibitors (10). The mechanistic basis for this selectivity of action against cancer cells is far from clear, although recent studies have implicated thioredoxin and intracellular thiol status, the accumulation of reactive oxygen species, and induction of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) (11,12).

For the reasons alluded to above, HDAC inhibitors provide an attractive avenue for drug development, and considerable attention has focused on potent, high-affinity agents for use in cancer therapy. However, recent work has shown that HDAC inhibitors also exist in the human diet and might be involved in cancer prevention. Thus, compounds such as butyrate, sulforaphane, and diallyl disulfide attenuate HDAC activity in the micromolar to millimolar range in vitro and alter HDAC activity and histone acetylation status in vivo (13–16).

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4 To whom correspondence should be addressed. E-mail: Rod.Dashwood@oregonstate.edu.

Abbreviations used: HDAC, histone deacetylases; RAR, retinoic acid receptors; SIRT, silent information regulator 2 NAD+-dependent histone/protein deacetylases; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand.
Dietary HDAC inhibitors: another double-edged sword?
In principle, the double-edged sword discussed above in connection with blocking agents also exists with HDAC inhibitors because of the existence of several different HDACs in cells. Class I HDACs occur in the nucleus and are expressed in most cell types; class II HDACs shuttle between the nucleus and cytoplasm and appear to have a more restricted tissue distribution; and Class III HDACs exhibit a distinct substrate specificity and fail to respond to classic inhibitors such as trichostatin A. This is further complicated by tissue-specific metabolism and the levels of HDAC inhibitor that might be achieved at the target site. In addition, certain dietary agents may increase rather than attenuate HDAC activity, as reported for theophylline in alveolar macrophages from patients with chronic obstructive pulmonary disease (17), as well as for resveratrol in the activation of human silent information regulator protein 2 (SIRT1) (18).

Studies with dietary HDAC inhibitors are in their infancy, but their ability to modulate gene expression is receiving increasing attention, including alteration of xenobiotic pathways with relevance to cancer.

Literature Cited