Published in final edited form as:

Curr Opin Toxicol. 2017 October ; 6: i–iii. doi:10.1016/j.cotox.2017.11.006.

Editorial overview of the special issue on genomic toxicology epigenetics

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This special “Genomic Toxicology: Epigenetics” issue of “Current Opinion in Toxicology” summarizes the current state of science at the intersection of epigenetics and toxicology. The opinions included herein examine the role of epigenetic events in responses to chemicals and drugs, the methodologies and model systems that have contributed to uncovering the role of epigenetics, and the impact that the evidence of epigenetic perturbations may have on decision-making with respect to human health assessments of chemicals and drugs. Importantly, all opinions highlight the existing gaps that need to be addressed for better understanding of the role of epigenetic events in the mechanisms and outcomes of adverse effects of chemicals and drugs.

“Epigenetics” encompasses the chromosome-associated molecular events that result in changes in gene expression without changes in the primary DNA sequence. In the mammalian genome, negatively charged linear DNA is compacted into chromatin, which is dynamic and subject to epigenetic modifications that include cytosine DNA methylation, posttranslational modifications of histone proteins, and nucleosome positioning along DNA. It is well established that environmental, occupational, or lifestyle exposures may affect both the genome, through DNA damage and mutations, and the epigenome [1,2]. Despite the growing body of evidence that the epigenome is a target for toxicants, there is still lack of clarity on what role, if any, these toxicant-induced epigenetic alterations may play with respect to causality of the associated adverse health outcomes. The fluidity of the epigenome suggests that these effects may be transitory in nature, or are signs of adaptation to protect the genome from harmful effects of exposures. The main reason for the paucity of information on the role of epigenetic events in the mechanisms of toxicity lies in the fact that many research tools for epigenetics research are still relatively new and the field is growing rapidly [3,4]. Future work will undoubtedly clarify the causal or associative role of epigenetic events, their value as biomarkers of adverse health outcomes, and chart the path for more confident use of this information in decision-making. The opinions presented in this issue provide a practical roadmap for epigenetics in toxicology and they shall serve as a valuable and realistic assessment of the state of science.

To date, most progress has been made in investigating the role of epigenetic alterations in chemical-induced carcinogenesis [1,5]. Indeed, “induce epigenetic alterations” is one of ten key characteristics of known human carcinogens [6]. Several articles in this issue are

focusing on the relationships between exposure to chemical carcinogens and epigenetic alterations. Chappell and Rager [10.1016/j.cotox.2017.06.007] describe cancer-related epigenetic abnormalities induced by genotoxic chemicals. Using examples of several known human carcinogens that act primarily through DNA damage and mutations, such as benzo[a]pyrene, 1,3-butadiene, and formaldehyde, the authors demonstrate the linkages between DNA damage caused by carcinogen exposure and epigenetic events. The interdependent nature of genotoxic and epigenotoxic alterations in the etiology of chemical-induced cancers is now well accepted [3,4]. The paper by Tryndyak [10.1016/j.cotox.2017.08.004] summarizes the state of current knowledge on the role of epigenetics in tumor induction by non-genotoxic carcinogens. This topic is of special importance because a 2-year rodent cancer bioassay is the primary evidentiary basis for identification of non-genotoxic carcinogens. This paper posits that epigenetic alterations induced by chemical carcinogens, regardless of whether they are directly damaging the DNA or not, are important mechanisms for carcinogenesis. This suggests that epigenetic signatures of chemical and drug exposure may be more indicative of the potential outcome (e.g., cancer), but not the etiology (e.g., genotoxicity or other mechanisms). It is also evident that some epigenetic alterations may drive the development of cancer, while others may be associated molecular events. It is the opinion of the authors of these papers that identification of the causal epigenetic signatures associated with carcinogen exposure will be a major step forward in the use of epigenetic data in toxicology.

The paucity of data and the gaps in our knowledge with respect to linkages between exposure, epigenetics and adverse health outcomes is demonstrated by Meakin et al. [10.1016/j.cotox.2017.06.003] using the case study of arsenic, one of the most ubiquitous environmental contaminants. This paper provides a comprehensive review of the arsenic-associated effects on DNA methylation, histone modification, and microRNA expression. Importantly, the authors present the challenges in establishing the causal links between these effects and human cancer and non-cancer pathologies associated with exposure to arsenic. They point to the need for a multi-prong approach, studies in vitro where the causality of epigenetic events from exposure to effect can be interrogated, and the validation of the causal role of epigenetic effects through additional readouts, including gene expression and protein activity. The role of epigenetics in the mechanisms of noncancer health outcomes is also being actively explored by toxicologists. McCullough et al. [10.1016/j.cotox.2017.07.001] examine the epigenetic mechanisms of air pollution leading to cardiopulmonary disorders, Cory-Slechta et al. [10.1016/j.cotox.2017.09.004] describe the role of epigenetics in neurotoxicity, and Aluru [10.1016/j.cotox.2017.07.004] demonstrates how alternative model systems may aid in studies of epigenetics and the developmental origins of health and disease. These papers not only describe the complexities of the overall mechanisms that have been suggested as linkages between exposures and outcomes, but they also point out the difficulties in studies of epigenetics as one of those mechanisms because of the multitude of potential molecular events that can be attributed to “epigenetics”. The paucity of the adverse health outcomes, epigenetic endpoints and assays, study designs and developmental stages that may need to be examined, as well as the need for careful considerations of time and dose, are well demonstrated by the authors. Still, the authors

paint a positive outlook and call for patience as the body of evidence develops that will allow more confident conclusions and, ultimately, decisions.

While most studies of epigenetics in toxicology examine the effects of treatments or use samples from diseased subjects, equally important is to understand “what is normal?” [7] in terms of the epigenetic landscape of different organisms, cells, and individuals. As described by Lee et al. [10.1016/j.cotox.2017.07.007], several largescale scientific community efforts provide information that allows better understanding of the variability in epigenetic landscapes. The epigenetics data in the Encyclopedia of DNA Elements (ENCODE) project, which is a publically accessible database for understanding genomic function, development and disease etiologies is an invaluable resource not only for the molecular biologists, but also for the toxicologists studying epigenetics. The authors make a convincing case that ENCODE and other online resources can help fast track novel insights in toxicology by utilizing already curated reference epigenome datasets.

The paper by Lewis et al. [10.1016/j.cotox.2017.08.006] addresses another largely unexplored dimension in epigenetics and toxicology, the linkages between genetic variants and epigenetic landscape in “control” and “exposed” individuals. The authors present a novel concept hypothesizing that an existence of “normal epigenome variability” may have a major impact on the individual’s susceptibility to toxicant exposure. This paper also points out that inclusion of the population variability into studies of toxicology and epigenetics is only feasible when the most informative assays and endpoints are to be evaluated. The authors posit that data from strand-specific RNA-seq and ATAC-seq represents a cost-effective approach to identify and resolve regions of active or repressed enhancers and promoters that contribute to susceptibility of damaging effects of toxicants.

Finally, three papers aimed to address the “so what?” question with respect to epigenetics and toxicology.

Datta and Kolaja [10.1016/j.cotox.2017.10.010] review the druggability of the epigenetic targets and describe six epigenetic agents that have been approved for cancer treatment. While these drugs show promise, this review also points out considerable potential risks that are associated with therapeutic manipulation of epigenetic regulation. LaRocca et al. [10.1016/j.cotox.2017.11.004] examined the role of epigenomic changes in the context of human safety assessment of industrial chemicals and products. This is a view from the “regulated” side of the decision-making process and the authors express an opinion that epigenetic endpoints may be promising in at least two areas within a product safety assessment paradigm of the future - as surrogate biomarkers, and in dose-response part of risk assessment. Notwithstanding the overall positive outlook, the paper also points to the reality that most of the currently available data on chemical effects on epigenome are not yet suitable for decision-making by the chemical industry. Similar viewpoint is expressed by the government risk assessors in Cote et al. [10.1016/j.cotox.2017.09.002]. These authors agree that despite the many recent advances to the field of epigenetics, application of this knowledge in environmental health risk assessment has been limited. The authors share the sentiment that epigenetic data provide very useful information, not only for mechanistic toxicology, but also for decision-making. Still, they posit that the path to wide acceptance of

the data on epigenomic modifications is through additional research that identifies which endpoints are most informative and can be causally linked to pathogenic alterations in gene expression or cell signaling, and that the most informative studies will be those that examine time and dose effects and thus can inform dose-response assessments.

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