Cancer Chemoprevention and Nutri-Epigenetics: State of the Art and Future Challenges.

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Abstract

The term "epigenetics" refers to modifications in gene expression caused by heritable, but potentially reversible, changes in DNA methylation and chromatin structure. Epigenetic alterations have been identified as promising new targets for cancer prevention strategies as they occur early during carcinogenesis and represent potentially initiating events for cancer development. Over the past few years, nutri-epigenetics - the influence of dietary components on mechanisms influencing the epigenome - has emerged as an exciting new field in current epigenetic research. During carcinogenesis, major cellular functions and pathways, including drug metabolism, cell cycle regulation, potential to repair DNA damage or to induce apoptosis, response to inflammatory stimuli, cell signalling, and cell growth control and differentiation become deregulated. Recent evidence now indicates that epigenetic alterations contribute to these cellular defects, for example epigenetic silencing of detoxifying enzymes, tumor suppressor genes, cell cycle regulators, apoptosis-inducing and DNA repair genes, nuclear receptors, signal transducers and transcription factors by promoter methylation, and modifications of histones and non-histone proteins such as p53, NF-κB, and the chaperone HSP90 by acetylation or methylation. The present review will summarize the potential of natural chemopreventive agents to counteract these cancer-related epigenetic alterations by influencing the activity or expression of DNA methyltransferases and histone modifying enzymes. Chemopreventive agents that target the epigenome include micronutrients (folate, retinoic acid, and selenium compounds), butyrate, polyphenols from green tea, apples, coffee, black raspberries, and other dietary sources, genistein and soy isoflavones, curcumin, resveratrol, dihydrocoumarin, nordihydroguaiaretic acid (NDGA), lycopene, anacardic acid, garcinol, constituents of Allium species and cruciferous vegetables, including indol-3-carbinol (I3C), diindolylmethane (DIM), sulforaphane, phenylethyl isothiocyanate (PEITC), phenylhexyl isothiocyanate (PHI), diallyl disulfide (DADS) and its metabolite allyl mercaptan (AM), cambinol, and relatively unexplored modulators of histone lysine methylation (chaetocin, polyamine analogs). So far, data are still mainly derived from in vitro investigations, and results of animal models or human intervention studies are limited that demonstrate the functional relevance of epigenetic mechanisms for health promoting or cancer preventive efficacy of natural products. Also, most studies have focused on single candidate genes or mechanisms. With the emergence of novel technologies such as next-generation sequencing, future research has the potential to explore nutri-epigenomics at a genome-wide level to understand better the importance of epigenetic mechanisms for gene regulation in cancer chemoprevention.

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