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The Time has Come for Clinical Toxicologists to Enter into the Post-Genomic Era

Asok Dasmahapatra*

National Center for Natural Product Research, School of Pharmacy, University of Mississippi, MS, USA

After the successful completion of the human genome project, a new era in science begins. Researchers from different disciplines are interested and put their efforts to resolve the mystery of some of the unsolved problems specifically which are related to human health. Unfortunately, the information we received from human genome project cannot provide us all the answers we need to know. With the further advancement of gene sequencing technology especially in the next generation sequencing techniques which provide us more opportunities to believe that there must be other additional layers to the primary sequences that may throw more light in these unsolved problems. Consequently, we have focused on another area of research which is known as epigenetics, the literal meaning of which is "above genetics." In general, epigenetics refers to the regulation of gene expression without altering DNA sequences of an organism. Such modifications include chemical marks that regulate the transcription of the genome. Mapping of epigenome provide us more information than the genomic map and also explain how a specific locus of a gene behaves in both during normal development as well as in disease. Epigenome data are very powerful and have multiple applications especially in the area of clinical toxicology.

Although, clinical toxicology evaluates the toxic effects of chemicals, drugs, environmental pollutants, and many other agents which are able to alter the human body physiology, after the initial phases of investigation, the toxic effects are later focused at the cellular levels starting from the morphology and biochemistry to the gene level. However, like other physiological events, only genetic analysis is not sufficient to understand the mechanisms of toxicity of chemicals in human body. Toxic agents could act at different levels by directly modifying both the genome and epigenome or indirectly by altering signaling pathways. These alterations in chromatin structure may or may not be heritable but probably are reversible. Currently, there are insufficient data to support inclusion of epigenetic profiling into pre-clinical evaluation studies. Many International collaborative efforts are necessary to generate data to determine whether epigenetic modifications have any link in health and diseases. Moreover, the current toxicological testing techniques are expected to identify the potential adverse effects at the epigenome. Therefore, the time has now come that clinical toxicologists should be focused on epigenetic modifications and develop the tools that will help to understand the potential mechanism of toxicity in the epigenome.

Since C.H. Waddington (1942) used the term epigenetics, substantial advancement has been made in this area. So far three principal mechanisms, DNA methylation, histone modification and later non-coding RNA or microRNA interference are considered as the major events associated with epigenetic modifications. Recently, it was also demonstrated that methylation of mRNA has an important role in obesity which opened the related field of RNA epigenetics. DNA methylation is the covalent addition of methyl groups mostly to the cytosine nucleotides catalyzed by DNA methyl transferase (DNMT) enzyme families. 5-Methylcytosine behaves like a regular cytosine and pairs with guanine. DNA methylation, are actively remodeled during early development in response to environmental factors. Histone modifications are controlled by acetylation, deacetylation, methylation, phosphorylation, ubiquitiniation, sumoylation, ribosylation reactions, which are also catalyzed by specific enzymes that modify histone proteins to either an accessible or inaccessible state for binding of various transcriptional activators or repressors for their binding to gene promoters. Histone proteins are subject to remodeling in response to environmental influences even at later stages of development. The non-coding RNAs (miRNAs) are nineteen to twenty four nucleotides long; regulate gene expression by sequence-specific binding to the 3' untranslated region of target mRNAs, resulting in either mRNA degradation or inhibition of mRNA translation. All these processes are enzyme based and increasing evidence from animal studies indicates that nutritional supplements, xenobiotic chemicals, and reproductive technologies can alter the epigenetic state of specific genomic regions. The investigations are so extensive that many commercial bio-tech companies are developing tools to critically access these processes. Therefore, it is the high time for the clinical toxicologists to put more effort in these exciting areas of research.

***Corresponding author:** Asok Dasmahapatra, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, MS, USA, E-mail: asok@olemiss.edu

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