

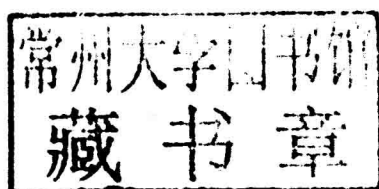
Epigenetics



Lyle Armstrong

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Lyle Armstrong



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Epigenetics

Preface

When this book was first conceived, the motivation to write was simple. My research program focused on analyzing the mechanisms through which epigenetic reprogramming functioned during somatic cell nuclear transfer. Several graduate students were interested in this project but there were few easily digestible texts that could provide an introduction to the subject of epigenetics. That is not to say that excellent textbooks did not exist on the subject, but these were perhaps less suitable for students whose projects were concerned with the impact of epigenetics on cellular functions rather than understanding the basis of epigenetics in its own right.

The book is the result of a long and iterative process. The field of epigenetics has advanced rapidly during the assembly of the text so that several updates have been necessary. I hope that the result is a general introduction that will enable students who need to appreciate how epigenetics can influence cell biology and the onset of human disease. **Epigenetics** is divided into three sections. Section 1 describes chromatin architecture before going on to the details of DNA methylation and histone acetylation. The second section explains how normal cellular functions (gene expression, the cell cycle, gene imprinting, and differentiation) are affected by epigenetics and how epigenetic modification patterns can be reversed to create pluripotent stem cells. The final section discusses the evidence for epigenetic involvement in disease, with emphasis on cognitive dysfunction and cancer.

For these reasons the book is aimed at a wider audience than those involved in understanding of purely epigenetic phenomena; my hope is that researchers in all areas of cell biology and medicine will find the text useful and informative, and if by reading this they are encouraged to add to the body of knowledge of epigenetics, I will consider the book to have been a success.

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For instructors

Figures

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CHAPTER 8	Locus-Specific Control of Histone-Modifying Enzyme Action

CHAPTER 6 Post-Translational Modification of Histones

CHAPTER 7 Histone Modification Machinery

CHAPTER 8 Locus-Specific Control of Histone-Modifying Enzyme Action

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INTRODUCTION TO THE STUDY OF EPIGENETICS

1.1 THE CORE ISSUE: CONTROLLING THE EXPRESSION OF SPECIFIC GENES

The inheritance of the genetic information contained in our DNA has been studied for the past 60 years, with the research efforts culminating in the Human Genome Project. The Human Genome Project aimed to map and sequence every gene in the human organism and to understand how these were positioned in our chromosomes. The successful completion of the project required an internationally coordinated effort by many research groups and has provided the basic information we need to understand how genes work at the molecular level. This latter effort has been described as being part of the “post-genomic” era, and its aims are to understand how information contained in the sequence of DNA bases can be turned into proteins that create the structures of the cell, and how this process is controlled.

The mechanism by which genes are controlled is probably the most active and fascinating area of research in science today. How does one type of cell, for example a fibroblast, “know” that it is different from a neuron or a muscle cell, given that all these cells have essentially the same information about protein synthesis contained in their genomes? At least some of this control of cell type comes from specific transcription factor proteins that instruct some genes to express while others remain silent, but this cannot explain how the cell remembers to only produce other cells of the same type when it divides. Maintaining cellular identity and function is most probably effected by using so-called “epigenetic” mechanisms.

1.2 DEFINING EPIGENETICS

The term **epigenetics** seems to be used to explain a wide range of biological observations, so it is useful to have a precise definition of its meaning. The word “epigenetics” was first used by Conrad Waddington in 1942, and his definition of the subject was as follows: “a branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.” With the benefit of modern hindsight, we can see that this is quite a broad description, as it covers most of the mechanisms by which cellular identity and function can be maintained. However, Waddington’s concept of a “gene” did not benefit from the investigations of the 1950 and 1960s. In spite of this, his original definition is remarkably close to the epigenetic control of gene transcription that we will cover in later chapters of this book.

- 1.1 THE CORE ISSUE: CONTROLLING THE EXPRESSION OF SPECIFIC GENES
- 1.2 DEFINING EPIGENETICS
- 1.3 THE NATURE OF EPIGENETIC MARKS
- 1.4 THE IMPORTANCE OF EPIGENETICS

Our increasing knowledge of genome functions has refined the definition of epigenetics, and today the term is generally accepted as meaning *the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in the sequence of DNA*. We cannot assume that this definition will be final, of course; even with our current knowledge we can see that restricting the focus of epigenetics to “gene” function alone might be viewed as erroneous because there is increasing evidence that epigenetic mechanisms can control the functions of noncoding sequences of DNA (that is, those sections of the genome that do not contain sequences formally identified as genes). However, for the purposes of this broad discussion of the topic of epigenetics, the definition is good enough.

1.3 THE NATURE OF EPIGENETIC MARKS

The literal meaning of “epigenetics” is that it is something that is outside the traditional study of genetics. Although it is unlikely that Waddington’s original definition would have been conceived with this in mind, the concept of an additional or external control system (that is, one that does not directly originate from the sequence of DNA bases) that is imposed upon genes fits very well with our modern knowledge of epigenetic modifications. Gene control is achieved by semi-reversible covalent chemical modifications of DNA bases and the proteins with which DNA is associated in the cell’s nucleus. The description of these modifications and their effects on gene and cell function forms a large part of the topics described in this book.

1.4 THE IMPORTANCE OF EPIGENETICS

A system capable of controlling gene function is interesting to most biologists, but some of the possible consequences of epigenetic control of gene expression have also attracted interest from nonscientists because of the impact that our lifestyles may have on the health or behavior of future generations. At a first glance this would seem to go against the “traditional” principles of genetics, because the bulk of the scientific data in the first 50 years of the twentieth century seemed to suggest that the phenotypes of animals and their offspring can be determined solely on the basis of the genes they possess and pass on to future generations. Any changes that occur in phenotype would thus be due only to alterations in the DNA sequences of the genes and would therefore fall under the heading of “evolution” in the Darwinian sense of that word.

The acceptance of Darwin’s theories took years, and Darwin’s concept of evolution had to compete with several nineteenth-century ideas. The most prevalent of these competing hypotheses was probably the theory of inheritance of acquired characteristics, published by Jean Baptiste Lamarck in 1801. Lamarck suggested that if an organism changes its phenotype to adapt to its environment, those changes could be passed on to its offspring. Darwin suggested that this would not occur and that the only mechanism by which phenotypic change could occur stemmed from some organisms’ having variations that help them to survive in their environment and be more successful at producing offspring. Because these useful traits arise from the parent’s genes, the only way that the offspring will acquire such a survival advantage is by receiving copies of the advantageous genes from their parents. Ultimately, the evidence generated by the study of genetics supported Darwin, and Lamarck’s theory was discredited, leading to a central dogma of twentieth-century biology that the only way for traits to be passed on was through the inheritance of

genes and that genes could not be affected by events in the outside world. This belief seemed to stand to reason; after all, it seemed to be common sense that something bad that happened during the life of one's grandfather could not have any effect on one's own health. However, some of the worst events of the twentieth century seem to suggest otherwise.

Epigeneticists often refer to the "Dutch Hunger Winter" of 1944, and we will be making our own references to this World War II event in the chapters describing the impact of epigenetic mechanisms on a variety of diseases. The Hunger Winter resulted from a German blockade of food and fuel shipments into western Holland from September 1944 until the liberation of the country from Nazi German rule in May 1945. The blockade, coupled with a harsh winter, caused widespread famine and resulted in a large number of deaths. Because the Hunger Winter was well documented, it has allowed us to measure the effects of famine on human health. The results of many of these studies suggest a link between starvation of pregnant women and the health of their offspring. Several epidemiological investigations found that the resulting children were more susceptible to diseases such as diabetes, heart disease, and obesity than the children of normally fed mothers. Furthermore, mental illnesses such as schizophrenia seemed to be more prevalent in the children of Hunger Winter mothers. More surprisingly, similar propensities to develop diseases were eventually observed in the grandchildren of Hunger Winter mothers, thereby countering a possible argument that starvation in the mother could simply lead to alteration in the development of her unborn fetus. These data seem to suggest that a grandmother's diet could affect the health of several generations, which further implies that an adaptation to her environment has produced a heritable trait—something that is not supposed to happen if we accept that Darwinian evolution is the only cause of phenotypic change.

One might still be tempted to argue that it was the mother's malnutrition that damaged the developing fetus and therefore caused some form of damage to the child's genes by introducing mutations in the DNA sequences whose harmful effects became evident only later, in adult life; however, recent research indicates otherwise. Prompted by the findings from the Dutch Hunger Winter, more recent studies have focused on the problems arising in the children of men who either are obese or have suffered starvation. It is known that there is a correlation between the pattern of epigenetic marks (mostly DNA methylations) on the insulin-dependent growth factor gene *IGF2* and the body mass index of the father, with hypomethylation of this gene being observed in newborns arising from couples in which the father is obese. These data imply that the nutritional state of the father may also contribute to the health of the children; this could only have been transmitted to the child via the father's spermatozoa. Although it is still possible that the starvation or obesity of the father could have introduced mutations into his own *IGF2* gene before the child's conception, it seems unlikely that similar mutations would occur in all obese individuals to confer similar *IGF2* hypomethylation in the offspring. It is noteworthy that hypomethylation of *IGF2* was also observed in the children of Hunger Winter mothers six decades after the children's birth in 1944–1945. There is therefore a considerable body of evidence supporting the acquisition of a heritable trait as a consequence of the nutritional state of the parents.

Other diseases can also be considered to have an epigenetic basis, regardless of how well a child's parents ate. Only 10% of breast cancers that run in families can be linked to known genetic mutations. Exposing pregnant rats to chemicals known to influence breast cancer risk in humans (such as a high-fat diet or the synthetic estrogen ethinyl estradiol) caused female

offspring to develop a higher incidence of mammary tumors than the offspring of rats that were not exposed to these risk agents. Interestingly, the increased risk of breast cancer does not seem permanent, at least for some of the risk agents. For example, the great-granddaughters of rats exposed to a high-fat diet had no greater tumor incidence than those of control pregnant rats. The effects of ethinyl estradiol, however, seemed to be more durable: the great-granddaughters also had an enhanced risk of developing cancer.

We do not know the exact mechanisms by which chemical exposure can alter the pattern of epigenetic modifications in the genomes of affected animals, and this is one of the reasons why epigenetics is such a fascinating and potentially fruitful area of investigation. After all, if certain environmental exposures or behavior patterns in previous generations can influence the health of the current generation, altering those exposures or behaviors in the current generation might improve the health of the next. Better still, if we understand the mechanisms that caused events such as the Dutch Hunger Winter to predispose the descendants of those affected to disease, we might be able to develop methods to prevent the accumulation of harmful epigenetic changes and reduce the disease risk, regardless of environmental influences. The influence of this on human health and well-being could be great indeed.

FURTHER READING

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