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HIGHLIGHTED TOPIC | *Epigenetics in Health and Disease*

Epigenetics: an emerging player in health and disease

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THE DECODING of the human genome in 2003 provided enormous opportunities to gain a greater understanding of the genetic intricacies underlying biological systems in both health and disease. Along with variations in the linear sequence of the genome that may predispose to certain pathologies, there is increasing evidence that epigenetic factors can profoundly influence gene expression and, in turn, resistance or susceptibility to disease (2, 10). The term “epigenetics” comes from the Greek word epigenesis and was coined by the developmental biologist Conrad Waddington (1905–1975) in the late 1940s. In recalling this, Waddington wrote, “Some years ago (e.g., 1947) I introduced the word ‘epigenetics,’ derived from the Aristotelian word ‘epigenesis,’ which had more or less passed into disuse, as a suitable name for the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being” (8, 12). In his seminal book, *The Strategy of Genes*, Waddington (13) described his epigenetic landscape theory. Waddington theorized, at a time when the function and regulation of genes was very poorly understood, that cellular development must be governed by a variety of factors outside the scope of genetic inheritance. This novel and innovative theory provided the framework for modern epigenetics.

Today, epigenetics is commonly defined as changes in gene expression that occur without a change in DNA sequence (4, 11). It can be viewed as a bridge between genotype and phenotype (5). Over the past decade, there has been mounting interest in the associations between epigenetic modifications and human conditions and diseases such as aging, cancer, lupus, schizophrenia, and cardiovascular disease. While many of these pathologies can be heavily influenced by heritable factors, environmental factors also play a role. Indeed, the impact of environmental factors (i.e., diet, smoking, physical activity, pollutants) on disease pathology is thought to be mediated, in part, by epigenetics (11). In addition, there is commercial interest in epigenetics, with pharmaceutical companies vying to identify potential therapeutic targets, diagnostic methods, and new treatments. Important epigenetic mechanisms include DNA methylation; posttranscriptional histone modifications that affect chromatin structure, such as methylation, acetylation, ubiquitylation, and phosphorylation; RNA associated gene silencing; and chromosome inactivation (14). With cancer, for example, aberrant DNA hypermethylation has been linked with silencing tumor suppressor genes, resulting in

a tumorigenic promoting state (11), whereas both increases and decreases in DNA methylation are associated with atherosclerotic vascular disease depending on gene loci (10).

In this and forthcoming issues of the *Journal of Applied Physiology*, epigenetics will headline the Highlighted Topics section. Six excellent mini-reviews from leaders in the field will provide an overview on hot topics in epigenetics ranging from heterochromatin regulation to methodological approaches to study epigenetic mechanisms. The first review by Hahn et al. (7) eloquently describes how changes in the conformation of chromatin from a loosely packed transcriptionally active state or euchromatin to a more densely packed less transcriptionally active state or heterochromatin affects gene expression patterns and development of a number of diseases including cancer, facioscapulohumeral muscular dystrophy, and Friedreich’s ataxia. The second review by Augilera et al. (1) focuses on the effects of environmental factors on the epigenome during embryonic development and adulthood. A fascinating discussion is provided on how environmental conditions such as maternal diet can affect the epigenotype of the offspring. During adult life, several factors can impact epigenetic status, including diet, living place/work place, pharmacological treatments, and unhealthy habits (e.g., smoking); each of these factors is clearly described.

The third and fourth reviews focus on cancer and aging, respectively. The third review by Kanwal and Gupta (9) provides an excellent overview of how epigenetic modifications influence cancer sensitivity in humans. Attention is given to how DNA methylation and histone modification at specific sites as well as specific microRNA expression changes determine gene expression patterns in cancer cells. There are several detailed examples of how these modifications regulate cancer initiation, promotion, invasion, metastasis, and chemotherapeutic resistance. Although not yet in widespread clinical use, a compelling case is put forth for the utility of epigenetic markers, such as methylated DNA sequences, to monitor and guide cancer therapy. The current state of epigenetic therapeutic agents for the treatment of cancers is also discussed. The fourth review by Gonzalo (6) exquisitely covers a rapidly expanding area of interest. In general, aging is associated with global decreases in DNA methylation with some site-specific hypermethylations that may be regulated by age-dependent changes in DNA methyltransferases. The contributions of histone alterations and microRNA expression are also covered. Interestingly, an overview of how the Sirtuins may influence longevity through epigenetic alterations is provided, citing specific examples with SIRT1 and SIRT6. This review nicely compliments the preceding review, by noting that aging represents the highest risk for cancer and presenting a number of

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age-related epigenetic mechanisms that may be responsible for this risk. While mechanisms underlying aging are very complex there are premature aging syndromes that have been critical for understanding the molecular process and these are described.

The fifth and sixth reviews conclude the highlighted topic on epigenetics. The fifth review by Yan et al. (15) discusses how epigenetic factors contribute to cardiovascular risk. Hutchinson-Gilford progeria syndrome is presented as a model for disruption of chromatin, causing premature severe atherosclerosis, myocardial infarction, and stroke. An excellent discussion is provided on how epigenetic mechanisms regulate endothelial nitric oxide synthase (eNOS) expression. For example, in endothelial cells, chromatin structure in the eNOS promoter is transcriptionally permissive with both DNA hypomethylation and activating histone modifications. In contrast, in nonendothelial cells, such as the structurally adjacent, vascular smooth muscle cell, the promoter demonstrates hypermethylation without activating histone alterations. These changes determine tissue specificity by inducing eNOS in the endothelium and not in the vascular smooth muscle. The review concludes by outlining how external stimuli such as laminar shear stress or cytokines might produce epigenetic changes, thereby promoting or preventing the development of atherosclerosis, using hypoxia as a concrete example. The sixth review by Evertts et al. (3) provides a timely description of techniques to identify and compare DNA methylation marks and combinatorial histone modifications. Approaches to quantify these epigenetic modifications including mass spectrometry techniques (i.e., middle-down and top-down mass spectrometry) and chromatin immunoprecipitation (ChIP) are carefully described. This review provides an outstanding tutorial on the required methodology for the accurate assessment of epigenetic events.

Many questions remain regarding the influence of epigenetic modifications in promoting both health and disease. In 2008, the National Institutes of Health launched the Roadmap Epigenomics Program to accelerate research in this area. Epigenetics is now center stage; it has the potential to reveal mechanisms of disease, new treatment options, and healthy lifestyle strategies.

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