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Review

Epigenetic alterations induced by genotoxic occupational and environmental human chemical carcinogens: A systematic literature review

Grace Chappell[a], Igor P. Pogribny[b], Kathryn Z. Guyton[c], Ivan Rusyn[a,*]

[a] Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, TX, USA
[b] National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR, USA
[c] International Agency for Research on Cancer, Lyon, France

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ABSTRACT

Accumulating evidence suggests that epigenetic alterations play an important role in chemically-induced carcinogenesis. Although the epigenome and genome may be equally important in carcinogenicity, the genotoxicity of chemical agents and exposure-related transcriptomic responses have been more thoroughly studied and characterized. To better understand the evidence for epigenetic alterations of human carcinogens, and the potential association with genotoxic endpoints, we conducted a systematic review of published studies of genotoxic carcinogens that reported epigenetic endpoints. Specifically, we searched for publications reporting epigenetic effects for the 28 agents and occupations included in Monograph Volume 100F of the International Agency for the Research on Cancer (IARC) that were classified as "carcinogenic to humans" (Group 1) with strong evidence of genotoxic mechanisms of carcinogenesis. We identified a total of 158 studies that evaluated epigenetic alterations for 12 of these 28 carcinogenic agents and occupations (1,3-butadiene, 4-aminobiphenyl, aflatoxins, benzene, benzidine, benzo[*a*]pyrene, coke production, formaldehyde, occupational exposure as a painter, sulfur mustard, and vinyl chloride). Aberrant DNA methylation was most commonly studied, followed by altered expression of non-coding RNAs and histone changes (totaling 85, 59 and 25 studies, respectively). For 3 carcinogens (aflatoxins, benzene and benzo[*a*]pyrene), 10 or more studies reported epigenetic effects. However, epigenetic studies were sparse for the remaining 9 carcinogens; for 4 agents, only 1 or 2 published reports were identified. While further research is needed to better identify carcinogenesis-associated epigenetic perturbations for many potential carcinogens, published reports on specific epigenetic endpoints can be systematically identified and increasingly incorporated in cancer hazard assessments.

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* Corresponding author at: Department of Veterinary Integrative Biosciences, Texas A&M University, 4458 TAMU, College Station, TX 77843-4458, USA.
E-mail address: irusyn@cvm.tamu.edu (I. Rusyn).

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1. Introduction

Epigenetic alterations represent non-genotoxic mechanisms of carcinogenesis that may occur independently or concomitantly with genotoxic aberrations. Further, the epigenomic landscape may directly influence the genotoxic potential of a chemical; for example, several studies have indicated preferential binding of reactive chemicals to regions of DNA that harbor specific histone modification marks and/or DNA methylation patterns [1–6].

There are several major types of epigenetic and epigenomic alterations: DNA methylation, histones/chromatin structure, nucleosome positioning, and expression of non-coding RNAs, all of which can alter gene activity without change to the DNA sequence. A wealth of data demonstrates that changes in these epigenetic marks may occur as a consequence of exposure to environmental chemicals [7,8], and may play a role in the etiology of various human diseases, including cancer [9]. It has been demonstrated that chemically-induced epigenetic alterations occur early during exposure and may also have significance as biomarkers of carcinogen exposure.

To enable incorporation of epigenetic endpoints in chemical safety assessments, further characterization of the role of epigenetic alterations induced by chemical exposure is necessary [10]. Specifically, additional studies are needed to characterize the relationship between epigenetic alterations and toxicity phenotypes, and the epigenetic-specific dose-response [11]. Several recent publications [9,12] reviewed the current state of knowledge of epigenetics and cancer, and the application of epigenetic endpoints in cancer hazard assessments, including for chemical carcinogens. Despite the fact that the utilization of epigenetic