Epigenetics in Health and Disease
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Igor Kovalchuk, Ph.D., MD
Olga Kovalchuk, Ph.D., MD
Dedicated to Anna.
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## Contents

1. Historical Perspective ................................................. 1
2. Chromatin Dynamics and Chromatin Remodeling in Animals .......................... 19
3. Chromatin Dynamics and Chromatin Remodeling in Plants .................................. 49
4. DNA Methylation as Epigenetic Mechanism .................................................. 75
5. Histone Modifications and Their Role in Epigenetic Regulation .......................... 119
6. Realm of Non-Coding RNAs—From Bacteria to Human ..................................... 147
7. Non-Coding RNAs Involved in Epigenetic Processes—A General Overview .............. 177
8. Non-Coding RNAs Across the Kingdoms—Bacteria and Archaea ................................ 203
9. Non-Coding RNAs Across the Kingdoms—Protista and Fungi .................................. 223
10. Non-Coding RNAs Across the Kingdoms—Animals .............................................. 267
11. Non-Coding RNAs Across the Kingdoms—Plants ............................................... 297
12. Non-Coding RNAs—Comparison of Biogenesis in Plants and Animals ..................... 327
13. Paramutation, Transactivation, Transvection, and Cosuppression—Silencing of Homologous Sequences .................................................. 343
14. Bacterial Adaptive Immunity—Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) ................................................................. 385
15. Gene Silencing—Ancient Immune Response and a Versatile Mechanism of Control over the Fate of Foreign Nucleic Acids ............................................. 409
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Epigenetics of Germline and Epigenetic Memory</td>
<td>435</td>
</tr>
<tr>
<td>17</td>
<td>Epigenetics of Health and Disease—Cancer</td>
<td>465</td>
</tr>
<tr>
<td>18</td>
<td>Epigenetics of Health and Disease—Behavioral Neuroscience</td>
<td>499</td>
</tr>
<tr>
<td>19</td>
<td>Epigenetics of Health and Disease—Diet and Toxicology, Environmental Exposures</td>
<td>523</td>
</tr>
<tr>
<td>20</td>
<td>Epigenetics and Technology—Hairpin-Based Antisensing</td>
<td>555</td>
</tr>
<tr>
<td></td>
<td>Index</td>
<td>577</td>
</tr>
</tbody>
</table>
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Historical perspective

*Genetics* can be broadly defined as the science studying the mechanisms of inheritance in general and genes in particular. *Epigenetics* can be, in part, defined as the branch of biology dealing with the mechanisms of inheritance. In contrast to genetics, epigenetics involves the control of gene expression that is not accompanied by any changes in DNA sequence. Epigenetics deals with the mechanisms of heredity which do not involve modifications of DNA sequence and are reversible in nature.

Success of a certain population depends on the fine balance between the ability to retain a given genotype in the stable environment and the ability to evolve by modification in response to substantial environmental changes. Changes in the genome can be dual in nature; they might deal with stable physical changes in DNA sequence leading to mutations and reversible chemical modifications of nucleotides or chromatin structure leading to epimutations. Mutations are the basis of genetic changes.

This book introduces you to the concept of epigenetics and epigenetic regulation. The book discusses processes of evolution in light of current understanding of the role of epigenetics and describes the role of epigenetic regulations in the growth and development of somatic cells, tissue differentiation, and the maintenance of epigenetic states in various cells of the same organisms. Furthermore, the book provides an introduction to an in-depth understanding of the role of epigenetics in the mechanisms of inheritance and interaction with the environment. The chapters also describe the role of epigenetics in health and disease. Finally, the book introduces you to the
concepts of silencing, co-suppression, and paramutations, and discusses the role of epigenetics in these processes.

This book is aimed primarily at students beginning to study epigenetics, whether at the undergraduate or graduate level. It may also be essential reading for research scientists in the field of epigenetics, genome stability, stress tolerance and adaptation, transgeneration effects, genome evolution, and other related fields, as well as anyone who simply wishes to know more about the field of epigenetics.

The mechanisms of environmental influences on the phenotypic appearance of organisms and inheritance were developed nearly two centuries ago and represented a prominent part of the descriptive work performed by Jean-Baptiste Lamarck and Charles Darwin. Although their ideas were often viewed as too preliminary and naïve, it was those ideas that laid a solid and important foundation for the development of the field of epigenetics. Epigenetics has a lot to do with an organism’s interaction with the environment; therefore, it is important to review how our understanding of the interactions between the organism’s genome, surroundings, and phenotype has developed over time.

The French biologist Jean-Baptiste Lamarck (1744–1829), who is credited with the first use of the word “biology,” was the first scientist who proposed a theory of evolution. He used the term transformation rather than evolution to suggest that organisms change and transform as the result of “a new need that continues to make itself felt.” His first reference to evolution as a process of less complex species becoming more complex appeared in 1800 in his Floreal lecture. Within next 20 years, Lamarck published three important works (Recherches sur l’organisation des corps vivants, 1802; Philosophie Zoologique, 1809; Histoire naturelle des animaux sans vertèbres (in seven volumes, 1815–1822) in which he developed his ideas of evolution and formulated the laws that described evolution as a process. Lamarck writes:

**Law 1:** Life, by its own forces, continually tends to increase the volume of every body which possesses it and to enlarge the size of its parts up to a limit which it brings about itself.

**Law 2:** The production of a new organ in an animal body results from the appearance of a new want or need, which continues to make itself felt, and from a new movement which this want gives birth to and maintains. **Law 3:** The
development of the organs and their strength of action are constantly in proportion to the use of these organs. **Law 4:** All that has been acquired, impressed upon, or changed in the organization of individuals during the course of their life is preserved by generation and transmitted to the new individuals that come from those which have undergone those changes.

Lamarck used these laws to explain the two forces he saw as comprising evolution; a force driving animals from simple to complex forms, and a force adapting animals to their local environments and differentiating them from each other.

Lamarck is remembered primarily for his belief in the inheritance of acquired characteristics and the use and disuse model by which, according to Lamarck, organisms develop their characteristics. The theory of evolution developed by Lamarck is frequently referred to as Lamarckism or Lamarckian evolution. This theory is also often referred to as soft inheritance. The term was first suggested by Ernst Mayr to explain the ideas of Lamarck and Étienne Geoffroy Saint-Hilaire (1772–1844) and to contrast those ideas with the modern idea of inheritance, which Mayr referred to as hard inheritance. Geoffroy, a French naturalist and a colleague of Lamarck, defended Lamarck’s idea of the influence of the environment on species evolution. He further developed Lamarck’s idea suggesting that the environment causes a direct induction of organic change that is the transmutation of species in time.

Perhaps the first attempt at rejection of soft inheritance was made by the English surgeon William Lawrence (1783–1867) in 1819. He stated that “The offspring inherit only connate peculiarities and not any of the acquired qualities” (Lawrence and William, 1819). The inheritance of acquired characteristics was also rejected by the German biologist August Weismann (1834–1914). In the 1880s, he performed an experiment in which he cut off the tails of 22 generations of mice, thus proving that the loss of tail cannot be inherited. Furthermore, in 1893, Weismann proposed his own theory of inheritance. He discovered that the cells that produce the germ plasm (now known as gametes) separate from somatic cells at an early stage of organismal development. Weissman could not understand how
somatic and gametic cells communicated with each other, and therefore, he declared that the inheritance of acquired characteristics was impossible. He further suggested that the organism’s body (the somatoplasm) exists for only one generation, whereas the hereditary material, which he called germ plasm, is immortal and passed from generation to generation. Although being rather naïve and futuristic, this view led to an important suggestion: Nothing that happens to somatic cells may be passed on with the germ plasm. Thus, this model underlies the modern understanding of inheritance in which germlines are main cells passing hereditary information from one generation to another. At the same time, because this model suggested that the germ plasm is a self-sufficient substance that is not influenced by the environment, it represented a unilateral understanding of evolutionary processes.

Another theory of evolution was synthesized and described by the English biologist and social philosopher Herbert Spencer. In 1857, he published his theory of evolution in his essay “Progress: Its Law and Cause.” Spencer characterized the process of evolution as “evolution of complexity”; he suggested that evolution was a process in which simple organisms always evolved into more complex ones, therefore, evolution itself was progressive in nature. Currently, this view of evolution is considered to be misleading; it is generally accepted that species evolve in response to the environment in the process of natural selection that does not have directionality. The absence of the logical explanation of natural selection did not allow Spencer’s theory of evolution to become more prominent. At the same time, it was Spencer who popularized the term evolution itself. Moreover, after reading Darwin’s The Origin of Species, published just two years after Spencer’s essay, Spencer attempted to use Darwin’s theory for explanation of the role of evolution in society. Moreover, he also tried to incorporate it into his own theory of evolution, coining the now-common phrase survival of the fittest.

In 1859, Charles Darwin published the work “On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life” (Darwin, 1859) (commonly known as The Origin of Species) that became a foundation of evolutionary biology and a reason for plenty of scientific discussions.
Darwin’s theory suggested that species in the population evolve through a process of natural selection. His book offered multiple examples of how the diversity of life on our planet arose by common descent with modification through a branching pattern of evolution. Darwin proposed that within a certain species, individuals that are less fit for their particular environment are less likely to survive and reproduce compared to those that are well-adapted and have better survival and reproductive potential. The more successful individuals leave more progeny, and thus pass their heritable traits to the next generation. As a result, a certain part of population adapts to the changed environment and eventually might become a separate species. One important thing to note here is that the environment plays a critical role in shaping species’ evolution. Darwin accepted a version of the inheritance of acquired characteristics proposed earlier by Lamarck.

Later on, Darwin set forth his provisional hypothesis describing the mechanisms of heredity. In 1868, he presented this idea in his work *The Variation of Animals and Plants under Domestication* (Darwin, 1868). The theory of pangenesis suggests that each individual cell of an organism not only experiences environmental changes and responds to them but also generates molecules that accumulate in germ cells. Darwin believed that these molecules, which he called gemmules (Darwin, 1868; Darwin, 1971), are capable of contributing to the development of new traits and organisms. Nowadays, it is a striking fact that small non-coding RNAs such as microRNAs (miRNAs) and small interfering RNAs (siRNAs) generated by somatic cells are indeed able to travel within the organism reaching the gametes and potentially influencing the phenotypic appearance of progeny.

**1-1. Ontogeny and phylogenetics**

**Ontogeny** (ontogenesis, morphogenesis) is a branch of science describing the development of an organism from the fertilized egg to its adult form.

**Phylogenetics** (phylogensis) is the study of evolutionary relatedness among various groups of organisms.
Neo-Darwinism is a comprehensive theory of evolution, frequently called the Modern Synthesis, that combines Mendelian genetics with Darwinian natural selection as a major factor in evolution and population genetics. The term Neo-Darwinism was first used by George Romanes (1848–1894) in 1895 to explain that evolution occurs solely through natural selection as it was proposed by Alfred Russel Wallace (1823–1913) and August Weismann. Neo-Darwinism suggests that evolution occurs without mechanisms involving the inheritance of acquired characteristics based upon interactions with the environment. Thus, this modernized Darwinism accepted some ideas developed by Darwin’s original theory of evolution via natural selection, but at the same time it separated them from Darwin’s hypothesis of pangenesis and the Lamarckian view of inheritance.

Historically, many scientists tried to prove or disprove Darwin’s theory of pangenesis. Francis Galton (1822–1911), a cousin of Darwin, conducted many experiments that led him to refute the pangenesis theory. Initially, he accepted the theory, and, in consultation with Darwin, he tried to detect how gemmules were transported in the blood. In his very simple hypothesis, he suggested that if gemmules were transferred to gametic cells though the blood then blood transfusion between various breeds of animals would generate new traits in progeny. In a long series of experiments initiated around 1870, he transfused the blood between dissimilar breeds of rabbits and found no evidence of characteristics transmitted by blood transfusion.

Darwin challenged the validity of Galton’s experiment. He wrote in 1871:

Now, in the chapter on Pangenesis in my “Variation of Animals and Plants under Domestication,” I have not said one word about the blood, or about any fluid proper to any circulating system. It is, indeed, obvious that the presence of gemmules in the blood can form no necessary part of my hypothesis; for I refer in illustration of it to the lowest animals, such as the Protozoa, which do not possess blood or any vessels; and I refer to plants in which the fluid, when present in the vessels, cannot be considered as true blood.

Until the end of the nineteenth century, Darwin’s theory of pangenesis was accepted by many scientists. The work of Gregor Johann
Mendel on plant hybridization fundamentally changed scientists’ understanding of the mechanism of inheritance. Although Mendel published his work in 1866, it was not until 1900 that his ideas were re-examined. Upon re-discovering the significance of Mendel's work, a new era of Mendelian genetics began in which scientists completely rejected the possibility of the transmission of information from somatic cells to gametes and thus to progeny. It was a real pushback for Lamarck’s theory of evolution.

Many scientists still considered the possibility of environmentally induced heritable changes. The Russian scientist Ivan Michurin (1855–1935), one of the founders of scientific agricultural selection, also assumed that genotypes could change upon environmental pressure. He worked on hybridization of plants of similar and different origins, developing strategies for overcoming species incompatibility upon hybridization and cultivating new methods in connection with the natural course of ontogenesis (1922–1934). He was also interested in directing the process of predominance, evaluation, and selection and in working out methods of acceleration of selection processes. In the early twentieth century, he proved that the dominant traits in generation of hybrids depend on heredity, ontogenesis, and phylogensis of the initial cell structure as well as on individual features of hybrids. Michurin was a true follower of Lamarck and Darwin, and he firmly believed that natural selection could be influenced by external factors, with man being the most influential one.

In the not-too-distant past, the ideas of Lamarck and Michurin seemed to be pseudo-scientific and impossible to believe in. But recently, a breakthrough publication describing changes in the genetic make-up of grafted plants appeared that became an eye-opener, suggesting many new possibilities for transmission of genetic material. Sandra Stegemann and Ralph Bock showed that transfer of genetic material from stock to scion is possible upon grafting of tobacco plants (Stegemann and Bock, 2009). The results of the study demonstrated that recipient plants acquired tolerance to an antibiotic in the same manner as donor plants, and they also confirmed the transfer of genetic material from a donor to a recipient. Although it is still unclear whether the acquisition of antibiotic resistance occurs via plastid transfer through plasmodesmata or via the transfer of a large portion of the plastid genome from a donor cell to a recipient cell, it
can be definitely considered as an example of changes not only in phenotypic appearance but also in the genetic make-up of a grafted plant.

The emergence of epigenetics as science was closely linked to the study of evolution and development. Nowadays, we know that chromosomes are associated with both genetic and epigenetic regulation, thus driving the developmental processes. Despite the early discovery of chromosomes by Walther Flemming (1843–1905), the founder of cytogenetics, in 1879, it took many more experiments to link chromosomes to function, phenotypes, and developmental programming. The experiments by Edmund Wilson (1856–1939), Theodor Boveri (1862–1915), Walter Sutton (1877–1916), and later on Thomas Hunt Morgan (1866–1944) provided several evidences that chromosomes were indeed involved in developmental processes, and changes in chromosomes resulted in changes in phenotype. The **Boveri-Sutton chromosome theory** suggested that Mendelian laws of inheritance could be applied to chromosomes and chromosomes might thus be units of inheritance. Morgan's work in *Drosophila* showed that the inheritance of many genes was linked to the X chromosome; among them were genes coding for eye color. This and other works enabled him to become the first scientist to receive a Nobel Prize (1933) for his work in genetics. The report by Watson and Crick (1953) describing DNA structure and proposing the mode of DNA replication further reinforced the notion that DNA is the cell's genetic material. Although the studies of chromosome morphology indicated that somatic cells contained all of the chromosomes, it was not clear why the somatic cells of different tissues had different phenotypic appearance, raising doubts whether somatic cells actually did carry all the genes and not only those that were necessary for their growth and development.

Although investigations of epigenetic regulation of an organism's development and cell fate were being actively pursued throughout the twentieth century, the actual name "epigenetics" did not emerge until 1942 when Conrad Hal Waddington (1905–1975) used it to describe how genes might interact with their surroundings to produce a phenotype. Waddington described several essential concepts, including **canalization**, **genetic assimilation**, and **epigenetic landscape**. The concept of canalization in Waddington's understanding was the capacity of the organisms of a given population to produce the same phenotype regardless of the extent of genetic and
environmental variations. He assumed that this robustness came as a result of evolution, shaping the developmental processes to perfection. Waddington’s idea of genetic assimilation suggested that an organism responds to the environment in such a way that the acquired phenotype would become part of the developmental process of the organism.

To demonstrate that the phenomenon exists, Waddington induced an extreme environmental reaction in the developing embryos of the fruit fly *Drosophila*. When exposed to ether vapor, a small percentage of the *Drosophila* embryos developed a second thorax. It was obvious that bithorax embryos represent an abnormal phenotype. Waddington continued selection of bithorax mutant embryos, and after about 20 generations of selection, he obtained *Drosophila* flies that developed bithorax without being exposed to ether vapor. Waddington suggested that in this particular case, selection led to the production of the desired effect, which became canalized, and, as a result, bithorax appeared regardless of environmental conditions. Thus, Waddington’s experiments demonstrated that Lamarckian ideas of inheritance of acquired characteristics could, at least in principle, be true. Finally, the epigenetic landscape, as suggested by Waddington, represents is a programmed cell fate where developmental changes would occur with increasing irreversibility, much like marbles rolling down a small-ridged slope toward the lowest elevation point. Nowadays, the term *epigenetic landscape* refers to the certain area of a chromatin in the cell with specific cytosine methylation and histone modifications involved.

During the past 50 years, the scientific community has witnessed a lot of rises and falls in an interest in epigenetics. Perhaps, the next important discovery in the area of epigenetics was Alexander Brink’s report on the phenomenon of *paramutation*. In 1956, Brink described a somewhat puzzling and controversial phenomenon of the inheritance phenotype associated with the *Red 1 (r1)* locus in maize (Brink, 1956). It was observed that the spotted seed allele (*R-st*) was able to transform the *R-r* (purple color seeds) phenotype allele into a colorless seed phenotype in subsequent generations. As a result of the cross, all of the *F₂* generation plants showed reduced anthocyanin in seeds, which was contrary to the expected segregation ratios according to the Mendelian law. The phenomenon that he
proposed to be called paramutation involved heritable transmission of epigenetically regulated expression states from one homologous sequence to another. For a more detailed description of paramutations in plants and animals, see Chapter 13, “Paramutation, Transactivation, Transvection, and Cosuppression: Silencing of Homologous Sequences.”

In her early work, Barbara McClintock (1902–1992) also suggested that the chromosomal position effect might influence on the behavior of mutable loci in maize. She assumed that the observed difference in mutability ratios of suppressor elements in maize had the mechanism similar to the earlier described phenomenon of position-effect variegation. The latter term was first brought up by Hermann Joseph Muller (1890–1967) and was meant to describe the effect of chromosomal position on gene expression. Having observed gross chromosomal rearrangements, Muller noted changes in gene expression, and the genes that were brought into the area of heterochromatin expressed poorly. McClintock noted that some controlling elements, such as Spm, would suppress gene expression rather than mutate a gene; she also noticed that the suppression of gene expression would take place not only at the locus where the elements had been inserted but also at the neighboring loci.

The work of David Nanney (published in 1958) showed that the cytoplasmic history of conjugating parents had an impact upon the mating-type determination of resulting progeny in *Tetrahymena* (Nanney, 1958). This phenomenon was suggested to be of epigenetic nature.

In the early 1960s, Mary Lyon and Walter Nance presented the mechanism of another epigenetically regulated process, **X-chromosome inactivation.** It was suggested that inactivation of the mammalian female X chromosome occurred before the 32-cell stage of the embryo. However, there was no clear assumption that this process was indeed of epigenetic nature. The fact that no changes were observed at the level of DNA allowed Riggs (1975) and Holliday and Pugh (1975) to propose that DNA methylation could be a mechanism of X-chromosome inactivation.
In the 1970s, Hal Weintraub’s work on the expression of globin genes revealed an influence of chromosomal location on the transcriptional activity. His observations were the source from which the suggestion came that the chromatin structure might regulate gene expression.

In the early 1980s, it became clear that there was an apparent correlation between the level of cytosine methylation at GpG DNA sequences and the level of gene transcription. Moreover, the mitotic heritability of DNA methylation patterns was also shown. Later on, by the mid-1980s, the influence of nuclear content on the genetic/phenotypic make-up of the organism was also revealed. It was found out that not only the DNA sequence of paternal or maternal alleles had an effect on the phenotype, but the origin of a particular chromosome itself could influence the phenotype. Thus, it was suggested that besides the DNA sequence, the chromosome also carried additional information.

In the 1990s, scientists presented more discoveries in the area of epigenetics, coming from studies of various organisms including protozoa, fungi, Drosophila, plants, and animals. In plants, it was found that the transgene coding for chalcone synthase (Chs) had various degrees of suppression of expression gene expression. It was perhaps the first well-documented event of gene silencing (Napoli et al., 1990).

In trypanosomes, it was discovered that silencing of the group of Variable Surface antigen Genes (VSG) is maintained by the incorporation of a novel base, β-D-glucosylhydroxymethyluracil (Borst et al. 1993). Because trypanosomes do not have the mechanism of cytosine methylation, it was suggested that the insertion of the modified base would also serve as a gene-silencing mechanism. Significant progress was made in understanding the mechanisms of X inactivation. A portion of the human X chromosome was identified to function as the X chromosome inactivation center; later on, the gene Xist was identified that appeared to be coding for a non-coding RNA expressed only in an inactive X chromosome (Willard et al., 1993). The analysis of the expression of the neighboring gene Igf2 and H19 pair provided a further understanding of the mechanism underlying chromosomal imprinting. The genes were mutually exclusively expressed depending on the maternal or paternal origin of the chromosome; if the Igf2 gene was expressed from the paternal chromosome, then the H19
gene was repressed, whereas if the \textit{H19} gene was expressed from the maternal chromosome, the \textit{Igf2} gene was repressed. Methylation analysis of the locus identified high frequency of occurrence of methylated CpGs. Therefore, it was proposed that methylation controlled the access to the enhancer element that functioned mutually exclusively for both genes. Indeed, in mice, it was found that a mutant impaired in the function of a 5-methyl-cytosine DNA methyltransferase lost the imprinting of the gene pair in ES cells.

The role of epigenetic regulation in control over gene expression was also demonstrated by the experiments on fungi. Gene duplication in \textit{Neurospora crassa} often resulted in the occurrence of two events: frequent mutations and hypermethylation of both gene copies, a phenomenon known as \textbf{repeat-induced point mutation (RIP)}. Furthermore, for the first time, it was shown that cytosine methylation in \textit{Neurospora} could occur at non-CpG sites. A similar phenomenon was observed in \textit{Drosophila}; the duplication of the brown gene translocated near heterochromatin increased the level of repression in the active copy. Because in \textit{Drosophila}, cytosine methylation is not used as a process of gene expression regulation, there should be a different repression mechanism. The research in this direction resulted in the development of the concept of chromosomal \textbf{boundary elements}, the areas of the chromosome that contained a 300 bp nuclease-resistant core surrounded by nuclease hypersensitive sites that were first described in \textit{Drosophila}. It was suggested that such elements allow the separation of a chromatin domain along the chromosome, thus leading to differential areas of chromosome compaction and gene expression. In yeasts, the Sir2, Sir3, and Sir4 proteins (silent information regulator proteins) were identified that were proposed to control repressive states near heterochromatic regions. The evidence that Sir3 and Sir4 interacted with the tails of histones H3 and H4 further confirmed the importance of both these proteins and histones in the maintenance of the chromatin state. By the end of the 1990s, histone-modifying enzymes such as acetylases and deacetylases were identified, and the MeCP2 protein complex that was able to bind to methylated DNA and histone deacetylases were described.

One more important discovery made in the late 1990s was the description of the phenomenon of \textbf{RNA interference}. A series of work by Craig Mello and Andrew Fire culminated in the famous
publication in *Nature* (Fire et al., 1998) that described the ability of double-stranded RNA molecules to inactivate the expression of genes in *C. elegans*; the effect of interference was evident in both injected animals and progeny. Because just a few molecules per cell were sufficient to trigger the effect, the authors suggested the existence of an amplification component, currently known as a mechanism that involves the function of RNA-dependent RNA polymerase. The importance of this work for studying organism development, the therapy of various human diseases, as well as for the development of biotechnology and basic science was recognized with the Nobel Prize awarded to Mello and Fire in 2006.

In 1990, Robin Holliday defined epigenetics as “the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms” (Holliday, 1990). Today, the definition of epigenetics has been changed; it is now described as the study of the mechanisms of inheritance and control of gene expression that do not involve permanent changes in the DNA sequence. Such changes occur during somatic cell division and sometimes can be transmitted transgenerationally through the germline.

The last ten years were marked by the most prominent achievements in epigenetic research. In 2000, it was discovered that the Sir2 protein of yeasts was in fact a histone deacetylase. Studies of the heterochromatin states, replication processes, the activity of the Sir3 protein in yeast, and the heterochromatin protein (HP1) in mammals showed that heterochromatin was not in a solid inert stage reversible only during replication but rather in an active equilibrium stage of protein exchange between the nuclear soluble compartment and heterochromatin itself, regardless of cell cycle status.

By the early 2000s, most of the histone modifications and the enzymes that catalyze them were discovered, and it was believed that besides histone methylation, all other modifications such as acetylation, phosphorylation, ubiquitination, and so on were reversible. Thus, various histone methylation states were regarded as a permanent epigenetic mark of chromatin status and were reversible only during replication. The results of studies by Cuthbert et al. (2004) and Henikoff et al. (2004) raised the possibility that histone methylation could be reversible, and their suggestions were met with true enthusiasm. In his works, Cuthbert demonstrated that
peptidylarginine deaminase was able to remove single methylation events at the arginine amino acid of histone H3 (Cuthbert et al., 2004). Henikoff et al. (2004) showed that H3.3, a histone H3 variant, was able to replace histone H3 in a transcription-dependent and replication-independent manner, opening the possibility for more flexible regulation of methylation after the process transcription was over.

Another breakthrough was the discovery that nuclear organization and silencing at telomeres were not necessarily completely interrelated. The experiment showed that if telomeres and the associated silencing complex were released from the periphery of the nucleus and were able to move throughout the nucleus, the silencing at telomeres was established with similar efficiency (Gasser et al., 2004). This is truly exciting—it suggests that chromatin compartmentalization and gene silencing processes are not rigid and pre-defined states; there indeed exists an active exchange between the nuclear pools of proteins and small RNAs that are able to establish a certain chromatin state at any given locus regardless of its nuclear location.

A curious phenomenon was reported for Arabidopsis; it was on the borderline of epigenetic regulation and described a non-Mendelian inheritance. An hth mutant is homozygous for the mutation in the HOTHEAD (HTH) gene that encodes a flavin adenine dinucleotide-containing oxidoreductase involved in the creation of the carpel during the formation of flowers. It was reported that in the progeny of the hth mutant, the percentage of the frequency of appearance of the HTH phenotype and HTH genomic sequence was ~15% (Lolle et al., 2005). It was first proposed that reversion was triggered by RNA synthesized by HTH/hth parents and stored in the progeny hth/hth plants. Four alternative explanations have been proposed: Two of them were in part similar to an original explanation made by Lolle et al. (2005) and dealt with template-directed gene conversion; the third one offered the process of mutation accumulation followed by selection; and the fourth one involved chimerism. Later on, two publications seemed to put everything in place: Peng et al. (2006) and Mercier et al. (2008) reported that the hth mutant showed a tendency toward outcrossing and recovered a normal genetic behavior when grown in isolation. Despite the fact that
Arabidopsis is an extreme self-pollinator (less than 0.1% of outcrossing), in the hth plants the frequency of outcrossing among neighboring plants was ~12%. This can be an excellent alternative explanation for the apparent genetic instability of hothead mutants.

Now that the genome sequences of model organisms such as C. elegans, Drosophila, Arabidopsis, human, mice, rice, and so on are available, more and more investigators have attempted to understand the organization of the genome and chromatin and explain the mechanisms of inheritance, maintenance of genome stability, and regulation of gene expression. What has become clear is that these mechanisms are both genetic and epigenetic in nature. As it was recently put by Daniel E. Gottschling (“Epigenetics: from phenomenon to field” in Epigenetics; eds. C.D. Allis, T. Jenuwein, D. Reinberg), it was time to move “above genetics”—a literal meaning of epigenetics as several important genomes have already been sequenced.

There are multiple examples of the influence of environment on the genetic and epigenetic make-up of the organism. The phenomena of stress-induced transposon activation, non-targeted mutagenesis, stress-induced communication between cells and organisms, and evidences of transgenerational changes induced by stress are just some representations of epigenetic effects of the environment on the organism.

The non-linear response to DNA damaging agents is one of the most interesting examples of an epigenetically controlled process. It has already been known that a higher dose of mutagen does not necessarily result in a higher level of damage to DNA. In fact, low doses of ionizing radiation often lead to disproportionally high levels of DNA damage. Doses of ionizing radiation that are believed to have a negligible effect on a cell often exert dramatic influence on DNA damage and cell viability.

In the past, cell-to-cell communication between neighboring cells as well as communication between cells of different tissues and organs in multicellular organisms were considered Lamarckian/Darwinian and thus improbable. There are multiple examples of physiological cell-to-cell communications in simple and complex organisms involving hormonal signaling, neurotransmission, and so
on. Moreover, it is believed that damaged tissues are able to communicate with non-damaged tissues—a phenomenon known as **bystander effect**. The phenomenon of bystander effect has also been observed between whole living organisms.

Can organisms communicate memory of stress across generations? According to Darwin, organisms evolve from the pool of individuals with spontaneous changes/mutations through the process of natural selection. The process of mutagenesis is believed to be random, and the majority of mutations are deleterious. The rare mutations that become beneficial under certain environmental conditions have a chance to be fixed in a population. Because mutagenesis does not occur frequently, the fixation of desired traits would take place very rarely. In contrast, processes of acclimation and adaptation are rapid ones that allow organisms to acquire protection against stress in a single generation after stress exposure. These processes cannot be explained by the laws of Mendelian genetics. In this book, you find multiple examples demonstrating the inheritance of stress memory in various organisms across generations.

This chapter attempted to explain what epigenetics is, how it is involved in the regulation of growth and development of the organism, how it controls interactions of the organism with the environment, and what roles epigenetics plays in the mechanisms of inheritance and evolutionary processes.

There have been many more important discoveries in the field of epigenetics, and we apologize to all those authors whose work, though relevant, is not mentioned in this chapter because of limitations of space.

**References**


Brink RA. (1956) A genetic change associated with the R locus in maize which is directed and potentially reversible. *Genetics* 41:872-879.

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Index

21U-RNAs, 267, 271-273
6S RNA, 208-209

A
A-to-I editing, humans/plants, 165-166
A-type lamins, 22
aberrant RNA (aRNA), 236
acetylation, histones, 121
animals, 126
plants, 137-138
acetyltransferases, plant histones, 137
ACF (chromatin-assembly factor) complex, 31
actin-related proteins (ARPs), 23-25
activation of translation, 282-283
activation-induced cytosine deaminase (AID), 99
active chromatin states, 55
active demethylation, 99-101, 110-113
active state, gene promoters, 122
AD (Alzheimer's disease), 508-510
adaptive immunity of bacteria, CRISPRs, 385-387
array structure, 387-389
evolutionary context, 403-404
function, 390-399
incorporation of new sequences into loci, 400-401
potential functions, 402-403
remaining questions, 404-405
adenine methylation, 90
Adomet (S-adenosylmethionine), 90
AGAMOUS-LIKE19 gene, 63
AGL19 gene, 63
AGO (ARGONAUTES), 298, 420
Agouti locus, 524
AGRIKOLA (Arabidopsis Genomic RNAi Knockout Line Analysis), 565
ahpRNA (artificial hpRNA), 556, 561
AID (activation-induced cytosine deaminase), 99
air pollution, influence on phenotypes, 529-534
algae-chloroplasts containing protists, ncRNAs, 233-236
alleles, 348
allelic interactions
co-suppression, 380-381
paramutation, 344-345
animals, 372-379
epigenetic regulation, 354-361
fungi, 371
historical view, 345-347
models, 361-370
plants, 347-354, 370-371
tandem repeats, 362-365
transvection, 379-380
Alleman, Mary, 356
allotetraploidization, 348
Alu elements, 199
Alzheimer's disease (AD), 508-510
animals
applications of hairpin RNAi, 569-570
chromatin structure, 125
characterization of histone modification by distribution in nucleus, 135-137
histone acetylation/
deacetylation, 126
histone methylation/
demethylation, 127-129
histone phosphorylation, 130-131
histone ubiquitination, 131-132
histone variants, 133-134
development, miRNAs, 291-292
epigenetic reprogramming, 440
gametes, 441-446
histone-mediated inheritance, 452-453
inheritance of disease, 454-456
methylation-mediated inheritance, 448-452
protamine-mediated inheritance, 447-448
sRNA-mediated inheritance, 453-454
histone modifications, 125
acetylation/deacetylation, 126
characterization by distribution in nucleus, 135-137
methylation/demethylation, 127-129
phosphorylation, 130-131
variants, 133-134
methylation, 92
active and passive mechanisms of demethylation, 99-101
de novo methylation, 93-97
maintenance, 98-99
ncRNAs, 267
C. elegans, 267-274
comparison to plants, 327-340
Drosophila melanogaster, 274-283
paramutation, 372
RNAs involved in phenotypic epigenetic inheritance, 374-379
white-tailed phenotype sample, 372-374
antisense ncRNAs, 180
antisense technology, 555-558
animal applications, 569-570
chimeric hairpins, 559
components of hairpin, 560-561
inducible hairpin RNAi, 562-563
limitations, 573
mammal applications, 570-573
targeting conserved sequences, 558-559
tissue-specific, 562
antisense transcript-derived RNAs (nat-siRNAs), 232
apolipoprotein B RNA-editing catalytic component 1 (APOBEC1), 99
apoptosis, regulation by tRNAs, 153
aptamer FC RNA, transcription prevention, 248
aptamer region (riboswitches), 204
Arabidopsis. See also plants
active chromatin states in, 55
Arabidopsis thaliana, 234
AtSYD and AtBRM proteins, 66-67
DCL proteins, 310
DDM1 protein, 68
PIE1 protein, 64-66
PRC complexes in, 54
seed development genes, 49
SN1 protein, 67-68
summer-annual state, 55, 61-63
winter-annual state, 55-61
Arabidopsis Genomic RNAi Knockout Line Analysis (AGRIKOLA), 565
Archaea, ncRNAs, 217-220
Argonaute protein, 196
ARGONAUTES (AGO), 298
aRNA (aberrant RNA), 236
ARPs (actin-related proteins), 23-25
array structure, CRISPRs, 387-389
artificial hpRNA (ahpRNA), 556, 561
asthma, 530
AtBRM protein, 66-67
AtMBD protein, 69-70
ATPases, in chromatin-remodeling complexes, 23-26
CHD complexes, 33-35
INO80 complexes, 35-36
ISWI complexes, 31-33
SWI/SNF proteins, 26-27, 30-31
ATRX syndrome, 507
ATSWP1 protein, 62
AtSYD protein, 66-67
B
B-type lamins, 22
b1 locus, paramutation in plants, 351-354
B2 RNA, transcription prevention, 248
bacteria
  adaptive immunity, CRISPRs, 385-387
    array structure, 387-389
  evolutionary context, 403-404
  function, 390-399
  incorporation of new sequences into loci, 400-401
  potential functions, 402-403
  remaining questions, 404-405

ncRNAs, 203
  cis- and trans-encoded small RNAs, 209-215
  CRISPRs, 216-217
  protein-binding ncRNAs, 207-209
  riboswitches, 204-206

phages, 387
  regulation of virulence, 84

bacteriophage-insensitive mutants (BIMs), 400

BAF complex, 27, 30-31

BAP (Brahman-associated proteins), 27

barrier insulators, 41
behavioral neuroscience, influence of epigenetic changes, 499
  chromatin remodeling, 500
  classical experiments of Meaney and Szyf, 503-505
  DNA methylation and the brain, 499
  histone modifications, 500
  ncRNAs, 501-502
  neurodegenerative disorders, 508-516
  neurodevelopmental disorders, 506-507
  psychiatric disorders, 516-517

benzene, 550

BFCs (bioactive food components), epigenetic effects, 536
  DNA methylation, 536-538
  histone modifications, 538-539
  influence of compound concentration, 540-541
  miRNAs, 539-540
  bidirectional ncRNAs, 180

BIMs (bacteriophage-insensitive mutants), 400
bioactive food components (BFCs), epigenetic effects, 536
  DNA methylation, 536-538
  histone modifications, 538-539
  influence of compound concentration, 540-541
  miRNAs, 539-540

biogenesis
  ncRNAs
    comparison of plants to animals, 327-340
    gRNAs, 197-199
    IncRNAs, 178-182
    miRNAs, 184-190
    piRNAs, 192-195
    RNase III-type endonucleases, 195
    siRNAs, 190-192
    small ncRNAs, 183

  plants, 298
  biomarkers, cancer, 480-482
  bivalent state, gene promoters, 122
  black carbon, 530
  blood transfusions, 6
  Bock, Ralph, 7
  boundary elements, 12
  Boveri, Theodor, 8
  Boveri-Sutton chromosome theory, 8
  BPTF proteins, 32
  Brahma-associated proteins (BAP), 27
  brain
    chromatin remodeling, 500
    DNA methylation, 499
    histone modifications, 500
    ncRNAs, 501-502
    BRG1 proteins, 30
    Brink, Alexander, 9, 345
    BRTF protein, 38
    BRU1 protein, 51
    bystander effects, 16, 543-545

C
  C nucleotides, insertion/deletion, 167-168
  C-to-U editing, 163-165
  C. elegans (Caenorhabditis elegans), 267
    as model for biological function of ncRNAs, 273-274
    ncRNAs, 287-287
C3 (chromosome conformation capture) methodology, 364
cas-siRNAs (cis-acting nat-siRNAs), 308
Caenorhabditis elegans
(C. elegans), 267
CAF1 protein, 51
Cajal body, 154
Cajal body-specific RNAs (scaRNAs), 154
canalization, 8
cancer
defined, 465
influence of epigenetic changes, 465
DNA methylation, 468-483
histone modifications, 484-492
therapeutic interventions, 492-493
stages of development, 466
canonical nucleosomes, 125
carcinogenesis, 465
carcinogens, epigenetic effects, 548-550
cas genes (CRISPR-associated genes), 387-389
CASS (CRISPR-Cas system), 217
CerM (cell cycle-regulated methylase), 78, 86-89
CECR2-containing remodeling factor (CERF) complex, 32
Celera Genomics, 523
cell cycle
histone deposition during, 141-142
regulation, 85-89
cell cycle-regulated methylase. See CerM
cell cycle-regulated methyltransferases, 88
cell-to-cell communication, 15
CERF (CECR2-containing remodeling factor) complex, 32
Chandler, Vicki, 356
chaperones (histone), 121
CHARGE syndrome, 34
CHD (chromodomain and helicase-like domain) ATPases, 26, 33-35
CHD1 proteins, 33-34
CHD3 proteins, 34
CHD4 proteins, 34
CHD7 proteins, 34
chemical carcinogens, epigenetic effects, 548-550
chimeric hairpins, 559
chimerism, 14

Chlamydomonas reinhardtii, 233
CHRAC (chromatin accessibility complex), 31
chromatin
architecture, 20-23
compaction, 19-20
defined, 119
modifiers, cancer and, 484-487
parachromatin, 363
remodeling, 20
Alzheimer's disease, 509
brain, 500
complexes, 25-36
effector proteins, 36-41
in plant development, 49-70
insulator proteins, 41-44
nuclear ARPs (actin-related proteins) in, 23-25
structure in animals, 125
characterization of histone modification by distribution in nucleus, 135-137
histone acetylation/deacetylation, 126
histone methylation/demethylation, 127-129
histone phosphorylation, 130-131
histone ubiquitination, 131-132
histone variants, 133-134
structure in trypanosomes, 123-125
chromatin accessibility complex (CHRAC), 31
chromatin-assembly factor (ACF) complex, 31
chromatin-remodeling complexes, developmental roles, 25
CHD complexes, 33-35
INO80 complexes, 35-36
ISWI complexes, 31-33
SWI/SNF proteins, 26-27, 30-31
chromodomain and helicase-like domain (CHD) ATPases, 26, 33-35
CHROMOMETHYLASE (CMT3), 102
chromosomal imprinting, 11
chromosome conformation capture (3C) methodology, 364
chromosome territories (CTs), 20, 135
chromosomes
boundary elements, 12
in developmental processes, 8
index

581

ciliates
epigenetic reprogramming, 436-440
ncRNAs, 223-229
cis natural antisense transcripts
(cis-NATs), 181
cis-acting nat-siRNAs (ca-siRNAs), 308
cis-acting ncRNAs, 170
cis-encoded ncRNAs, 209-211
cis-nat-siRNAs, 306
cis-NATs (cis natural antisense
transcripts), 181, 276
cloning vectors (hairpins), 564
closed non-permissive chromatin, 484
CMT3 (CHROMOMETHYLASE), 102
cosuppression, 236, 297, 380-381, 409-411
Coe, Edward, 346
Coffin-Lowry syndrome, 507
Commonwealth Scientific and
Industrial Research Organization
(CSIRO), 564
communication, cell-to-cell, 15
conjugation, 385
defined, 386
repression of, 83-84
cortical inheritance, ciliates, 436
CpG dinucleotide pairs, 92
CpG islands, 92
CRISPR RNAs (crRNAs), 391, 396
CRISPR-associated (cas) genes. See
cas genes, 387-389
CRISPR-Cas complexes, 388
CRISPR-Cas system, 416
CRISPR-Cas system (CASS), 217
CRISPRs (clustered regularly
interspaced short palindromic
repeats), 216-217
bacterial adaptive immunity, 385-405
comparison to piRNAs, 395
comparison to RNAi pathway, 391
defined, 385
inheritance, 404
related proteins, 389-390
cross-protection, 410
crRNAs (CRISPR RNAs), 391, 396
cryptic unstable transcripts (CUTs), 250-251
CSIRO (Commonwealth Scientific
and Industrial Research
Organization), 564
CsrB RNA, 207
CsrC RNA, 207
CT-IC (interchromatin compartment
model), 21
CTCF proteins, 42-43
CTs (chromosome territories), 20, 135
CUTs (cryptic unstable transcripts), 250-251
cytosine methylation, 11
animals, 92
active and passive mechanisms
of demethylation, 99-101
de novo methylation, 93-97
maintenance, 98-99
fungi, 91-92
non-symmetrical methylation, 110
plants, 101
active and passive
demethylation, 110-113
de novo DNA methylation,
104-108
maintenance, 108-110
methyltransferases involved,
102-104
symmetrical methylation, 92
D
Dam (DNA methyltransferase), 75,
78-79, 468
DNA repair, 81
maintenance and inheritance of
DMFs, 85-87
organization of nucleoid region, 80
regulation of bacterial virulence, 84
regulation of gene expression, 78
repression of conjugation, 83-84
role in DNA replication, 80
transposition, 82-83
Darwin, Charles, 2, 4-6, 16
DCL (Dicer-like) proteins, 195
DCL1 protein, 301, 417
DCL2 protein, 417
DCL3 protein, 417
DCL4 protein, 417
DCLs (DICERs), 298
DDM1 protein, 68-70
ddRNAi (DNA-directed RNAi), 556
DdRP (DNA-dependent RNA
Polymerases), 238
de novo DNA methylation, 93-97
germline cells, 97
plants, 104-108
de novo methyltransferases
(DNMTs), 92-93
deacetylation, 126, 137-138
deletion
  C or G nucleotides, 167-168
uridines (editing), 162-163
demethylation, 127-129
developmental functions, ncRNAs in plants, 319-320
developmental stages of cancer, 466
diagnostic markers, miRNAs and cancer, 491
diagnostic value of epigenetics, 492-493
dicer proteins, 409
dicer-independent small interfering RNAs (disiRNAs), 247-248
Dicer-like (DCL) proteins, 195
DICERs (DCLs), 298
*Dictyostelium discoideum*, 230
diet, epigenetic effects, 536-541
differentially methylated regions (DMRs), 95, 449
dimorphic bacterium, 88
direct IR exposure, epigenetic changes, 542-543
disease and health, influence of epigenetics
  behavioral neuroscience, 499-517
cancer, 465-493
chemical carcinogens, 548-550
diet, 536-541
environmental exposures, 523-535
radiation-induced changes, 542-548
disease inheritance, 454-456
disiRNAs (dicer-independent small interfering), 247-248
DMs (DNA methylation patterns), 79, 85-87
DMRs (differentially methylated regions), 95, 449
DNA damaging agents, non-linear response to, 15
DNA methylation, 113-114
  Alzheimer’s disease, 508-509
animals, 92-97
  active and passive mechanisms of demethylation, 99-101
  maintenance, 98-99
bacteria, 75-78
  CreM, 86-89
  Dam (DNA adenine methyltransferase), 78-87
brain, 499
cancer, 468-470
  as a biomarker, 480-482
  detection and analysis of methylomes, 482-483
  hypermethylation, 476-480
  hypomethylation, 470-476
correlation to histone modifications, 142-143
defined, 75
effects of bioactive food components, 536-538
eukaryotes, 90-91
fungi, 91-92
Huntington’s disease, 513
Multiple Sclerosis, 515-516
non-symmetrical, 110
Parkinson’s disease, 512
plants, 101
  active and passive demethylation, 110-113
  de novo DNA methylation, 104-108
  epigenetic reprogramming, 456
  maintenance, 108-110
  methyltransferases involved, 102-104
  schizophrenia, 517
  symmetrical, 92
DNA methylation patterns (DMPs), 11, 79, 85-87
DNA methyltransferase. See Dam
DNA pairing model, 361
DNA repair, 81
DNA replication, 80
DNA unscrambling, 227
DNA viruses, 417
DNA-dependent RNA Polymerases (DdRP), 238
DNA-directed RNAi (ddRNAi), 556
DNMTs (de novo methyltransferases), 92-93
 DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2), 102
 DOMAINS REARRANGED METHYLTRANSFERASE 3 (DRM3), 161
double-strand breaks (DSBs), 112
double-stranded RNA-binding domains (dsRBDs), 166, 276
double-stranded RNA-binding proteins (DRBs), 419
double-stranded RNAs (dsRNAs), 159, 177, 556
gene silencing, 412
viruses, 416
DRAGs (dsRNA-activated genes), 248
DRBs (double-stranded RNA-binding proteins), 419
DRD1 protein, 69-70
DRM2 (DOMAINS REARRANGED METHYLTRANSFERASE 2), 102
DRM3 (DOMAINS REARRANGED METHYLTRANSFERASE3), 161
Drosophila melanogaster. See also chromatin, methylation
antagonistic functions of trxG and PcG proteins, 28-29
BAP (Brahma-associated proteins) in, 27
CHD1 proteins in, 33
CHD7 proteins in, 34
gypsy insulators in, 44
histone modification, 119
ISWI complexes in, 31-32
ncRNAs, 274-283
protein insulators in, 42-43
DSBs (double-strand breaks), 112
dsRBDs (double-stranded RNA-binding domains), 166, 276
dsRNA-activated genes (DRAGs), 248
dsRNA-induced transcriptional program, 248-249
dsRNAs (double-stranded RNAs), 159, 177, 556
gene silencing, 412
viruses, 416
Dutch Hunger Winter, 526

E

E. coli dam, gene expression, 78 editing
A-to-I editing, 165-166
C-to-U editing in humans, 163-165
flagellated protists, 161-163
role of gRNAs, 197-199
effector complexes, 124
effector proteins, 36-41, 121
EFS/SDG8 protein, 58
egg cell, 107
embryoblast, 94
embryonic stem cells (ESCs), 29
ENCODE (Encyclopedia Of DNA Elements), 171
endo-siRNAs (endogenous siRNAs), 276-279
endosperm cells, 106
enhancer blocking, 41
environmental exposures, influence on phenotypes, 523-524
air pollution, 529-534
prenatal environment, 525-527
psychological environment, 527-529
twin models to study environmental effects, 534-535
enzymes, histone-modifying, 485-487
epigenetic landscape, 8-9
epigenetic memory, 435
reprogramming in animals, 440
gametes, 441-446
histone-mediated inheritance, 452-453
inheritance of disease, 454-456
methylation-mediated inheritance, 448-452
protamine-mediated inheritance, 447-448
sRNA-mediated inheritance, 453-454
reprogramming in ciliates, 436
cortical inheritance, 436
homology-dependent inheritance, 436-440
reprogramming in plants, 456
DNA methylation in gametes, 456
gene imprinting, 458-459
histone modifications, 457-458
passing to progeny, 459-460
epigenetic regulation, 354-361
epigenetic somatic inheritance, 435
epigenetics
defined, 1, 13
health and disease
behavioral neuroscience, 499-517
chemical carcinogens, 548-550
diet, 536-541
environmental exposures, 523-535
radiation-induced changes, 542-548
historical background, 2-16
influence on health and disease, 465-493
technology, 555-573
epimutations, 1
epistasis, 357
epistatic interaction, 357
esBAF complex, 29-31
ESCs (embryonic stem cells), 29
establishment of paramutation, 345
eukaryotes, methylation, 90-91
evolution, historical background, 2-8
evolutionary conservation, plant
miRNAs, 303-304
evolutionary context, CRISPRs, 403-404
exo-siRNAs (exogenous siRNAs), 274-276
expression
E. coli dam gene, 78
genes, influence of histone modifications, 122-123
platform (riboswitches), 204

F
families
DNMTs (de novo methyltransferases), 93
plant histone acetyltransferases, 137
famine, epigenetic effects, 526
FAS1 gene, 51
FIE (fertilization independent endosperm) genes, 53
Fire, Andrew, 12
FIS (fertilization independent seed) genes, 54
flagellated protist, editing with gRNAs, 161-163
flagellates, ncRNAs, 229-230
FLC expression
in summer annuals, 61-63
in winter annuals, 57-61
repression of, 59-61
Flemming, Walther, 8
flowering (in plants), chromatin remodeling in, 53-64
AGL19 genes, 63
Snf2-like genes, 64-70
summer-annual state, 61-63
winter-annual state, 57-61
flowering locus t (FT) floral integrator, 56

fragile X syndrome, 507
Friedrich’s ataxia, 507
FT (flowering locus t) floral integrator, 56
functional genomics, 564
functional groups (ncRNAs), 150-152
functions
CRISPRs, 390-403
miRNAs and cancer, 490
ncRNAs, 178-183
animals, 267-283
Archaea, 217-220
cis- and trans-encoded ncRNAs, 209-215
comparison of plants to animals, 327-340
CRISPRs, 216-217
fungi, 236-249
gRNAs, 197-199
mammals/humans, 283-292
miRNAs, 184-189
piRNAs, 192-195
plants, 297-323
protein-binding ncRNAs, 207-209
protozoa, 223-229
riboswitches, 204-206
RNase III-type endonucleases, 195
siRNAs, 190-192
yeasts, 249-261
rRNAs, 155-161
VSRs (viral suppressors of RNA silencing), 426-430
fungi
methylation, 91-92
ncRNAs, 236-242
dsiRNAs, 247-248
dsRNA-induced transcriptional program, 248-249
miRNAs, 245-247
MSUD, 243-245
qiRNAs, 242-243
paramutation, 371
future, ncRNAs, 170-171

G
G nucleotides, insertion/deletion, 167-168
Galton, Francis, 6
gametes. See also germline
   cells, 4
epigenetic reprogramming, 441-446
transgenerational inheritance of
epigenetic states, 441
gemmules, 5
gene activation, DNA
   hypermethylation and cancer, 477-478
gene expression
   influence of histone modifications, 122-123
   ncRNA-mediated regulation in S. cerevisiae, 254-257
   regulation
   co-suppression, 380-381
   paramutation, 343-379
   role of CerM, 88
   role of Dam, 78
   transvection, 379-380
gene imprinting, epigenetic
   reprogramming in plants, 458-459
gene promoters, 122
gene silencing, 11, 343. See also
   RNAi (RNA interference)
   at telomeres, 14
   co-suppression, 380-381
   hairpin-based antisensing, 555-557
   animal applications, 569-570
   chimeric hairpins, 559
   components of hairpin, 560-561
   inducible hairpin RNAs, 562-563
   limitations, 573
   mammalian applications, 570-573
   plant applications, 563-569
   targeting conserved sequences, 558-559
   tissue-specific, 562
   history of, 410-413
   protection of plants against
   viruses, 413
   PTGS as antiviral mechanism, 413-415
   purpose of, 413
   RdDM pathway, 312-317
   summary of ncRNAs involved, 327
   TGS (transcriptional gene
   silencing), 421-423
   trans-silencing, 359
   transgenerational inheritance
   (epigenetic states)
   reprogramming in animals, 440-456
   reprogramming in ciliates,
   436-440
   reprogramming in plants,
   456-460
   transitive silencing, 423-426
   VIGS (virus-induced gene
   silencing), 416-421
   viral suppressors, 426-430
generative cell, 105
genetic assimilation, 8
genetics, 1
   genomic imprinting, 95, 356, 470
   genotoxic carcinogens, 549
   Geoffroy Saint-Hilaire, Étienne, 3
   germ plasm, 3
   germline. See also gametes
   cells, de novo DNA methylation, 97, 105-108
   genome, ciliates, 223
   GINA (Global Initiative in Asthma)
   scores, 531
   GlnY RNAs, 208
   GlnZ RNAs, 208
   global genome hypomethylation
   (cancer cells), 470
   Global Initiative in Asthma (GINA)
   scores, 531
   glycosylases, 111
   Gottschling, Daniel E., 15
   grafted plants, 7
gRNAs (guide RNAs)
   A-to-I editing, 165-166
   C-to-U editing in humans, 163-165
   editing in flagellated protists,
   161-163
   editing of miRNA/riRNA, 197-199
   insertion/deletion of C or G
   nucleotides, 167-168
   reasons for RNA editing, 168-169
   groups, ncRNAs, 150-152
   guide RNAs. See gRNAs
   guide strand, 191, 421
   gypsy insulators, 44
H
H2AX histone variant, 133
H2AZ histone variant, 133
H3 histone variants, 134
H3K acetylation, 121, 134
H3K27me, histone methylation, 139
H3K36me, histone methylation, 140
H3K4me, histone methylation, 138
H3K9me, histone methylation, 140
Hagemann, Rudolf, 346
hairpin RNAi construct, 555-558
  animal applications, 560-570
  chimeric hairpins, 559
  components, 560-561
  inducible hairpin RNAi, 562-563
  limitations, 573
  mammal applications, 570-573
  plant applications, 563-569
  targeting conserved sequences, 558-559
  tissue-specific, 562
hairpin RNAs (hpRNAs), 279, 556, 570-571
haplotypes, 348
hard inheritance, 3
HAT (histone acetyl transferase) enzymes, 121
hc-siRNAs (heterochromatic siRNAs), 308
HD (Huntington's disease), 513-514
HDAC (histone deacetylase) enzymes, 121
health and disease, influence of epigenetics
  behavioral neuroscience, 499-517
  cancer, 465-493
  chemical carcinogens, 548-550
  diet, 536-541
  environmental exposures, 523-535
  radiation-induced changes, 542-548
Heat-shock RNA1 (HSR1 RNA), 291
HEN1 protein, 420
heterochromatic siRNAs
  (hc-siRNAs), 308
Hfq RNA-binding protein, 214
HGFS (Hutchinson-Gilford progeria), 23
HGT (horizontal gene transfer), 385-386
histone acetyl transferase (HAT) enzymes, 121
histone code, 124
histone core, 119
histone deacetylase (HDAC) enzymes, 121
histone-mediated inheritance, 452-453
histones
  acetylation, 121, 135
  chaperones, 121
  defined, 119
H2AX, 133
H2AZ, 133
in chromatin compaction, 19
methylation, 13
modifications, 119
  Alzheimer's disease, 509
  animals, 125-137
  brain, 500
  cancer, 484-492
  effects of bioactive food components, 538-539
  epigenetic reprogramming, 457-458
  gene expression states, 122-123
  Huntington's disease, 513
  Parkinson's disease, 512
  plants, 137-143
  transcription regulation, 120-122
  trypanosomes, 123-125
  phosphorylation, 130-131
  ubiquitination, 131-132
historical background of epigenetics research, 2-16
history
  ncRNAs, 148-149
  of gene silencing, 410-413
  paramutation, 345-347
  RNA, 148-149
Hollliday, Robin, 13
homologous recombination, 67, 134
homology-dependent inheritance, ciliates, 436-440
homology-dependent silencing, ciliates, 224
horizontal gene transfer (HGT), 385-386
horizontal inheritance, CRISPR elements, 404
HOTAIR RNA (Hox antisense intergenic RNA), 291
HOTHEAD (HTH) gene, 14
Hox antisense intergenic RNA (HOTAIR RNA), 291
HP1 protein, 37
hpRNAs (hairpin RNAs), 279, 556, 570-571
HR (hypersensitive response), 423-424
HSR1 RNA (Heat-shock RNA), 291
humans
  A-to-I editing, 165-166
  C-to-U editing, 163-165
ncRNAs, 283
  HOTAIR RNA, 291
  HSR1 RNA, 291
  miRNAs, 283-292
  piRNAs, 288-290
  siRNAs, 287-288
  Xist and Tsix RNAs, 290
Huntington’s disease (HD), 513-514
Hutchinson-Gilford progeria syndrome (HGPS), 23
hypermethylation, cancer
  gene activation, 477-478
  mechanisms, 479-480
  miRNA genes, 478-479
  mutagenic potential, 476
hypersensitive response (HR), 423-424
hypomethylation, cancer, 470
  development and progression, 474-476
  loss of imprinting, 473
  mechanisms, 473-474
  oncogenes, 472-473
  repetitive sequences, 471

I
IAP (intracisternal A-particle)
  retrotransposons, 448
IC (imprinting center), 455
ICD (interchromosome domain) model, 21
ICRs (imprinting control regions), 94-95, 443
ICs (interchromatin compartments), 20, 135
IES (internally eliminated sequences), 224, 437
IGS (intergenic spacer), 156
initiation switch (ISWI) ATPases, 26, 31-33
imprinted genes, 442
imprinting center (IC), 455
imprinting control regions (ICRs), 94-95, 443
inactive state, gene promoters, 122
incorporation of new sequences, CRISPR loci, 400-401
indirect IR exposure, epigenetic changes, 543-548
inducible hairpin RNAi, 562-563
inheritance
  DMPs (DNA methylation patterns), 85-87
  hard inheritance, 3
  histone-mediated, 452-453
  historical background, 3-8
  methylation-mediated, 448-452
  non-Mendelian mechanism, 440
  of stress memory, 16
  phenotypic epigenetic inheritance, 374-379
  protamine-mediated, 447-448
  soft inheritance, 3
  sRNA-mediated, 453-454
  transgenerational, 435
    reprogramming in animals, 440-456
    reprogramming in ciliates, 436-440
    reprogramming in plants, 456-460
INO80 ATPases, 26, 35-36
insertion
  C or G nucleotides, 167-168
  uridines (editing), 162-163
insulator proteins, 41-44
integrons, 385
interchromatin compartment model (CT-IC), 21
interchromatin compartments (ICs), 20, 135
interchromosome domain (ICD) model, 21
intergenic ncRNAs, 180
intergenic spacer (IGS), 156
internal lamins, 22
internal ribosome entry site (IRES), 285
internally eliminated sequences (IES), 224, 437
intracisternal A-particle (IAP)
  retrotransposons, 448
intronic ncRNAs, 180
invasion and metastases (cancer), 472
inversely amplified responses, co-suppression, 380
ionizing radiation (IR) exposure, epigenetic changes, 542-548
IR (ionizing radiation) exposure, epigenetic changes, 542-548
IRES (internal ribosome entry site), 285
ISWI (imitation switch) ATPases, 26, 31-33
J–K–L
Kaiso protein, 40
kinetic model, 168
Knudson’s “two-hit” cancer hypothesis, 466
Lamarck, Jean-Baptiste, 2-3
lamin-associated polypeptides (LAPs), 23
lamins, 23
LAPs (lamin-associated polypeptides), 23
lariats, 189
lateral gene transfer, 386
Lawrence, William, 3
Lewis, Edward B., 379
LHP1 protein, 69-70
LHP1/TFL2 protein, 54
like heterochromatin protein 1 (LHP1)/terminal flower 2 (TFL2), 54
limitations, hairpin-mediated RNAi, 573
lncRNAs (long ncRNAs), 310
biogenesis and function, 178-183
categories, 179-180
modes of action, 182
transcriptional repression, 181
LOI (loss of imprinting), cancer, 473
long ncRNAs. See lncRNAs
long siRNAs (lsiRNAs), 308
loss of imprinting (LOI), cancer, 473
lsiRNAs (long siRNAs), 308
lunasin, 541
Lyon, Mary, 10

M
MAC (macronucleus), 437
macronucleus (MAC), 437
Macronucleus Destined Segments (MDSs), 437
maintenance
DMPs (DNA methylation patterns), 85, 87
DNA methylation, 98-99, 108-110
methyltransferase, 92
paramutation, 345
malignant cells, 465
mammals/humans
applications of hairpin RNAi, 570-573
BAF complex, 27, 30-31
CHD1 proteins in, 34
CHD7 proteins in, 34
HP1 protein in, 37
INO80 complexes in, 35-36
ISWI complexes in, 32-33
MBD3 proteins in, 40
ncRNAs, 283
\textit{HOTAIR} RNA, 291
\textit{HSR1} RNA, 291
\textit{miRNAs}, 283-292
\textit{piRNAs}, 288-290
\textit{siRNAs}, 287-288
\textit{Xist} and \textit{Tsix} RNAs, 290
NURD complexes in, 34
protein insulators in, 42-43
manipulation of biosynthetic pathways, plant applications for hairpin-based RNAi, 566-567
maternal diet (prenatal environment), epigenetic effects, 525-527
Mattick, John, 149
maturation, tRNAs, 153
maxicircle molecules, 162
Mayr, Ernst, 3
MBD (methylbinding domain), 39, 469
MBD1 protein, 39
MBD2 protein, 39
MBD3 protein, 40
MBD4 protein, 40
McCIntock, Barbara, 10
MCSs (multiple cloning sites), 564
MDSs (Macronucleus Destined Segments), 437
Meaneey, Michael, 503-505
mechanisms (epigenetic), DNA methylation
animals, 92-101
bacteria, 75-89
eukaryotes, 90-91
fungi, 91-92
plants, 101-113
MeCP1 protein complex, 39
MeCP2 protein complex, 39
MED1 protein, 40
meiotic silencing by unpaired DNA (MSUD), 243-245
meiotic transsensing, 243
meiotic transvection, 243
meiotic unannotated transcripts (MUTs), 237-258
Mello, Craig, 12
memory
    epigenetic, 435
    animals, 440-456
ciliates, 436-440
plants, 456-460
formation, 499
Mendel, Gregor Johann, 7, 148
MET1 (METHYLTRANSFERASE 1), 102
metals, exposure to, 550
metameres, 362
metastasis, miRNAs and cancer, 491-492
methyl-CpG-binding domain (MBD) proteins, 469
methylated DNA, binding to, 39
methyltransferase
    Alzheimer's disease, 508-509
    animals, 92
    active and passive mechanisms of demethylation, 99-101
de novo methylation, 93-97
    maintenance, 98-99
bacteria, 75
    CcrM, 86-89
    Dam (DNA adenine methyltransferase), 78-87
brain, 499
cancer, 468-470
    as a biomarker, 480-482
detection and analysis of methylomes, 482-483
hypermethylation, 476-480
hypomethylation, 470-476
defined, 75
effects of bioactive food components, 536-538
eukaryotes, 90-91
fungi, 91-92
histones
    animals, 127-129
    plants, 138
Huntington's disease, 513
Multiple Sclerosis, 515-516
non-symmetrical, 110
plants, 101
active and passive demethylation, 110-113
de novo DNA methylation, 104-108
epigenetic reprogramming, 456
maintenance, 108-110
methyltransferases involved, 102-104
schizophrenic patients, 517
symmetrical, 92
methylation-mediated inheritance, 448-452
methylbinding domain (MBD), 39
Methylome DB study, 517
methylomes, detection and analysis, 482-483
METHYLTRANSFERASE 1 (MET1), 102
methyltransferases, plant demethylation, 102-104
mi-RISC, 302
MIC (micronucleus), 437
Michurin, Ivan, 7
miRNA (mRNA-interfering complementary RNA), 204
micronucleus (MIC), 437
microRNAs. See miRNAs
miRNAs (miRNA-like small RNAs), 245-247
minicircle molecules, 162
miRISC (miRNA-RISC), 302
miRNA recognition elements (MREs), 187
miRNA-like small RNAs (miRNAs), 245-247
miRNA-mediated translational inhibition, 332-335
miRNA-responsive element (MRE), 302
miRNA-RISC (mi-RISC), 302
miRNA/AGO ribonucleoprotein (miRNP), 186
miRNAs (microRNAs), 183
    Alzheimer's disease, 510
    biogenesis and function, 184-189
    comparison of plants to animals, 329-332
    mirtrons, 189-190
    C. elegans, 268-270
cancer and, 488
diagnostic and prognostic markers, 491
function, 490
metastasis, 491-492
oncogenes, 489
tumor-suppressors, 489-490
DNA hypermethylation and cancer, 478-479
Drosophila melanogaster, 281-282
diaphragm editing by gRNAs, 197-199
effects of bioactive food components, 539-540
PAMs (proto-spacers adjusting motifs), 401
pANDA vector, 564
pangenesis, 5-6
parachromatin, 363
paramecium, silencing, 224
paramutable alleles, 344
paramutagenicity, 358
paramutagenic alleles, 344
paramutation, 9, 343
animals
  RNA involved in phenotypic epigenetic inheritance, 374-379
  whitetail phenotype, 372-374
epigenetic regulation, 354-361
fungi, 371
historical view, 345-347
models, 361
  physical interaction, 368-370
  RNA, 366-368
plants, 347
  b1 locus in maize, 351-354
  importance and significance, 370-371
  R1 locus in maize, 348-351
tandem repeats, 362-365
parasite-derived resistance (PDR), 411
parental imprinting control regions, 94-95
Parkinson's disease (PD), 511-513
passenger strand, 191
passive demethylation, 110-113
passive DNA demethylation, 99-101
passive DNA replication-dependent demethylation, 86
pathogen resistance, plant
  applications for hairpin-based RNAi, 567-569
pathogen-derived resistance (PDR), 411
Pc-G (polycomb group) proteins
  antagonistic functions of, 28-29
  cancer and, 487-488
Pc-G (Polycomb-group) protein complexes, 52-55, 128
PD (Parkinson’s disease), 511-513
PDR (pathogen-derived resistance), 411
penetration, 345
peripheral lamins, 22
permissive state, gene promoters, 122
pFGC vector, 564
PGCs (polycistronic gene clusters), 124
PGCs (primordial germ cells), 94, 441
phage transduction, 385
phages (bacterial), 387
pHANNIBAL cloning vector, 564
phosphorylation, histones, 130-131
photoperiod-independent early flowering 1 (PIE1) protein, 64-66
phylogenesis, 7
phylogenetics, 5
physical interaction model, paramutation, 368-370
PIE1 protein, 64-66
Pikaard, Craig, 315
piRNAs (PIWI-interacting RNAs), 97, 183, 267
  biogenesis and function, 192-195
  C. elegans, 271-273
  comparison to CRISPRs, 395
  Drosophila melanogaster, 279-281
  mammals/humans, 288-290
PIWI (P-element-induced wimpy testis)-interacting RNAs. See piRNAs
PIWI-interacting RNAs. See piRNAs
pKANNIBAL cloning vector, 564
pKNOCKOUT vector, 564
plants
  A-to-I editing, 165-166
  applications of hairpin RNAi, 563
    functional genomics, 564
    manipulation of biosynthetic pathways, 566-567
    pathogen resistance, 567-569
    removal of undesirable traits, 565
  biogenesis, 298
  chromatin remodeling in, 49
    flowering, 55-64
    organ development, 52-55
    RAM (root apical meristem), 51
    SAM (shoot apical meristem), 50-52
    seed development, 49-50
    Snf2-like genes, 64-70
  epigenetic reprogramming
    DNA methylation in gametes, 456
    gene imprinting, 458-459
    histone modifications, 457-458
    passing to progeny, 459-460
  grafting, 7
histone modifications
  acetylation/deacetylation, 137-138
correlation to DNA
  methylation, 142-143
deposition during cell cycle, 141-142
  methylation, 138
  variants, 140-141
methylation, 101
  active and passive
demethylation, 110-113
de novo DNA methylation,
  104-108
  maintenance, 108-110
  methyltransferases involved, 102-104
ncRNAs, 297-300
  comparison to animals, 327-340
  functions, 319-323
  long ncRNAs, 310
  miRNAs, 301-304
RdDM and gene silencing,
  312-317
  redundant mechanisms for
  ncRNA production, 310-311
siRNAs, 304-310
paramutation, 347
  b1 locus in maize, 351-354
  importance and significance,
  370-371
  R1 locus in maize, 348-351
  protection against viruses, 413-415
  transgenesis, 347
pluripotency, esBAF complex and,
  29-31
pollen siRNAs, 300-310
pollution, influence on phenotypes,
  529-534
PollIV, as component of RdDM
  pathway, 315-317
PolV, as component of RdDM
  pathway, 315-317
polyclustering gene clusters
  (PGCs), 124
polycomb group (PcG) proteins
  antagonistic functions of, 28-29
  cancer and, 487-488
polycomb repressive complex 1
  (PRC1), 28, 128
polycomb repressive complex 2
  (PRC2), 28, 128
Polycomb-group (PcG) protein
  complex, 52-55, 128
  position-effect variegation, 10
  post-transcriptional gene silencing
  (PTGS), 177, 297, 410
  as antiviral mechanism, 413-415
  fungi, 236
post-traumatic stress disorder
  (PTSD), 527
PRC complexes, repressive states
  and, 53-55
PRC1 (Polycomb Repressive
  Complex 1), 28, 128
PRC2 (Polycomb Repressive
  Complex 2), 28, 128
PRC2-MEA complex, 54
pre-miRNAs (precursor-miRNAs),
  184, 281, 297
pre-pachytene piRNAs, 289
pre-tRNAs (precursor tRNAs), 153
primary miRNAs, 557
primary paramutation, 352
primary siRNAs, 270-271
primary transcript (pri-miRNA), 184
primordial germ cells (PGCs), 94, 441
priRNAs (primal small RNAs), 260
pRNAs (RNA products), 208
Processing (P) bodies, 185
prognostic markers, miRNAs and
cancer, 491
promotional stage of
carcinogenesis, 465
protection
  CRISPRs, 385-405
  stress responses, 386-387
  plants, 413-415
protein-binding ncRNAs, bacteria,
  207-209
proteins
  CRISPR-related, 389-390
  in chromatin remodeling
  chromatin-remodeling
  complexes, 25-36
  effector proteins, 36-41
  insulator proteins, 41-44
ncRNA biogenesis, 338-340
PcG (polycomb group), cancer and, 487-488
plant biogenesis, 298
RAMPs (Repeat-Associated Mysterious Proteins), 389
TrxG (trithorax group), cancer and, 487-488
protists, editing flagellated protists with gRNAs, 161-163
proto-spacer adjacent motif end (PAME), 401
proto-spacers adjusting motifs (PAMs), 401
protozoa, ncRNAs
ciliates, 223-229
flagellates, 229-230
pseudopodia-containing protists, 230-233
pseudopodia-containing protists, ncRNAs, 230-233
psychiatric disorders, influence of epigenetic changes, 516-517
psychological environment, influence on phenotypes, 527-529
PTGS (post-transcriptional gene silencing), 177, 297, 410
as antiviral mechanism, 413-415
fungi, 236
PTSD (post-traumatic stress disorder), 527
Q–R
qiRNAs, 242-243
quelling, 236, 240, 410-411
R1 locus, paramutation in plants, 348-351
ras-siRNAs (repeat-associated siRNAs), 308
radiation-induced epigenetic changes
  direct IR exposure, 542-543
  indirect IR exposure, 543-548
RAM (root apical meristem), chromatin remodeling in, 51
RAMPs (Repeat-Associated Mysterious Proteins) family, 389
RdDM (RNA-directed DNA methylation), 102, 159, 423
RdDM pathway, gene silencing, 312-317
RDRC (RNA-dependent RNA polymerase complex), 258
RdRP (RNA-dependent RNA polymerase), 191, 270, 298, 337, 537
recessive mutation, 354
redundant mechanisms, ncRNA production in plants, 310-311
regulation
  apoptosis, 153
  bacterial virulence, 84
  cell cycle, 88-89
  gene expression
    CcrM, 88
    co-suppression, 380-381
    Dam, 78
    paramutation, 343-379
    S. cerevisiae, 254-257
    transvection, 379-380
  paramutation, 354-361
  transcription, 120-122
regulatory RNAs
  algae-chloroplasts containing protists, 233-236
  animals, 257-283
  comparison to plants, 327-340
  Archaea, 217-220
  bacteria, 203-217
  fungi, 236-249
  mammals/humans, 283-292
  plants, 297-323
  comparison to animals, 327-340
  protozoa, 223-233
  yeasts, 249-261
relative frequency, RM systems in cell population, 76
repair of DNA, 81
Repeat-Associated Mysterious Proteins (RAMPs) family, 389
repeat-associated siRNAs (ra-siRNAs), 308
repeat-counting mechanisms, paramutation, 362-365
repeat-induced point mutation (RIP), 12
replication, 80
Replication Protein A, 238
repression
  of conjugation, 83-84
  of FLC expression, 59-61
repressive states, PRC complexes and, 53-55
response to stress
  bacteria, 386-387
  ncRNAs in plants, 320-323
restriction-modification (RM) system, 76, 387
restrictive state, gene promoters, 122
Rett syndrome (RTT), 506
reverse genetics, 564
Ribonuclease P (RNase P), 169
ribosomal RNAs (rRNAs), 149, 155-161
riboswitches, 204-206, 223
RIP (repeat-induced point mutation), 12
RISC (RNA-Induced Silencing Complex), 183, 302, 410, 558
RITS (RNA-Induced Transcriptional Silencing Complex), 183, 308
RM (restriction-modification) system, 76, 387
RNA editing, 168-169
history of, 148-149
paramutation model, 366-368
phenotypic epigenetic inheritance, 374-379
silencing, viral suppressors, 426-430
thermometers, 205
RNA Dependent RNA Polymerases (RDRs), 298
RNA interference. See RNAi
RNA polymerases (RNAPs), 69-70, 167
RNA products (pRNAs), 208
RNA-based model, paramutation, 361
RNA-dependent RNA polymerase complex (RDRC), 258
RNA-dependent RNA polymerases (RdRPs), 191, 337
RNA-directed DNA methylation (RdDM), 102, 159, 423
RNA-Induced Silencing Complex (RISC), 183, 410
RNA-Induced Transcriptional Silencing Complex (RITS), 183, 308
RNA-mediated epigenetic inheritance, 228
RNAi (RNA interference pathway), 12, 178, 265, 409
comparison to CRISPR, 391
hairpin RNAi construct, 555-558
animal applications, 569-570
chimeric hairpins, 559
components, 560-561
inducible hairpin RNAi, 562-563
limitations, 573
mammal applications, 570-573
plant applications, 563-569
targeting conserved sequences, 558-559
tissue-specific, 562
history of silencing, 410-413
protection of plants against viruses, 413
purpose of, 413
siRNAs in C. elegans, 270-271
RNAPs (RNA polymerases), 167
RNase III-type endonucleases, 195
RNase P (Ribonuclease P), 169
roles, biogenesis and function of ncRNAs, 177
comparison of plants to animals, 327-340
gRNAs, 197-199
lncRNAs, 178-182
miRNAs, 184-190
piRNAs, 192-195
RNase III-type endonucleases, 195
siRNAs, 190-192
small ncRNAs, 183
Romanes, George, 6
root apical meristem (RAM), chromatin remodeling in, 51
RPA1, 238
rRNAs (ribosomal RNAs), 149, 155-161
RTT (Rett syndrome), 506
Rubinstein-Taybi syndrome, 507

S
S-adenosylmethionine (SAM or Adomet), 90
S. cerevisiae (Saccharomyces cerevisiae), ncRNAs, 249
cryptic site origination, 253
CUTs, 250-251
MUTs, 257-258
regulation of gene expression, 254-257
short sense ncRNAs upstream of mRNA sites, 251, 253
S. pombe (Schizosaccharomyces pombe), ncRNAs, 249, 258-261
Saccharomyces cerevisiae. See S. cerevisiae
SAGOs (secondary Argonautes), 270
SAM (S-adenosylmethionine), 90
SAM (shoot apical meristem), chromatin remodeling in, 50-52
SAR (systemic acquired resistance), 423-424
transitive silencing, 423-424
scan RNA model, 225
scan RNAs (scanRNAs), 225
scaRNAs (Cajal body-specific RNAs), 154
schizophrenia, 517
Schizosaccharomyces pombe (S. pombe), 249, 258-261
scnRNA-mediated elimination of genomic sequences, 227
scnRNAs (scan RNAs), 225
sdRNAs, 152
second-hand smoke exposure, 524
secondary Argonautes (SAGOs), 270
secondary nat-siRNAs, 307
secondary paramutation, 352
secondary siRNAs, 270-271
seed development, chromatin remodeling in, 49-50
seed regions, 187
self-renewal process of cells, 571
sense ncRNAs, 180
shoot apical meristem (SAM), chromatin remodeling in, 50-52
short hpRNAs (shRNAs), 556, 569-573
short interfering RNAs. See siRNAs
short interspersed element (SINE), 199
shRNAs (short hpRNAs), 556, 569-573
sigma (s) factor, 208
signal recognition particle (SRP), 169
silencing (gene). See gene silencing
SINE (short interspersed element), 199
siRNAs (small interfering RNAs), 183, 297, 413, 556
biogenesis and function, 190-192, 335-338
C. elegans, 270-271
Drosophila melanogaster
end-siRNAs, 276-279
exo-siRNAs, 274-276
editing by gRNAs, 197-199
mammals/humans, 287-288
plants
nat-siRNAs, 306-309
pollen siRNAs, 309-310
trans-acting siRNAs, 304-306
qiRNAs, 242
SKB1 protein, 62
Skipper retrotransposon, 232
slicing, 420
small interfering RNAs. See siRNAs
small ncRNAs
biogenesis and function, 178-183
miRNAs, 183-190
piRNAs, 183, 192-195
siRNAs, 183, 190-192
small nuclear ribonucleic acid
(snRNAs), 153
small nuclear ribonucleoproteins (snRNPs), 154
small nucleolar RNAs (snORNA), 154-155
small RNAs (siRNAs), 62-63, 203
smoke (tobacco), 549
Smn2-like genes, 64-70
SNF2H proteins, 33
SNF2L proteins, 32
SNF1 protein, 67-68
snoRNAs (small nucleolar RNAs), 154-155
snRNAs (small nuclear ribonucleic acids), 153
snRNPs (small nuclear ribonucleoproteins), 154
SOC1 (suppressor of overexpression of CO) floral integrator, 56
socioeconomic status, influence on phenotypes, 524
soft inheritance, 3
somatic cells, 4
somatic genome, 224
somatoplasm, 4
SOS DNA damage response, 386
soy, 541
Spencer, Herbert, 4
sperm cells, 105
spliRNAs, 152
sRNA-mediated inheritance, 453-454
snRNAs (small RNAs), 62-63, 203
SRP (signal recognition particle), 169
SRP ribonucleoprotein complex, 169
stages, cancer development, 466
stalked cells, 88
Stegemann, Sandra, 7
stress
influence on phenotypes, 527-529
memory, 16
response
bacteria, 386-387
ncRNAs in plants, 320-323
structure, RNase III-type endonucleases, 195
stuttering model, 167
summer annuals, 55
summer-annual state, 61-63
suppression. See gene silencing suppressor of overexpression of CO (SOC1) floral integrator, 56
survival of the fittest, 4
Sutton, Walter, 8
swarmer cells, 88
SWI/SNF (SWITCH/SUCROSE NONFERMENTING) ATPases, 26-27, 30-31, 52
SWI/SNF chromatin-remodeling ATPase, 52
symmetric cytosine methylation, 92
systemic acquired resistance (SAR), 423-424
Szyf, Moshe, 503-505

T
T-boxes, 205
ta-siRNAs (trans-acting siRNAs), 304-306
tandem repeats, paramutation, 362-365
targeting Alu elements, 199
tasiRNAs, 276
technology, influence on epigenetics, 555-573
telomeres, silencing at, 14
terminator structures, 205
TEs (transposable elements), 97
*Tetrahymena thermophila*, 225
TGS (transcriptional gene silencing), 159, 343, 410, 421-423
transcription
facilities, 21-23
regulation, 120-122
transcriptional antitermination, 205
transcriptional gene silencing (TGS), 159, 343, 410, 421-423
transcriptional repression, 181
transcriptional-repression domain (TRD), 39
transcriptionally silent information (TSI), 159
transduction, 386
transfer RNAs, 149-153
transformation, 385-386
transgenerational inheritance (epigenetic states), 435, 546-548
reprogramming in animals, 440-456
reprogramming in ciliates, 436-440
reprogramming in plants, 456-460
transgenes, 347
transgenesis, plants, 347
transitive silencing, 423-426
transitivity, 419
translation activation, ncRNAs, 282-283
translational inhibition
mi-RNA-mediated, 332-335
models, 254-287
transposable elements (TEs), 97
transposition, 82-83
transvection, 368, 379-380
TRD (transcriptional-repression domain), 39
TREs (trxG response elements), 28
tRFs (tRNA fragments), 153
trithorax group (TrxG) proteins, cancer and, 487-488
tRNA fragments (tRFs), 153
tRNAs (transfer RNAs), 149, 152-153
trophoectoderm, 94
TrxG (trithorax group) proteins
antagonistic functions of, 28-29
cancer and, 487-488
plant organ development, 52-55
*Trypanosoma brucei*, 229
trypanosomes, 11, 123-125
TSI (transcriptionally silent information), 159
Tsix RNAs, 181, 290
tumor-suppressors, miRNAs, 489-490
twins model, 534-535
“two-hit” cancer hypothesis (Knudson), 466
type I antitoxin proteins, 211
type I RM systems, 76
type II antitoxin proteins, 211
type II RM systems, 76
type III antitoxin proteins, 211
type III RM systems, 76

**U–V**

UAS (upstream activating sequence), 54
ubiquitination, histones, 131-132
UHRF1 protein, 41
uridines, insertion/deletion editing, 162-163
use and disuse model, 3
variants, histones
  animals, 133-134
  plants, 140-141

*The Variation of Animals and Plants under Domestication* (Darwin), 5
vegetative cell, 105
Venter, Dr. Craig, 523
vernalization, 56-57
  FLC repression, 59-61
  steps in, 61
vernalization 1 (VRN1) protein, 57
vernalization insensitive 3 (VIN3) protein, 57
vertical inheritance, CRISPR elements, 404
VIGS (virus-induced gene silencing), 409, 416-421, 567
VIN3 (vernalization insensitive 3) protein, 57
viral suppressors of RNA silencing (VSRs), 427
viRNA RISC complexes (vi-RISC), 419
viRNAs (virus-derived small RNAs), 409, 417
viroids, 568
virulence, bacteria, 84
virus-derived small RNAs (viRNAs), 409, 417
virus-induced gene silencing (VIGS), 409, 416-421, 567

viruses
  protection against, 413-415
  silencing suppressors, 426-430
VRN1 (vernalization 1) protein, 57
VRN2-PRC2 complex, 60
VSRs (viral suppressors of RNA silencing), 427

**W–Z**

Waddington, Conrad Hal, 8
Wallace, Alfred Russel, 6
Watson and Crick, proposed model of DNA structure, 148
Weintraub, Hal, 11
Weismann, August, 3, 6
white tail phenotype, paramutation example, 372-374
WICH complex (WSTF (Williams-Beuren syndrome transcription factor)-ISWI chromatin remodeling), 32
Williams-Beuren syndrome, 33
Wilson, Edmund, 8
winter annuals, 55
winter-annual state, 57-61
Xi (X chromosome inactivation), 10-11, 22
Xist RNAs, 181, 290

yeasts, ncRNAs
  *S. cerevisiae*, 249-258
  *S. pombe*, 258-261