The ultimate enigma: the epi-language of cells

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Abstract

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Ethics statement

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Abstract

While I think about the most important fundamental mystery in biology today, epigenetic is the first field comes to my mind. I believe if the mystery will be unlocked by basic research, it would yield the greatest dividends for human health. This essay briefly describes the unresolved mechanisms in epigenetic and highlights the importance of the field in different disease pathogenesis.

Introduction

Communication is an irreplaceable tool for defining, processing, and solving complex problems. We started to truly understand our cells first by learning the “4-letter alphabet” with groundbreaking discoveries of Watson and Crick. These findings paved the way for the human genome project, which was completed in 2003. Although delighted to have access to complete libraries of cells and species, James Watson recognized an important trend in modern genetic research when he said “the major problem, I think, is chromatin… what determines whether a given piece of DNA along the chromosome is functioning, since it’s covered with the histones? You can inherit something beyond the DNA sequence. That’s where the real excitement of genetics is now” (1). In other words, it is not enough to know the 4-letter alphabet and read the entire library. Anticipating the complexity of interpreting the 4-letter DNA alphabet, Conrad Waddington first used the term “epigenetics” in 1939 to refer “the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being” (2). Over years, highlighting its unique importance, epigenetics became of interest to a broad segment of the scientific community; researchers in many distinct fields (e.g., oncology, regenerative medicine, environmental health) began to recognize the wide-ranging significance of epigenetic mechanisms. This essay focuses on persisting mysteries in the “epi-language” of cells with the aims of establishing a better understanding of our cells and addressing critical human health problems.

Unresolved Mechanisms and Future Perspective

DNA methylation is the most extensively studied epigenetic mechanism. The mechanisms functioning to preserve specific methylation patterns that promote appropriate differentiation in particular lineages are fairly well understood. However, when or how a cell decides to initiate *de novo* methylation, which sometimes involves inappropriate methylation of

tumor-suppressor genes and decreased methylation of tumor-promoting genes, is not fully understood (3). Histone modification is perhaps the fastest changing and advancing research topic in epigenetics. Each histone protein has many residues that covalently modified via methylation, acetylation, phosphorylation, and/or ubiquitination. Moreover, methylation codes can become highly complex with mono-, di-, or tri-methylation of histones; each such modification can introduce meaningful changes to the physical properties of histones, interactions with DNA, and finally gene expression. These epigenetic modifications can be seen as an epi-language that is governed by histone modifiers known as “writers”, “readers” and “erasers” (4). Clearly, an epigenetic conversation occurs within each cell, but how a newly formed zygote initiates, manages and inherits such conversations remains unknown. Even more striking is the fact that crosstalk between DNA modifications and histone modifications remain largely unexplored; such crosstalk is certainly important to lineage determination (5). Understanding epigenetic effects on lineage determination hold great promise for the field of regenerative medicine and for clinical applications to diseases caused by organ failure—including heart, liver, kidney or lung failure (6).

A major challenge in epigenetics is to understand the conversation between the environment and the epigenome. The recent emergence of environmental epigenetic research has provided important insights into the effects of gestational exposure to synthetic estrogens; these effects include promoting late-stage reproductive cancers in offspring. Additionally, exposures to polycyclic aromatic hydrocarbons and bisphenol A-polycarbonate plastics are associated with asthma and prostate cancer, respectively. The causative mechanisms are mostly explained by DNA methylation-based imprinting. Moreover, environmental factors are important to phosphorylation-dependent regulation of histone methyl modifiers. This growing field is expected to elucidate important mechanisms mediating the conversation between the epigenome and environment to improve clinical management of diseases heavily influenced by environmental factors (e.g., obesity, diabetes, cardiovascular disease, and cancer) (7).

The big picture of epigenetics encompasses the entire life span; from conception to death, every stage of human development is affected by epigenetics. Maternal diet, tobacco use, mental health, and social environment can cause epigenetic changes *in utero*. Surprisingly, delivery mode (e.g., vaginal or cesarean) also affects the epigenome. Early childhood parental care can affect epigenetic modifications, cause changes in brain development, and affect child psychology. During adolescence and puberty, the importance of epigenetics is clearly evident with global changes in histone acetylation during the menstruation cycle. Similar epigenetic changes are evident during menopause. In adulthood many diseases can be understood via epigenetics; Alzheimer’s disease, psychiatric disease, coronary artery disease, pulmonary disease, diabetes, reproductive system abnormalities, and many cancers have epigenetic components (8). Currently, histone deacetylase inhibitors and DNA methyltransferase inhibitors are among the epigenetic therapies being explored to treat these diseases. The successful use

of histone deacetylase inhibitors in cancer therapy is a very promising indicator of the epigenetic therapy potential (9).

Approach for the investigations and emerging hypothesis

Epigenetic mechanisms and today's challenges in understanding epi-language of cells are probably not limited to chromatin or genome modification; they may not even be confined to the nucleus. Cell morphology, the arrangement of organelles, and cellular position within the body may each be important to epigenetics. The current border around the field of epigenetics is likely to fall away. In taking the language metaphor for epigenetic seriously, we must recognize that various modifications will not have the same meaning in different cell lineages. If we consider the human body as a world of cells, a single type of epigenetic modification will not mean the same thing or cause same effect in two different cells from two different organs. As cell lineages differentiate from one another, they may begin to speak different epigenetic languages. To better handle the challenges of understanding cells and caused problems, we should keep an open mind about epigenetic mechanisms functioning beyond the levels of DNA and chromatin.

In summary, the ultimate enigma surrounding the inheritance and regulation of epigenetic mechanisms is key to an improved understanding of human cells and to solving many different human health problems. Leading causes of death include cardiovascular diseases, neoplastic diseases, chronic lower respiratory diseases, and diabetes; therefore, investigations of molecular mechanisms in epigenetics will help to deliver better treatments and preventive approaches for these diseases.

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