ANTIOXIDANTS & REDOX SIGNALING
Volume 17, Number 2, 2012

DOI: 10.1089/ars.2012.4562

Factors Influencing Epigenetic Mechanisms and Related Diseases

Tom C. Karagiannis[1,2] and Nilanjana Maulik[3]

Abstract

It is becoming clear that epigenetic mechanisms are associated with disease. To date, a myriad of epigenetic alterations, including altered DNA methylation and aberrant histone post-translational modifications, have been linked with various conditions. The most widely investigated example is the link between aberrant DNA methylation and malignancy that has lead to the clinical use of the DNA methyltransferase inhibitors, azacitidine and decitabine, for the treatment of myelodysplastic syndromes. Similarly, defective histone acetylation status has been associated with malignancy, providing the basis for the clinical use of the histone deacetylase inhibitors suberoylanilide hydroxamic acid and depsipeptide for the treatment of cutaneous T-cell lymphoma. In addition, there is an emerging association between perturbed fetal epigenetic programming and developmental origins of disease due to both nutritional and environmental factors. In particular, epigenetic events associated with metabolic syndrome have been identified. Related epigenetic mechanisms as well potential pharmacological and dietary interventions at critical periods of development form a large part of the discussion in this Forum. Further, this Forum provides an in-depth account of the association between epigenetic mechanisms and carcinogenesis with a focus on disease prevention with dietary chromatin-modifying compounds. Finally, the association between aberrant epigenetic events and neurodegenerative conditions, such as Alzheimer's disease (AD), is becoming apparent. A research article in this Forum identifies a potential new polymorphism associated with one-carbon metabolism that may contribute to the pathogenesis of AD. Overall, this Forum provides a detailed account of known epigenetic processes in developmental programming and human disease. *Antioxid. Redox Signal*. 17, 192–194.

The term "epigenetics" is attributed to the British scientist Conrad Waddington. In the 1940s Waddington introduced the word "epigenetics" to incorporate all of the factors controlling gene expression and cell differentiation (genetic and environmental interactions) (18). The term is derived from the virtually redundant Aristotelian word of epigenesis, which appeared in his writings in ca. 350 BC related to the generation of animals—although the term is beginning to reappear in the modern literature. The term "epigenesist" was used by the Hellenic philosopher to describe his concept of gradual and progressive developmental changes, a thesis that challenged the prevailing idea of preformed embryos. Today, the term epigenetics has been expanded to reflect a greater biological scope rather than only developmental biology. In simplified form, epigenetics is currently typically defined as inherited phenotypic changes that are not due to changes in a gene sequence. However, more qualified definitions have been communicated by contemporary epigeneticists (2).

Epigenetic mechanisms regulate chromatin architecture and modulate DNA metabolic processes, including gene transcription, replication, and repair (10). The basic repeating unit of chromatin is the nucleosome. Nucleosomes consist of 146 base pairs of DNA wrapped, in 1.7 superhelical loops, around an octameric core comprised of a tetramer of H3 and H4 histones and two H2A-H2B histone dimers. This nucleosomal repeating unit creates the familiar 11-nm beads-on-a-string fiber. Chromatin is further organized into a higher-order 30-nm fiber *via* binding of the linker histones H1 or H5. The structural features of this higher-order organization remain more obscure with two-classical models, the solenoid and zig-zag, typically used to describe this level of

[1]Epigenomic Medicine, Baker IDI Heart and Diabetes Institute, The Alfred Medical Research and Education Precinct, Melbourne, Victoria, Australia.
[2]Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia.
[3]Molecular Cardiology and Angiogenesis Laboratory, Department of Surgery, University of Connecticut School of Medicine, Farmington, Connecticut.

compaction (11). Chromatin compaction is necessary in eukaryotic cells to allow the ~2 m of DNA to physically fit inside the nucleus. Given the organization of the genetic code within the nucleus, all DNA metabolic processes and differentiation are tightly associated with the regulation and remodeling of chromatin. How epigenetic mechanisms influence chromatin structure and DNA metabolism is a research theme currently undergoing exponential growth.

Briefly, epigenetic processes can be categorized into various major classes, including (i) DNA methylation, (ii) histone modifications and chromatin remodeling, (iii) noncoding RNAs, and (iv) RNA and DNA editing. DNA methylation is one of the most well-characterized epigenetic mechanisms. It is mediated by a group of enzymes known as DNA methyltransferases (DNMT). These enzymes catalyze the transfer of a methyl group from *S*-adenosyl-L-methionine (SAM) onto the 5′ position of the cytosine ring found in cytosine phosphate guanine (CpG) dinucleotides (regions found at 5′ ends of genes are referred to as CpG islands). DNA methylation is established during development by *de novo* DNMTs (DNMT3A and DNMT3B) and maintained by maintenance DNMTs (DNMT1, which has a strong preference for hemimethylated DNA). Typically, methylated DNA is associated with transcriptional repression and hypomethylation is associated with active chromatin.

Epigenetic alterations are now accepted to be major characteristics of human cancers (8). In general, malignancy is associated with a global reduction in DNA methylation and focal CpG island hypermethylation in cancer-associated (tumor suppressor) genes (5). Given the association between aberrant DNA methylation and cancer has prompted the clinical development of DNMT inhibitors. To date, the DNMT inhibitors azacitidine (5-azacytidine, Vidaza®) and decitabine (5-aza-2′-deoxycytidine, Dacogen™) have been approved by the U.S. Food and Drug Administration for the treatment of myelodysplastic syndromes. Further, the potential benefit of DNMT inhibitors for other malignancies is consistently being explored. In addition to clinical development, it is thought that a constant uptake of dietary DNA demethylating agents may have chemopreventive effects. The prime example of a dietary compound with DNMT1 inhibition activity is the green tea polyphenol (−)-epigallocathecin-3-gallate, which has received much attention for its health benefits.

There is still some debate as to whether chromatin modifications represent truly epigenetic mechanisms and is an ongoing discussion in the field. Nevertheless, particularly histone acetylation and methylation are chromatin modifications that have been relatively well characterized and are widely discussed in this Forum. First, histone acetylation is regulated by the opposing actions of two groups of enzymes: histone acetyltransferases (HAT) and histone deacetylases (HDAC) (14). HAT enzymes catalyze the addition of acetyl groups on ε-lysine residues of core histones, in general, resulting in an open, transcriptionally active chromatin conformation. HDAC enzymes remove acetyl groups, resulting in a more condensed, transcriptionally repressive chromatin state. HDAC enzymes have critical roles in survival and proliferation, and aberrant acetylation has been observed in numerous malignancies. This has prompted the development of HDAC inhibitors as anticancer agents. To date, suberoylanilide hydroxamic acid (Vorinostat, Zolinza®) and depsipeptide (Romidepsin, Istodax®) have been approved for the treatment of advanced cutaneous T-cell lymphoma. Numerous compounds are currently undergoing evaluation in clinical trials either for monotherapy or in combination with other cancer modalities. In addition, the potential clinical utility of HDAC inhibitors has been extended to nononcological applications, including cardiac hypertrophy, asthma, and neurodegenerative conditions (14). The functional role of histone methylation that may occur on lysine (mono-, di-, or tri-methylation) or arginine (mono- or symmetric/asymmetric-dimethylation) side chains, in health and disease, is only starting to become appreciated (10). Chromatin modifications and chromatin-modifying compounds, including detailed discussion of dietary HDAC inhibitors, form part of this Forum.

The concept of *in utero* fetal programming is strongly linked with the field of epigenetics. Indeed, fetal epigenetic programming forms the basis of the first four review articles in this Forum. Essentially these are in accordance with the Barker hypothesis of fetal programming, which postulates that perturbations in nutritional or environmental conditions *in utero* result in altered developmental programming of organs, influencing the propensity to develop the disease later in life (1). First, the epigenetic landscape of stem cells is reviewed by Han and Yoon (6), and epigenetic fetal programming associated with aberrant epigenetic changes during critical periods of development due to endogenous or exogenous stress are explored by Hussain (7) in this Forum. This concept is also explored by Strakovsky and Pan (16), who give a detailed account of the *in utero* epigenetic regulation of the antioxidant defense system. Also in this Forum, Chaudhary *et al.* (3), discuss the epigenetic basis of metabolic syndrome and the potential benefits of dietary supplementation during critical periods. *In utero* epigenetic events and metabolic syndrome and possible pharmacological and dietary interventions are also analyzed in this Forum by Wang *et al.* (19). Further, in this Forum Ly *et al.* (13) provide a detailed account of folate and DNA methylation during early development and discuss aberrant methylation associated with aging. Overall, they provide a comprehensive review related to the effects of folate in health and disease with a distinct focus on malignancy.

The following review articles in this Forum have a strong emphasis on the epigenetic effects of dietary compounds and cancer. First, Parinandi *et al.* (15) discuss aspects of the emerging field of disease prevention by targeting the epigenome with phytochemical antioxidants. Licciardi *et al.* (12) provide an in-depth account of dietary and synthetic HDAC inhibitors. An important focus is on the anticancer effects of dietary isothiocyanate, sulforophane, and dietary short-chain fatty acids. The epigenetic basis of cancer and the potential of dietary compounds in cancer prevention and treatment are further explored by Verma (17) in this Forum. Also in this Forum, Koturbash *et al.* (9) provide a more focused review of cancer and epigenetics, specifically highlighting the role of histone H4 lysine 20 methylation in carcinogenesis induced by carcinogens.

The complex interaction between genetic and environmental interactions in the pathobiology of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis, is becoming evident. For example, age-related aberrant DNA methylation has been observed in late-onset AD (LOAD) (20). In a research article in this Forum, Coppedè *et al.* (4) investigated genetic polymorphisms associated with one-carbon metabolism in AD. They

identified a potential new polymorphism that may contribute to the pathogenesis of LOAD and correlated their findings with increased plasma homocysteine and decreased folate levels supporting the one-carbon metabolism hypothesis.

Overall, epigenetic mechanisms regulate and interpret genetic information. Epigenetic regulation and inheritance are now recognized as important determinants in the context of the developmental origins of disease. Further, it is now clear that epigenetic aberrations are involved in numerous disease states and these are particularly well-characterized in cancer. The purpose of the reviews and the original article in this Forum is to provide a comprehensive and up-to-date account of epigenetic mechanisms and their functional role in development and various human diseases.

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Address correspondence to:
Dr. Nilanjana Maulik
Molecular Cardiology and Angiogenesis Laboratory
Department of Surgery
University of Connecticut School of Medicine
Farmington Ave.
Farmington, CT 06032

E-mail: nmaulik@neuron.uchc.edu

Date of first submission to ARS Central, February 11, 2012; date of acceptance, February 11, 2012.

Abbreviations Used

AD = Alzheimer's disease
CpG = cytosine phosphate guanine dinucleotides
DNMT = DNA methyltransferase
HAT = histone acetyltransferase
HDAC = histone deacetylase
LOAD = late-onset Alzheimer's disease
SAM = *S*-adenosyl-L-methionine

This article has been cited by:

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