Review Article:

Exploring the Epigenetic Landscape: Unraveling the Intricacies of Gene Regulation

Jobran M Moshi[1,2]

1. Department of Medical Laboratory Technology, College of Nursing and Health Science, Jazan University, Jazan, Kingdom of Saudi Arabia.
2. Health Research Centre, Jazan University, Jazan, Kingdom of Saudi Arabia.

Received on Oct 19, 2024, accepted for publication on Feb 27, 2025, dx.doi.org/10.5455/mjhs.2025.02.015

Corresponding author:

Jobran Moshi, Ph.D. Department of Medical Laboratory Technology, College of Nursing and Health Science, Jazan University, Jazan, Kingdom of Saudi Arabia, Health Research Centre, Jazan University, Jazan, Kingdom of Saudi Arabia. Arabia, E-mail: Jmoshi@jazanu.edu.sa

OPEN ACCESS Distributed under Creative Commons CC BY-NC-ND 4.0

Abstract

Epigenetics, a rapidly developing field within genetics, involves the study of heritable alterations in gene expression that are not caused by changes in the DNA sequence. Notable modifications include histone modifications, non-coding RNA, and DNA methylation molecules, which collectively regulate gene expression without modifying the genetic code. This review underscores the influence of physiological, pathological, and environmental factors on these modifications, utilizing Angelman syndrome and Rett syndrome as examples. Furthermore, this review highlights the broader impact of epigenetic alterations caused by lifestyle choices, including smoking and poor diet, on increasing the probability of chronic illnesses such as diabetes and cancer. The dynamic nature of epigenetic regulation emphasizes the need to consider environmental and lifestyle factors in understanding complex diseases, such as Angelman syndrome, offering significant implications for both etiological comprehension and the development of potential therapeutic interventions.

Keywords:

Epigenetics; Gene Expression; DNA Methylation; Angelman Syndrome; Rett Syndrome

Introduction:

The scientific community has been encouraged by the rapidly expanding field of epigenetics [1]. This is the examination of molecules and mechanisms that may maintain alternative gene activity states within the context of the same DNA sequence. Gene expression alterations or cellular phenotypes that dont involve alterations to the DNA sequence itself are referred to as epigenetics, that is derived from the Greek word "epi"(that translates as above/ on top of) [2]. Epigenetics is frequently used to describe any non-Mendelian unexpected mode of inheritance. The investigation of the mechanisms that determine how the genotype produces the phenotype in the context of progression was an early description of epigenetics by Conrad Waddington[3]. He proposed an alternative definition of "epigenetics" by defining two cellular control mechanisms: auxiliatory mechanisms that regulate the cellular expression of genes and template replication mechanisms of DNA sequences [4]. Currently, Waddington's interpretation of epigenetics is considered to be a tool for controlling gene expression. Although it might be classified as epigenetic in accordance with, it is crucial to highlight that this investigation was inherently genetic rather than epigenetic. Furthermore, Waddington et al. were unaware of prokaryotes as organisms recommended for genetic investigations[1-3].

A theoretical framework has been developed by certain scholars, in which genes at various hierarchical concentrations of control interact to be detected. Fate of cells during progression via differential gene expression[5,6]. The aforementioned model not only offered an initial complete comprehension of genetic regulation in greater organisms, but also proposed significant evolutionary consequences. It was hypothesized that transcriptional mechanisms might be influenced by changes in regulatory regions, which might result in stable gene systems that stimulate evolutionary innovations. Empirical studies on the regulation of genes during the process of development and the examination of evolutionary factors that impact changes in body plans further refined the model, which concentrates on the consolidation of DNA sequences responsible for genetic expression[7].

There was a significant contribution to the field of epigenetics during the 1980s and 1990s, when numerous expanded meanings for the concept were proposed [8]. These contributions have facilitated the progression of various interpretations and understandings associated with the term epigenetics. This theory proposes that epigenetic alterations must be classified as changes in gene expression, which are the consequence of

DNA methylation or demethylation processes. Additionally, the author proposed that abnormalities in germline cells at the epigenetic level have the potential to be passed down to subsequent generations, thereby contradicting Waddington's perspective and highlighting the critical role of intergenerational heredity in the field of epigenetic phenomena [9, 10]. Subsequently, the investigation of modifications in histone proteins was acknowledged as a process that contributes to the phenomenon of "epigenetic inheritance," thereby expanding the conceptual framework surrounding this concept [11]. Regarding[12], a researcher studying chromatin changes made a humorous remark about the intriguing nature of these changes, attributing their appeal to their epigenetic categorization. In an effort to accurately capture the fundamental nature of epigenetics, the multitude of meanings has increased. According to[13], it is "the investigation of heritable alterations in gene function that are the outcome of meiotic and mitotic processes and can't be explained by alterations in DNA sequences." Correspondingly, [14], it is characterized as "the alteration of chromosomal regions to report, communicate, or keep altered activity states."

However, it is crucial to acknowledge which of these descriptions cannot consistently distinguish between scenarios where changes are transmitted throughout cell division, thereby preserving gene expression patterns, and cases in which changes are merely components of the transcriptional machinery [15]. Consequently, the concept of "epigenetics" is subject to a variety of interpretations. A substantial portion of medical epigenetic studies relate to the examination of correlations, rather than the establishment of causal correlations. The role of epigenetic factors in the regulation of gene expression has been the subject of numerous studies with a specific focus on the genome as the predominant determinant. According to the molecular immunologist Ellen Rothenberg, sequence-specific transcription factors are the primary catalysts for changes in the epigenetic environment. These parameters are essential for establishing the initial positions for histone modifications and their effect on the accessibility of DNA[16]. These variables indicate a dynamic point of convergence between regulatory history and future trajectories, significantly influencing the restructuring of the epigenetic landscape.

The contemporary definition of the term "epigenetics" presents significant challenges because of the recognition that certain epigenetic modifications are not inherited during cell division or transmitted through the germline. Rather than being restricted by a specific designation, these systems play

a critical role in controlling gene expression. Therefore, more detailed research is required. A previously presented perspective [16] is consistent with the idea that the distinctions between epigenetics and genetics have grown less apparent, which is a positive development. Genetic and genomic investigations have not been displaced by the current surge in epigenetic investigations, which encompasses the investigation of chromatin modification, DNA methylation, and correlated areas. Additionally, this has resulted in the investigation of new pathways that pertain to the long-standing inquiry into gene regulation during the development of more complex organisms, in addition to their potential applications in medicine. The prevailing belief that genomic information is the primary factor affecting heredity and advancement is not challenged by epigenetic research. Kuhn's concept should be taken into account when considering the aspiration for a paradigmatic transformation through the lens of epigenetics: scientific paradigms, which include genetics, help scientists acquire a more profound understanding of reality rather than completely substitute them [17].

The objective of this review is to provide an easily understood overview of epigenetics, which encompasses its meaning, categorization, and role in human illness. Furthermore, this study investigated the influence of environmental factors and lifestyle on epigenetics and focused on several epigenetic syndromes.

Understanding Epigenetic Modifications:

Histone modifications, non-coding RNA molecules, and DNA methylation (Figure 1) are examples of epigenetic modifications that control gene expression without altering the underlying genetic code [18, 19]. DNA methylation involves the addition of methyl groups to DNA, whereas histone modifications change the structure of chromatin, affecting gene accessibility and frequently leading to gene silencing.

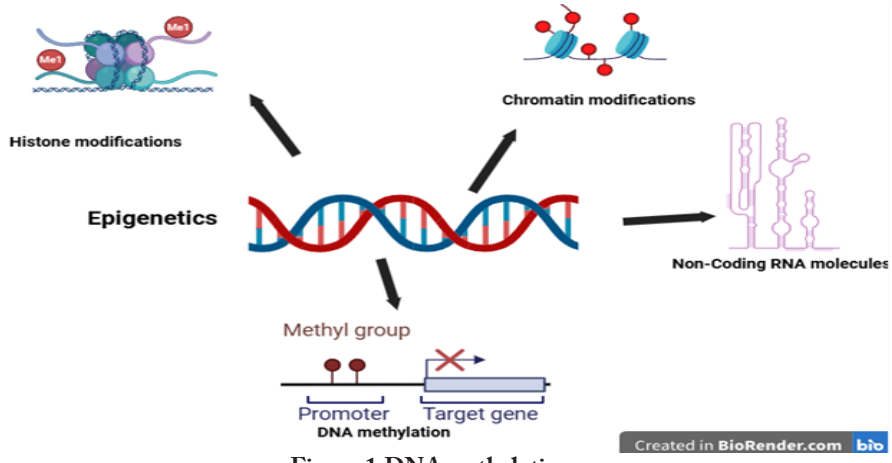


Figure 1:DNA methylation.

Figure 1. Histone modifications, non-coding RNA molecules, and DNA methylation are examples of epigenetic modifications that control gene expression without altering the underlying genetic code.

1. DNA methylation:

An essential epigenetic alteration discovered in DNA primarily involves the addition of a methyl group (Figure 2) to the cytosine base. This modification is predominantly observed in CpG dinucleotides, which are frequently identified in aggregates known as CpG islands. These islands are relatively uncommon, representing approximately one percent of the entire genome, and are distinguished by their extent of more than 200 bases, with a G + C composition exceeding 50%. They are present in mammalian DNA. It is important to mention that a significant percentage of human gene promoters are correlated with CpG islands and frequently lack methylation in healthy cells. However, tissue-specific methylation has been observed in a small proportion of CpG islands, approximately six percent, during the early stages of progression [1, 20, 21].

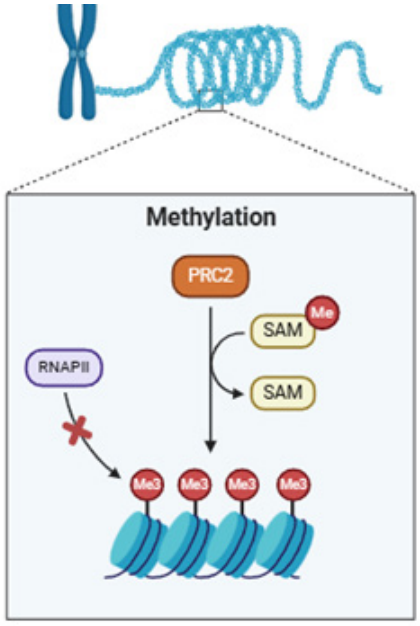


Figure 2:DNA methylation process.

Hypomethylation, which is the term used to describe the global reduction in methylation concentrations throughout the genome, has significant functional implications if it occurs within the coding regions of genes. Alterations in the composition or abundance of messenger RNA may result from this phenomenon. The DNA of lesions in patients with colon cancer shows extensive hypomethylation, which is one of the primary epigenetic anomalies identified [22].

Hypomethylation has the potential to influence the progression of malignancy via various pathways, such as the promotion of chromosomal instability and the reactivation of transposable elements. As a tumor advances, hypomethylation increases [23].

In contrast, the phenomenon of hypermethylation, which involves the addition of methyl groups to specific genes, is well-established. Transcriptional silencing of the gene and the consequent reduction in protein production have been correlated with the prevalence of hypermethylation in the CpG promoter region. The biophysical properties of DNA are altered by the protrusion of methyl groups into the major groove. These alterations can influence the binding affinity of DNA with specific proteins in either a positive or negative manner. The transcription process of converting DNA into RNA is impaired when RNA polymerase shows inaccurate binding to DNA. Hyper-methylation has also been associated with carcinogenesis[4,21,22].

2. Chromatin modifications:

Chromatin is composed of DNA and histones. Histones are crucial proteins that are abundant in arginine and lysine residues [24]. They are primarily located in the nuclei of eukaryotic cells. These entities act as cylindrical structures that allow for the coiling of DNA, thus serving as essential components of its structural organization. The cell nucleus contains a significant amount of DNA molecules in each chromosome. To achieve this, DNA undergoes a process in which it coils around histone protein complexes, thereby enhancing the compaction of the chromosome structure[25]. The histone repertoire comprises five different families: H1/H5 (linker histones), H2A, H2B, H3, and H4 (core histones). The nucleosome core consists of two H2A-H2B dimers and one H3-H4 tetramer. The fundamental reason for the compact coiling of DNA around histones is primarily the electrostatic attraction between the negatively charged phosphate backbone of DNA and positively charged histones [26].

Furthermore, histones play a crucial role in the regulation of gene expression[27]. Histones are susceptible to alterations that simulate the function of the closed and open indicators commonly found in commercial establishments[15,19]. Distinctive changes in histones around a gene, resembling accessibility markers, indicate that the gene is engaged and active in transcription[28]. Conversely, when these histones show particular changes, such as closed signs, it signifies that the gene is in a state of transcriptional repression or inactivity. Analysis of histones and their modifications has provided significant insights into the mechanisms underlying gene activation or suppression in many cellular contexts [29].

Histones undergo several modifications at different sites, with over 60 unique residues on histones displaying alterations that can be identified using specific antibodies or mass spectrometry methods. Nonetheless, this figure significantly underestimates the potential modifications that may occur in histones [30]. The complexity increases due to the existence of three unique forms of methylation at arginine or lysine residues. An extensive array of modifications has significant potential for various functional responses. It is essential to recognize that previously described modifications cannot occur simultaneously on a single histone [30].

One technique for modifying chromatin structure involves the introduction of chemical groups, including phosphate, acetyl, or multiple methyl groups, into histone residues. Additionally, it is feasible to covalently adhere tiny peptides, including ubiquitin and SUMO, to particular lysine residues [31].

3. Non-Coding RNA molecules:

The discovery of long non-coding RNA segments (lncRNA) is one of the most intriguing explorations in the era of modern genetics. Numerous studies have shown that specific lncRNAs may influence a variety of cellular functions through gain- and loss-of-function, as well as the genesis and development of diseases [32]. Furthermore, the regulation of genes is significantly influenced by widely recognized long non-coding RNAs, such as Xist [33]. It is interesting to observe that the preponderance of haplotype blocks associated with genetic conditions does not commonly contain genes for protein coding; rather, they commonly encode long non-coding RNAs. Unexpectedly, mutations at a number of long non-coding RNA loci are heritable in human disorders, indicating that these loci may play a role in Mendelian genetics [34]. In summary, these findings indicate that long non-coding RNAs are a frontier in the field of genetic regulation in the human genome.

The first step in gene production is the assembly of factors and RNA polymerase II (PII) at the promoters. This is followed by elongation, intron splicing, addition of a methyl guanine cap, and a polyadenine tail[35]. These biogenesis pathways are essentially shared by mRNAs and long non-coding RNAs. However, long non-coding RNAs and mRNAs demonstrate a wide range of outcomes, regardless of their shared characteristics [36]. lncRNAs are typically less prevalent than mRNAs and are commonly found in the nucleus, whereas mRNAs are abundant and rapidly disseminated throughout the cytoplasm. Consequently, it is necessary to consider that distinct regulatory mechanisms are involved in similar production routes [37].

Epigenetic Syndromes:

Often involving DNA methylation, histone alterations, and chromatin remodeling, epigenetic syndromes are illnesses brought on by aberrant gene expression without changes to the basic DNA sequence [38]. Among the most well-known disorders is Angelman syndrome, which results from the lack of maternal UBE3A gene expression on chromosome 15q11–q13, causing developmental delays, speech difficulties, and a pleasant disposition [39]. Caused by a lack of paternal gene expression in the same area, Prader-Willi syndrome presents with intellectual impairments, hypotonia, and obesity. With Beckwith-Wiedemann syndrome (BWS), overgrowth, macroglossia, and cancer risk result from dysregulation of imprinted genes on chromosome 11p15. On the other hand, growth retardation caused by hypomethylation at 11p15.5 or maternal uniparental disomy of chromosome 7 defines Silver-Russell syndrome (SRS). MECP2 gene mutations produce Rett syndrome, which causes stereotyped hand-wringing, motor and verbal retardation, and seizures. Associated with CGG repeat expansion and hypermethylation of the FMR1 gene, fragile X syndrome causes intellectual impairments and behavioral problems. Finally, DNMT3B mutations cause ICF syndrome—Immunodeficiency, Centromeric Instability, and Facial Anomalies—which results in intellectual impairments, facial anomalies, and immunodeficiency. These diseases show the important role epigenetic control plays in human development and the consequences of its disturbance [40-42].

1. Rett syndrome:

An early indicator of neurological disorders is the slow development of the head, which ultimately results in microcephaly by the second year of life. A German physician initially identified this phenomenon. Microcephaly is characterized by weak posture, weight loss, and overall growth delays as developmental progress diminishes. This is due to muscle hypotonia [43].

Scientists have, for the first time, identified a correlation between heritable differences in DNA methylation and gene expression [44]. They focused on the effects of this modification on gene function and determined that CpG dinucleotides are the primary sites of DNA methylation in mammalian genomes. CpG islands have been shown to be unmethylated in their natural state, with the exception of segments on the dormant X chromosome. Modifications in chromatin structure and gene silencing are correlated with CpG methylation [44-46].

Two pathways have been identified for DNA methylation-mediated gene repression. In the first mechanism, methylation of CpG sites in gene promoters prevents

the binding of transcription factors to particular sequences. In the second, more prevalent mode of repression, methyl-CpG binding proteins bind specifically to methylated CpGs and modify the structure of chromatin to prevent it from being accessible to the transcription machinery [47]. At the same time, the investigation of DNA methylation discovered repression mechanisms, including methyl-CpG binding proteins, and the Rett community was attempting to discover the underlying mechanisms of this perplexing situation [48]. The RTT study achieved significant progress in 1999 with the determination of its genetic foundation. The fields of neuroscience and epigenetics have been linked through the unexpected discovery that RTT is caused by mutations in the extensively expressed MECP2 gene. The X chromosome is also correlated with Rett syndrome, as a greater percentage of cases occur in women [49].

2. Angelman Syndrome:

The illness, now referred to as Angelman syndrome (AS), was initially defined by the English physician Angelman. Current estimates indicate that the disease affects 1 in 15,000 individuals. It is characterized by hyperactivity, seizures, verbal difficulties, and movement problems, and is commonly associated with autism spectrum disorders[49]. The first step in diagnosing the illness is to assess the DNA methylation status of chromosome 15q11–q13 [50]. When the methylation pattern exclusively demonstrates a paternal imprinting pattern, additional testing is required to confirm the diagnosis of Angelman syndrome. Investigations in human genetics have identified four molecular mechanisms causing Angelman syndrome, all involving defects in chromosome 15q11–q13 that alter the expression of the inherited UBE3A gene (3–5%) [51]. The size of the deletion may be determined by chromosomal microarray analysis, with larger deletions often associated with more severe symptoms. Angelman syndrome can also be attributed to a DNA imprinting fault if no chromosomal deletion is detected but abnormal DNA methylation patterns are evident [52]. Abnormal DNA methylation has been identified in 80–90 percent of Angelman syndrome cases. The remaining cases, which exhibit a typical pattern of DNA methylation, are attributed to UBE3A point mutations or minor intragenic rearrangements [25, 45].

Effect of Lifestyle and Environment:

Epigenetic profiles of complex organisms are subject to modifications. As organisms grow, a multitude of epigenetic modifications are necessary for regulating the regular growth and differentiation of cells. Despite the apparent stability of epigenetic modifications, they may be affected by various factors, including environmental,

pathological, and physiological conditions [31]. Epigenetic modifications are influenced by factors such as stress, diet, toxins, and socioeconomic status. Aberrant epigenetic alterations, including those caused by negative lifestyle habits, such as smoking or inadequate nutrition, have the potential to increase the probability of chronic illnesses, such as diabetes and cancer. In contrast, the dynamic nature of epigenetic regulation is illustrated by the potential for positive lifestyle adjustments, such as exercise and a healthy diet, to repair detrimental epigenetic changes [53].

Environmental influences on epigenetics are possible even when the fetus is in the uterus. The phenotypic progression of the progeny may be influenced by the environment in the womb. These changes may lead to long-term alterations in gene expression that persist throughout an individual's lifetime. These consistent gene regulations are affected by epigenetic mechanisms, as indicated by current investigations. The epigenetic profile of the progeny is influenced by factors such as uterine size and nutritional intake during embryo growth. Similarly, epigenetic modifications in the embryo are associated with maternal obesity [50, 53].

The epigenetic profile of the offspring has been analyzed with regard to maternal environmental factors, including the mother's diet. Agouti mice illustrate the consequences of specific epigenetic modifications on their offspring [54]. The agouti alleles regulate pigment production in each hair follicle. Agouti mice are thin and free of diabetes due to the expression of agouti proteins, which results from DNA methylation of the agouti promoter. Interestingly, methylation of the agouti gene in the progeny of pregnant female mice significantly increased when methyl donors were administered before and during gestation[55, 56].

It has recently been discovered that the long-term epigenetic traits of a mother's progeny in humans can be significantly influenced by the mother's diet. Methylation levels of the IGF2 gene were found to be lower in individuals who experienced prenatal hunger during the Dutch Hunger Winter than in their non-exposed siblings of the same sex, even 60 years later [57]. These epigenetic modifications occur during the periconceptional phase, demonstrating the significance of early mammalian development in the imprinting and maintenance of epigenetic patterns. The theory that the creation and preservation of epigenetic signatures are significantly influenced by early developmental stages is supported by previous investigations. This suggests that environmental factors encountered during early life can cause permanent alterations in an individual's epigenetic structure [58].

The impact of environmental exposure

on development and health is pervasive, and epigenetic modifications are believed to be significant mediators of these effects. In mammals, conditions before, during, and after conception can influence DNA methylation, non-coding RNA expression, and histone modifications[58]. The potential effects of these alterations on genomic transcription may, in turn, influence developmental trajectories. Research on intergenerational epigenetics has traditionally focused on maternal environmental exposure, but laboratory and epidemiological studies suggest that paternal environmental exposure is also significant [59]. Such exposures are linked to various outcomes in offspring, including behavioral, metabolic, and neurological characteristics, with effects potentially lasting across multiple generations. This demonstrates the influence of developmental plasticity and environmental factors on epigenetic inheritance[54,55].

Various studies have investigated the relationship between environmental exposure to chemicals and epigenetic changes, identifying numerous detrimental agents that may induce these alterations. While most research has focused on DNA methylation, recent investigations have explored how environmental contaminants affect histone modifications[60-64]. Animal models have demonstrated that these epigenetic mechanisms can be transmitted across generations [65]. However, it remains unclear whether this inheritance occurs in humans or if transgenerational epigenetic effects from environmental exposure are present in human populations.

Nonetheless, growing evidence indicates that epigenetics may serve as a valuable tool in developing biological markers to identify individuals at higher risk of disease or increased susceptibility to specific exposures. Achieving this requires laboratory methods that are highly sensitive, precise, and comprehensive in human studies. These methods enable the detection of epigenetic changes prior to disease onset. Research indicates that toxins can alter epigenetic marks following repeated exposures, with such marks found in tissues affected by associated illnesses [65]. Further prospective research is necessary to determine whether individuals exposed to these chemicals experience gradual alterations in their epigenetic profiles over time and whether these changes increase their disease risk.

Conclusions:

Without changing the underlying DNA sequence, epigenetic mechanisms—including DNA methylation, histone changes, and chromatin remodeling—have a vital function in controlling gene expression. The dynamic character of these changes emphasizes the great impact on gene con-

trol across development and across generations of environmental, physiological, and pathological elements. The data provided emphasizes the possibility of both good and negative environmental exposures—such as nutrition, pollutants, and stress—can cause epigenetic modifications that might last beyond the lifetime and, occasionally, be passed on to next generations.

Research on prenatal influences—such as the Dutch Hunger Winter and model animals like the agouti mouse—showcases the ongoing effect of early environmental factors on gene expression. Furthermore, the intergenerational consequences of mother and father exposures highlight the need of addressing both parental surroundings while assessing epigenetic factors on health and disease.

Reliable epigenetic biomarkers developed as research improves could offer important instruments for early illness identification, risk assessment, and focused treatments. Future studies should concentrate on determining the long-term consequences of environmental exposures on the epigenome and elucidating the human epigenetic inheritance mechanism. Knowing these mechanisms will help us to develop better plans for treating diseases having an epigenetic base, therefore strengthening our knowledge of gene-environment interactions in both health and illness.

Conflict of interest:

No conflict of interest.

Funding:

This study did not receive external funding.

Data Availability Statement:

This study did not generate any new data; however, the documents and literature that were utilized may be provided upon appropriate request.

Acknowledgments:

The authors acknowledge the financial support provided by the Deanship of Graduate Studies and Scientific Research at Jazan University, Saudi Arabia, under Project Number: GSSRD-24.

References:

1. Li Y. Modern epigenetics methods in biological research. Methods. 2021;187:104-13, doi:10.1016/j.ymeth.2020.06.022.
2. Peixoto P, Cartron PF, Serandour AA, Hervouet E. From 1957 to Nowadays: A Brief History of Epigenetics. Int J Mol Sci. 2020;21(20), doi:10.3390/ijms21207571.
3. Noble D. Conrad Waddington and the origin of epigenetics. J Exp Biol. 2015;218(Pt 6):816-8, doi:10.1242/jeb.120071.
4. Sánchez-Romero MA, Casadesús J. Waddington's Landscapes in the Bacterial World. Front Microbiol. 2021;12:685080, doi:10.3389/

fmicb.2021.685080.

5. De Vlaminck K, Van Hove H, Kancheva D, Scheyltjens I, Pombo Antunes AR, Bastos J, et al. Differential plasticity and fate of brain-resident and recruited macrophages during the onset and resolution of neuroinflammation. Immunity. 2022;55(11):2085-102 e9, doi:10.1016/j.immuni.2022.09.005.
6. Zhang H, Ji X, Li P, Liu C, Lou J, Wang Z, et al. Liquid-liquid phase separation in biology: mechanisms, physiological functions and human diseases. Sci China Life Sci. 2020;63(7):953-85, doi:10.1007/s11427-020-1702-x.
7. Romero IG, Ruvinsky I, Gilad Y. Comparative studies of gene expression and the evolution of gene regulation. Nat Rev Genet. 2012;13(7):505-16, doi:10.1038/nrg3229.
8. Recillas-Targa F. Cancer Epigenetics: An Overview. Arch Med Res. 2022;53(8):732-40, doi:10.1016/j.arcmed.2022.11.003.
9. Raju A, Siggia ED. A geometrical perspective on development. Dev Growth Differ. 2023;65(5):245-54, doi:10.1111/dgd.12855.
10. Raju A, Xue B, Leibler S. A theoretical perspective on Waddington's genetic assimilation experiments. Proc Natl Acad Sci U S A. 2023;120(51):e2309760120, doi:10.1073/pnas.2309760120.
11. Haig D. Commentary: The epidemiology of epigenetics. Int J Epidemiol. 2012;41(1):13-6, doi:10.1093/ije/dyr183.
12. Deans C, Maggert KA. What do you mean, "epigenetic"? Genetics. 2015;199(4):887-96, doi:10.1534/genetics.114.173492.
13. Russo VE, Martienssen RA, Riggs AD. Epigenetic mechanisms of gene regulation1996.
14. Bird A. Perceptions of epigenetics. Nature. 2007;447(7143):396-8, doi:10.1038/nature05913.
15. Felsenfeld G. The evolution of epigenetics. Perspect Biol Med. 2014;57(1):132-48, doi:10.1353/pbm.2014.0004.
16. Deichmann U. Epigenetics: The origins and evolution of a fashionable topic. Dev Biol. 2016;416(1):249-54, doi:10.1016/j.ydbio.2016.06.005.
17. Orman TF. Paradigm" as a central concept in Thomas Kuhn's thought. International Journal of Humanities and Social Science. 2016;6(10):47-52.
18. Qu Y, Dang S, Hou P. Gene methylation in gastric cancer. Clin Chim Acta. 2013;424:53-65, doi:10.1016/j.cca.2013.05.002.
19. Wang N, Ma T, Yu B. Targeting epigenetic regulators to overcome drug resistance in cancers. Signal Transduct

Target Ther. 2023;8(1):69, doi:10.1038/s41392-023-01341-7.

20. Mattei AL, Bailly N, Meissner A. DNA methylation: a historical perspective. Trends Genet. 2022;38(7):676-707, doi:10.1016/j.tig.2022.03.010.
21. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013;38(1):23-38, doi:10.1038/npp.2012.112.
22. Zafon C, Gil J, Pérez-González B, Jordà M. DNA methylation in thyroid cancer. Endocr Relat Cancer. 2019;26(7):R415-R39, doi:10.1530/erc-19-0093.
23. Mettler E, Fottner C, Bakhshandeh N, Trenkler A, Kuchen R, Weber MM. Quantitative Analysis of Plasma Cell-Free DNA and Its DNA Integrity and Hypomethylation Status as Biomarkers for Tumor Burden and Disease Progression in Patients with Metastatic Neuroendocrine Neoplasias. Cancers (Basel). 2022;14(4), doi:10.3390/cancers14041025.
24. Frade-Sosa B, Sanmartí R. Neutrophils, neutrophil extracellular traps, and rheumatoid arthritis: An updated review for clinicians. Reumatol Clin (Engl Ed). 2023;19(9):515-26, doi:10.1016/j.reumae.2023.10.002.
25. Hamilton JP. Epigenetics: principles and practice. Dig Dis. 2011;29(2):130-5, doi:10.1159/000323874.
26. Hergeth SP, Schneider R. The H1 linker histones: multifunctional proteins beyond the nucleosomal core particle. EMBO Rep. 2015;16(11):1439-53, doi:10.15252/embr.201540749.
27. Yang T, Peng J, Zhang Z, Chen Y, Liu Z, Jiang L, et al. Emerging therapeutic strategies targeting extracellular histones for critical and inflammatory diseases: an updated narrative review. Front Immunol. 2024;15:1438984, doi:10.3389/fimmu.2024.1438984.
28. van Leeuwen F, Gottschling DE. Genome-wide histone modifications: gaining specificity by preventing promiscuity. Current Opinion in Cell Biology. 2002;14(6):756-62, doi:https://doi.org/10.1016/S0955-0674(02)00393-9.
29. Meyn RE, Munshi A, Haymach JV, Milas L, Ang KK. Receptor signaling as a regulatory mechanism of DNA repair. Radiother Oncol. 2009;92(3):316-22, doi:10.1016/j.radonc.2009.06.031.
30. Gelato KA, Fischle W. Role of histone modifications in defining chromatin structure and function. Biol Chem. 2008;389(4):353-63, doi:10.1515/bc.2008.048.
31. Shogren-Knaak M, Ishii H, Sun JM, Pazin MJ, Davie JR, Peterson CL. Histone H4-K16 acetylation controls chromatin structure and protein inter-

actions. Science. 2006;311(5762):844-7, doi:10.1126/science.1124000.

32. Wu Y-L, Lin Z-J, Li C-C, Lin X, Shan S-K, Guo B, et al. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Signal Transduction and Targeted Therapy. 2023;8(1):98, doi:10.1038/s41392-023-01333-7.
33. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22(2):96-118, doi:10.1038/s41580-020-00315-9.
34. Rinn JL, Chang HY. Long Noncoding RNAs: Molecular Modalities to Organismal Functions. Annu Rev Biochem. 2020;89:283-308, doi:10.1146/annurev-biochem-062917-012708.
35. Rambout X, Dequiedt F, Maquat LE. Beyond Transcription: Roles of Transcription Factors in Pre-mRNA Splicing. Chem Rev. 2018;118(8):4339-64, doi:10.1021/acs.chemrev.7b00470.
36. Lanzillotti C, De Mattei M, Mazziotta C, Taraballi F, Rotondo JC, Tognon M, et al. Long Non-coding RNAs and MicroRNAs Interplay in Osteogenic Differentiation of Mesenchymal Stem Cells. Front Cell Dev Biol. 2021;9:646032, doi:10.3389/fcell.2021.646032.
37. Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs. Nature. 2012;482(7385):339-46, doi:10.1038/nature10887.
38. Sun L, Zhang H, Gao P. Metabolic reprogramming and epigenetic modifications on the path to cancer. Protein Cell. 2022;13(12):877-919, doi:10.1007/s13238-021-00846-7.
39. Maranga C, Fernandes TG, Bekman E, da Rocha ST. Angelman syndrome: a journey through the brain. FEBS J. 2020;287(11):2154-75, doi:10.1111/febs.15258.
40. Gonzalez-Lugo JD, Chakraborty S, Verma A, Shastri A. The evolution of epigenetic therapy in myelodysplastic syndromes and acute myeloid leukemia. Semin Hematol. 2021;58(1):56-65, doi:10.1053/j.seminhematol.2020.12.003.
41. Lui JC, Baron J. Epigenetic Causes of Overgrowth Syndromes. J Clin Endocrinol Metab. 2024;109(2):312-20, doi:10.1210/clinem/dgad420.
42. Sélénou C, Brioude F, Giabicani E, Sobrier ML, Netchine I. IGF2: Development, Genetic and Epigenetic Abnormalities. Cells. 2022;11(12), doi:10.3390/cells11121886.
43. Chahrour M, Zoghbi HY. The story of Rett syndrome: from clinic to neurobiology. Neuron. 2007;56(3):422-37, doi:10.1016/j.neuron.2007.10.001.

44. Vilvarajan S, McDonald M, Douglas L, Newham J, Kirkland R, Tzannes G, et al. Multidisciplinary Management of Rett Syndrome: Twenty Years' Experience. Genes (Basel). 2023;14(8), doi:10.3390/genes14081607.
45. Gold WA, Percy AK, Neul JL, Cobb SR, Pozzo-Miller L, Issar JK, et al. Rett syndrome. Nat Rev Dis Primers. 2024;10(1):84, doi:10.1038/s41572-024-00568-0.
46. Kyle SM, Vashi N, Justice MJ. Rett syndrome: a neurological disorder with metabolic components. Open Biol. 2018;8(2), doi:10.1098/rsob.170216.
47. Medvedeva YA, Khamis AM, Kulakovskiy IV, Ba-Alawi W, Bhuyan MSI, Kawaji H, et al. Effects of cytosine methylation on transcription factor binding sites. BMC Genomics. 2014;15(1):119, doi:10.1186/1471-2164-15-119.
48. Nan X, Bird A. The biological functions of the methyl-CpG-binding protein MeCP2 and its implication in Rett syndrome. Brain Dev. 2001;23 Suppl 1:S32-7, doi:10.1016/s0387-7604(01)00333-3.
49. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet. 1999;23(2):185-8, doi:10.1038/13810.
50. Butler MG, Miller JL, Forster JL. Prader-Willi Syndrome - Clinical Genetics, Diagnosis and Treatment Approaches: An Update. Curr Pediatr Rev. 2019;15(4):207-44, doi:10.2174/1573396315666190716120925.
51. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. Genetics in Medicine. 2010;12(7):385-95, doi:https://doi.org/10.1097/GIM.0b013e3181def138.
52. Kalsner L, Chamberlain SJ. Prader-Willi, Angelman, and 15q11-q13 Duplication Syndromes. Pediatr Clin North Am. 2015;62(3):587-606, doi:10.1016/j.pcl.2015.03.004.
53. Waterland RA. Assessing the effects of high methionine intake on DNA methylation. J Nutr. 2006;136(6 Suppl):1706S-10S, doi:10.1093/jn/136.6.1706S.
54. Morgan HD, Sutherland HG, Martin DI, Whitelaw E. Epigenetic inheritance at the agouti locus in the mouse. Nat Genet. 1999;23(3):314-8, doi:10.1038/15490.
55. Wolff GL, Kodell RL, Moore SR, Cooney CA. Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. FASEB J. 1998;12(11):949-57.
56. Zeisel S. Choline, Other Methyl-Do-

nors and Epigenetics. Nutrients. 2017;9(5), doi:10.3390/nu9050445.

57. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Hum Mol Genet. 2009;18(21):4046-53, doi:10.1093/hmg/ddp353.
58. Gopinathan G, Diekwisch TGH. Epigenetics and Early Development. J Dev Biol. 2022;10(2), doi:10.3390/jdb10020026.
59. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol. 2011;31(3):363-73, doi:10.1016/j.reprotox.2010.12.055.
60. Genchi G, Sinicropi MS, Lauria G, Carocci A, Catalano A. The Effects of Cadmium Toxicity. Int J Environ Res Public Health. 2020;17(11), doi:10.3390/ijerph17113782.
61. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015;36(6):E1-E150, doi:10.1210/er.2015-1010.
62. Kim S, Thapar I, Brooks BW. Epigenetic changes by per- and polyfluoroalkyl substances (PFAS). Environ Pollut. 2021;279:116929, doi:10.1016/j.envpol.2021.116929.
63. Pan Z, Gong T, Liang P. Heavy Metal Exposure and Cardiovascular Disease. Circ Res. 2024;134(9):1160-78, doi:10.1161/circresaha.123.323617.
64. Puvvula J, Braun JM, DeFranco EA, Ho SM, Leung YK, Huang S, et al. Gestational exposure to environmental chemicals and epigenetic alterations in the placenta and cord blood mononuclear cells. Epigenetics Commun. 2024;4(1):4, doi:10.1186/s43682-024-00027-7.
65. Sales VM, Ferguson-Smith AC, Patti ME. Epigenetic Mechanisms of Transmission of Metabolic Disease across Generations. Cell Metab. 2017;25(3):559-71, doi:10.1016/j.cmet.2017.02.016.