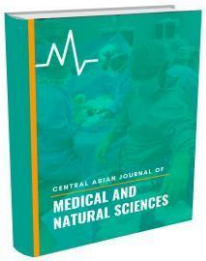

CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.centralasianstudies.org/index.php/CAJMNS
Volume: 07 Issue: 02 | April 2026 ISSN: 2660-4159

Article

Pathophysiological Epigenetic Mechanisms in the Development of Chronic Diseases

Bizhanova D.K[1], Sharipova P.A[2]

1. 3rd-year student, Faculty of Medicine, Tashkent State Medical University, Tashkent
2. PhD (Candidate of Medical Sciences), Associate Professor of the Department of Physiology and Pathology, Tashkent State Medical University, Tashkent

* Correspondence: bizhanova@gmail.com[1], sharipova@gmail.com[2]

Abstract: Epigenetic mechanisms, which are processes that regulate the expression of genes without changing the DNA sequence. These mechanisms are critical for adaptation of cells to various environmental cues and the ability of cells to sustain transcriptional activity. Recent research indicates that epigenetic changes are associated with the initiation and progression of various chronic diseases as cardiovascular disease, metabolic syndrome, type 2 diabetes mellitus, autoimmune diseases, neurodegenerative diseases, and chronic inflammatory diseases. This influence modifies cellular signalling pathways, phenotypic plasticity and immune regulation as well as metabolic pathways. While there has been groundbreaking progress in understanding genetic determinants of common chronic diseases, classical genetic approaches separate from the epigenome cannot explain all the variance in disease expression and disease processing among those with the same genotype. Such features underline the importance of probing epigenetic regulation and implication of environmental forces including nutrition, stress, lifestyle, and microbiota. We contribute to this knowledge gap by providing a systematic review regarding major epigenetic mechanisms and their role in the pathogenesis of chronic disease, including their potential application as diagnostic markers and therapeutic targets. Epigenetic processes (including DNA methylation, histone modification, and microRNA regulation) and resultant persistent transcriptional changes related to these disturbances are able to affect the molecular pathways in inflammation, metabolic imbalance, immune dysfunction, and cellular phenotypic alteration associated with chronic diseases. This research highlights how the epigenome serves as a unifying linking pin between genetic susceptibility, environmental exposure, metabolic status and immune activity in chronic disease pathogenesis. Knowledge of epigenetic regulation offers prospects for early diagnostic markers, risk stratification and the design of personalised therapeutic strategies with the goals of correcting stable regulatory disturbances that underlie chronic pathology.

Keywords: epigenetics, chronic diseases, DNA methylation, histone modifications, microRNA, inflammation, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders

Citation: D. K Bizhanova., P. A Sharipova. Pathophysiological Epigenetic Mechanisms in the Development of Chronic Diseases. Central Asian Journal of Medical and Natural Science 2026, 7(2), 407-417.

Received: 10th Dec 2025
Revised: 21th Jan 2026
Accepted: 20th Feb 2026
Published: 17th Mar 2026

Introduction

Chronic diseases are the leading cause of mortality and deterioration in quality of life worldwide. Understanding classical genetic factors is important; however, it does not fully explain differences in the manifestation and progression of chronic diseases in individuals with identical genotypes.

Epigenetics studies mechanisms of gene regulation that are not associated with changes in the DNA sequence. These mechanisms integrate the influence of environmental factors, nutrition, lifestyle, stress, and the body's microbiota on cellular condition and disease development [1][2].

The study of epigenetic alterations is critically important for understanding how diseases become chronic, as well as for clarifying mechanisms of cellular phenotypic plasticity, age-related chronic inflammatory changes, and transgenerational transmission of epigenetic modifications. All of this is significant for the development of new diagnostic markers and therapeutic targets.

Such an approach opens opportunities for creating individualized strategies for the prevention and treatment of chronic diseases.

The Concept of Epigenetics and Its Key Mechanisms

Epigenetics encompasses a set of processes that influence gene activity without altering the DNA sequence. The main mechanisms of epigenetic regulation include:

- **DNA methylation**, particularly in specific regions (CpG islands), which suppresses transcription [3].
- **Histone modifications** (acetylation, methylation, phosphorylation), which affect chromatin packaging and the accessibility of transcription factors [4].
- **Non-coding RNAs** (microRNAs and long non-coding RNAs), which regulate mRNA stability and post-transcriptional regulation of proteins [5].

These processes are dynamic and reversible. This ensures adaptation of cellular transcriptional activity to environmental changes without alterations in DNA sequence [6].

Methodology

This study methodology is based on a broad analytical framework to assess the contribution of epigenetic mechanisms to chronic disease from development to manifestation. This investigation is based upon a systematic review and synthesis of modern scientific literature relating to epigenetic regulation and its pathophysiological consequences. We searched the literature for articles in international biomedical journals, basic studies in molecular biology and clinical studies for chronic disease imprinting major epigenetic mechanisms (DNA methylation, histone modification, and non-coding RNA [ncRNA] regulation). The methodological framework combines comparative, conceptual, and theoretical approaches to illuminating associations between epigenetic changes and chronic disease processes including cardiovascular disease, metabolic syndrome, autoimmune disease, neurodegenerative disease, and disease of chronic inflammation. Particular stress was given on mechanisms of action by which environmental factors, including nutrition, smoking, stress and microbiota composition, regulate epigenetics and combine to affect gene expression without changes in DNA sequence. Finally, the review assesses novel data on epigenetic signatures as biomarkers and the promise of reversible epigenetic alterations as therapeutic targets. Other analyzed topics comprise the processes of metabolic and epigenetic memory, transgenerational transmission and age-dependant epigenomic alterations that underpin the development and sustainability of chronic diseases. The methodology integrates molecular, clinical, and environmental perspectives and permits an integrative interpretation of epigenetic regulation as one of the key mediators of genetic susceptibility, environmental exposure, and disease outcome. This approach enables to discern the central epigenetic pathways underlying chronic disease pathogenesis and lays the scientific foundation for subsequent studies investigating biomarker development and personalized epigenetic treatments. Thus, the methodological approach combines literature-based evidence synthesis with

interdisciplinary fundamental research to enable a cohesive interpretation of epigenetic contributions to chronic disease mechanisms.

Findings and Discussion

DNA Methylation and the Pathophysiology of Chronic Diseases

Methylation of cytosine in CpG islands is generally associated with decreased gene activity. Pathological alterations in methylation are frequently observed in chronic diseases:

- In metabolic disorders, changes in methylation of genes controlling insulin production and lipid metabolism are associated with an increased risk of developing type 2 diabetes mellitus and obesity [7].
- During aging, global changes in DNA methylation levels are observed, including regions of decreased and increased methylation, which are associated with age-related diseases [8].
- Methylation of specific regions (CpG sites), forming the basis of so-called epigenetic clocks, is considered a potential marker of biological age and the risk of age-associated diseases [9].

Histone Modifications and Chronic Inflammation

Histone modifications influence chromatin structure, which directly affects gene accessibility:

- Changes in histone acetylation and methylation have been identified in chronic inflammatory processes such as cardiovascular diseases and rheumatoid disorders.
- Epigenetic alterations in vascular smooth muscle cells may contribute to phenotypic switching, enhancing inflammation and promoting the progression of vascular remodeling and atherosclerosis [10].
- Non-coding RNAs participate in the regulation of enzymes that modify histones and also regulate the expression of genes associated with inflammation.

Thus, histone modifications function as a connecting link between environmental signals and the transcriptional response of the cell.

The Role of microRNAs and Non-Coding RNAs in Chronic Diseases

MicroRNAs are short non-coding RNAs that regulate mRNA stability and translational activity. Alterations in their function are observed in various chronic diseases:

- In metabolic syndrome and type 2 diabetes mellitus, microRNAs influence insulin signaling pathways and inflammation [11].
- In cardiovascular diseases, numerous microRNAs regulate vascular cell proliferation and migration, as well as myocardial function [12].
- In neurodegenerative diseases, alterations in microRNAs associated with apoptosis and neuroinflammation are observed [13].

MicroRNAs are considered promising targets for therapeutic intervention and biomarkers of disease progression.

Interaction Between Epigenetics and Environmental Factors

Environmental factors (nutrition, stress, tobacco smoking) can induce epigenetic alterations that influence the risk of developing chronic diseases:

- Smoking causes changes in DNA methylation that persist for a long time and increase the risk of chronic diseases of the respiratory and cardiovascular systems [14].

- Nutrition and methylation status may interact, thereby influencing metabolism and energy balance.

Epigenetic regulation plays an important role in mediating the influence of the external environment on the phenotypic manifestations of diseases.

Epigenetic Markers and Diagnostics

Epigenetic alterations are used as potential markers for diagnosis and prognosis:

- Changes in DNA methylation levels may indicate early stages of diseases such as type 2 diabetes mellitus and cardiovascular diseases.
- Circulating microRNA profiles reflect the risk of development and severity of chronic diseases.
- Epigenetic markers are applied for patient stratification into clinical groups and for predicting therapeutic response [15].

Thus, epigenetics offers new tools for an individualized approach to treatment.

Prospects for Therapeutic Intervention

Since epigenetic modifications are reversible, they represent promising targets for directed therapy:

- Histone deacetylase inhibitors and DNA methyltransferase inhibitors are already used in the treatment of certain oncological diseases and are considered promising agents for the therapy of chronic inflammatory and metabolic disorders [16].
- Epigenetic therapy may correct impaired gene function without inducing permanent genetic alterations.
- Personalized epigenetic approaches (epigenome modification, specific micro RNA-based therapies are being actively investigated.

Epigenetic "Memory" and the Phenomenon of Metabolic Memory

One of the significant pathophysiological phenomena in chronic diseases is the so-called metabolic memory, in which pathological effects of hyperglycemia or inflammation persist even after normalization of metabolic parameters. This phenomenon has been particularly studied in type 2 diabetes mellitus and its vascular complications.

The mechanism of metabolic memory is обусловлен by stable epigenetic alterations in endothelial cells, vascular smooth muscle cells, and monocytes. Hyperglycemia induces oxidative stress, activation of nuclear factor κB (NF-κB), and changes in methylation of promoters of proinflammatory cytokine genes [17]. Simultaneously, alterations occur in acetylation of histones H3 and H4 in regions of genes regulating the inflammatory response. These modifications may persist even after normalization of blood glucose levels, which explains the progression of microvascular complications.

An important aspect is that epigenetic memory is formed due to stable changes in chromatin structure that закрепляют pathological gene activity within the cell. Similar mechanisms have been described in atherosclerosis, where macrophages exposed to atherogenic lipids acquire a trained innate immunity phenotype with enhanced cytokine production [18].

Therefore, epigenetic memory represents a fundamental pathophysiological mechanism underlying the transition of a pathological process into a chronic form.

Epigenetics and Chronic Systemic Inflammation

Chronic diseases are closely associated with the phenomenon of low-grade systemic inflammation. This phenomenon is linked to aging. Epigenetic changes play a central role in the formation of this state [19].

With aging, the following occur:

- global DNA hypomethylation;
- local hypermethylation of suppressor gene promoters;
- alteration of histone modification profiles;
- microRNA dysregulation.

These processes lead to enhanced expression of proinflammatory genes (IL-6, TNF-α), decreased antioxidant defense, and impaired reparative processes. As a result, a stable proinflammatory phenotype develops, increasing the risk of cardiovascular, metabolic, and neurodegenerative diseases.

Epigenetic clocks based on the analysis of methylation of specific CpG sites demonstrate that accelerated epigenetic aging correlates with increased mortality risk and chronic diseases [20]. These findings emphasize the clinical significance of epigenetic markers.

Epigenetic Mechanisms in Autoimmune Chronic Diseases

In the pathogenesis of autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, bronchial asthma), disruption of epigenetic control in immune cells plays a crucial role.

DNA hypomethylation in T lymphocytes leads to excessive expression of genes activating the immune response [21]. Altered histone acetylation in cytokine genes enhances the T helper 17 (Th17) response and IL-17 production, thereby promoting chronic inflammation.

Specific microRNAs regulating T-cell differentiation and B-cell activity have also been identified. Dysregulation of these microRNAs contributes to loss of immune tolerance and maintenance of chronic autoimmune inflammation [22].

These data confirm that epigenetic alterations may represent not only a consequence but also an initiating cause of autoimmune pathology.

Epigenetics of Neurodegenerative Diseases

Neurodegenerative diseases are chronic progressive disorders of diverse etiology. Epigenetic changes play a significant role in regulating genes associated with neuroinflammation, apoptosis, and synaptic plasticity.

Altered methylation of genes encoding proteins of the amyloid cascade, as well as disturbances in histone acetylation, affect the production of factors essential for neuronal survival. Imbalance in histone deacetylase activity leads to reduced expression of genes required for neuroplasticity.

Experimental models demonstrate that histone deacetylase inhibitors may partially restore cognitive functions. This confirms the role of epigenetic regulation in the development of neurodegenerative diseases.

Epigenetic Changes in Chronic Lung Diseases

Chronic obstructive pulmonary disease (COPD) and bronchial asthma are also characterized by epigenetic disturbances.

Smoking induces DNA methylation changes in genes involved in inflammation and oxidative stress, contributing to COPD development. In patients with asthma, alterations in microRNAs regulating the expression of proinflammatory cytokines and immune cell receptors have been identified [23].

These findings confirm the role of epigenetic mechanisms as mediators between environmental exposure and the development of chronic respiratory pathology.

Epigenetic Interactions with the Microbiota

Recent studies demonstrate that intestinal bacteria can influence host epigenetic mechanisms through metabolites.

Butyrate acts as a histone deacetylase inhibitor. This promotes changes in histone acetylation and regulation of inflammatory genes. Alterations in microbiota composition may lead to changes in the epigenetic profile of intestinal epithelial and immune cells, contributing to the development of metabolic syndrome and inflammatory bowel diseases.

Thus, the microbiota represents an important factor influencing the epigenetic state of the organism.

Interaction of Epigenetics with Environmental Factors

Environmental factors (nutrition, stress, smoking) can induce epigenetic changes that influence the risk of developing chronic diseases:

- Smoking induces methylation changes that persist for a long time and increase the risk of chronic diseases of the respiratory and cardiovascular systems [24].
- Nutrition and methylation status may interact, thereby influencing metabolism and energy balance.

Epigenetic regulation plays an important role in mediating the effects of the external environment on phenotypic manifestations of disease.

Epigenetic Markers and Diagnostics

Epigenetic changes are used as potential markers for diagnosis and prognosis:

- Alterations in DNA methylation levels may indicate early stages of diseases such as type 2 diabetes mellitus and cardiovascular diseases.
- MicroRNA profiles in blood reflect the risk and severity of chronic diseases.
- Epigenetic markers are applied to stratify patients into clinical groups and predict therapeutic response.

Thus, epigenetics offers new tools for an individualized approach to treatment.

Prospects for Therapeutic Intervention

Because epigenetic changes are reversible, they are of interest as targets for directed therapy:

- Histone deacetylase inhibitors and DNA methyltransferase inhibitors are already used in the treatment of certain oncological diseases and are being considered as promising therapeutic agents for chronic inflammatory and metabolic disorders [25].
- Epigenetic therapy may correct dysregulated gene function without permanent genetic alterations.
- Personalized epigenetic approaches (epigenome editing, specific microRNA-based therapies) are actively being investigated [26].

Epigenetic "Memory" and the Phenomenon of Metabolic Memory

One of the significant pathophysiological phenomena in chronic diseases is the so-called metabolic memory, in which the pathological effects of hyperglycemia or inflammation persist even after normalization of metabolic parameters. This phenomenon has been particularly well studied in type 2 diabetes mellitus and its vascular complications.

The mechanism of metabolic memory is обусловлен persistent epigenetic alterations in endothelial cells, vascular smooth muscle cells, and monocytes. Hyperglycemia induces oxidative stress, activation of nuclear factor κB (NF-κB), and changes in promoter methylation of proinflammatory cytokine genes [27].

Simultaneously, alterations in acetylation of histones H3 and H4 occur in genomic regions regulating inflammatory responses. These changes may persist even after normalization of blood glucose levels, explaining the progression of microvascular complications [28].

An important aspect is that epigenetic memory is formed through stable changes in chromatin structure that consolidate pathological gene activity within the cell. Similar mechanisms have been described in atherosclerosis, where macrophages exposed to atherogenic lipids acquire a trained innate immunity phenotype with enhanced cytokine production.

Therefore, epigenetic memory represents a fundamental pathophysiological mechanism underlying the transition of a pathological process into a chronic form.

Epigenetics and Chronic Systemic Inflammation

Chronic diseases are closely associated with the phenomenon of low-grade systemic inflammation, which is linked to aging. Epigenetic alterations play a central role in the development of this condition.

With aging, the following occur:

- Global DNA hypomethylation;
- Local hypermethylation of tumor suppressor gene promoters;
- Alterations in histone modification profiles;
- Dysregulation of microRNAs.

These processes lead to increased expression of proinflammatory genes (IL-6, TNF-α), decreased antioxidant defense, and impaired reparative processes. As a result, a stable proinflammatory phenotype develops, increasing the risk of cardiovascular, metabolic, and neurodegenerative diseases.

Epigenetic clocks, based on methylation analysis of specific CpG sites, demonstrate that accelerated epigenetic aging correlates with increased mortality risk and chronic diseases. These findings underscore the clinical significance of epigenetic markers.

Epigenetic Mechanisms in Autoimmune Chronic Diseases

In the pathogenesis of autoimmune diseases such as Systemic lupus erythematosus, Rheumatoid arthritis, and Asthma, disruption of epigenetic control in immune cells plays a crucial role.

DNA hypomethylation in T lymphocytes leads to excessive expression of genes activating immune responses. Changes in histone acetylation in cytokine genes enhance T helper 17 (Th17) responses and IL-17 production, contributing to chronic inflammation.

Specific microRNAs regulating T-cell differentiation and B-cell activity have also been identified. Dysregulation of these microRNAs contributes to loss of immune tolerance and maintenance of chronic autoimmune inflammation.

These data confirm that epigenetic alterations may represent not only a consequence but also an initiating cause of autoimmune pathology.

Epigenetics of Neurodegenerative Diseases

Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are chronic progressive pathologies of various etiologies. Epigenetic changes play a significant role in regulating genes associated with neuroinflammation, apoptosis, and synaptic plasticity.

Alterations in methylation of genes encoding proteins of the amyloid cascade, as well as disruptions in histone acetylation, affect the production of factors necessary for neuronal survival. Imbalance in histone deacetylase activity leads to reduced expression of genes essential for neuroplasticity.

Experimental models show that histone deacetylase inhibitors may partially restore cognitive functions, confirming the role of epigenetic regulation in the development of neurodegenerative diseases.

Epigenetic Changes in Chronic Lung Diseases

Chronic obstructive pulmonary disease (COPD) and asthma are also characterized by epigenetic disturbances.

Smoking induces DNA methylation changes in genes related to inflammation and oxidative stress, contributing to the development of COPD [4]. In patients with asthma, alterations in microRNAs regulating proinflammatory cytokine expression and immune cell receptors have been identified.

These data confirm the role of epigenetic mechanisms as mediators between environmental exposures and the development of chronic airway pathology.

Epigenetic Interactions with the Microbiota

Recent studies demonstrate that gut bacteria can influence host epigenetic mechanisms through metabolites.

Butyrate acts as a histone deacetylase inhibitor, promoting changes in histone acetylation and regulation of inflammatory genes. Alterations in microbiota composition may lead to changes in the epigenetic profile of intestinal epithelium and immune cells, contributing to the development of metabolic syndrome and inflammatory bowel diseases.

Thus, the microbiota represents an important factor modifying the organism's epigenetic state.

Transgenerational Epigenetic Inheritance

Particular attention should be given to the phenomenon of transmission of epigenetic alterations between generations. Exposure to environmental factors during the intrauterine period may lead to persistent DNA methylation changes in offspring, increasing the risk of chronic diseases in adulthood.

These data support the "Developmental Origins of Health and Disease" concept and emphasize the role of epigenetics in programming chronic pathology.

Limitations and Future Research Directions

Despite significant progress, limitations remain:

- Tissue and cellular heterogeneity;
- Complexity of interpreting causal relationships;
- Influence of multiple environmental factors;
- Differences in methods for assessing methylation and chromatin structure alterations.

Future research is directed toward:

- Integrated analysis of epigenomic, transcriptomic, and proteomic data;
- Development of epigenetic biomarkers for early diagnosis;
- Creation of therapeutic agents targeting epigenetic mechanisms.

Epigenetic Regulation of Cellular Differentiation and Phenotypic Plasticity in Chronic Diseases

A key pathophysiological mechanism in chronic disease development is disruption of normal cellular differentiation and acquisition of pathological phenotypic plasticity. Epigenetic mechanisms play a central role in stabilizing cellular phenotype by determining gene accessibility for transcription and maintaining tissue specificity.

In chronic diseases, pathological epigenomic alterations lead to:

- Phenotypic switching of vascular smooth muscle cells in atherosclerosis;
- Transformation of fibroblasts into myofibroblasts in chronic fibrosis;
- Metabolic alterations in hepatocytes in non-alcoholic fatty liver disease;
- Persistent activation of macrophages and monocytes in chronic inflammation.

For example, in atherosclerosis, vascular smooth muscle cells lose contractile function and acquire proliferative and proinflammatory capacities. This is accompanied by changes in DNA and histone methylation in genes regulating cytoskeleton and synthetic activity. These epigenetic rearrangements consolidate the pathological state even when external conditions change.

Similarly, in chronic liver and lung fibrosis, epigenetic activation of collagen and growth factor genes sustains fibrotic progression. This is based on imbalance between histone acetyltransferase and histone deacetylase activity [29].

Thus, epigenetics provides the molecular foundation of cellular phenotypic plasticity, a central link in chronic disease development.

Epigenetic Instability and Oxidative Stress

Chronic diseases are accompanied by enhanced oxidative stress, which not only damages macromolecules but also affects epigenetic regulation.

Reactive oxygen species (ROS):

- Alter DNA methyltransferase activity;
- Influence demethylation enzymes;
- Modify histone structure;
- Alter microRNA expression.

DNA methylation is a key mechanism regulating gene expression and maintaining cellular specialization. Oxidative stress may cause both hypo- and hypermethylation of genomic regions, disrupting the balance between antioxidant defense gene expression and proinflammatory mediators. In type 2 diabetes mellitus and cardiovascular diseases, such changes contribute to endothelial dysfunction and progression of vascular complications [30].

A particularly important aspect is the link between mitochondrial dysfunction and epigenetic mechanisms. Disturbed energy metabolism affects concentrations of metabolites (S-adenosylmethionine, acetyl-CoA, NAD^+) required for epigenetic enzyme activity. Thus, cellular metabolic state directly regulates its epigenetic profile.

These data indicate that metabolism and epigenetics are tightly interconnected, and metabolic disturbances become consolidated at the chromatin level.

The Epigenome as a Linking Element of Systemic Pathology

Modern evidence supports viewing the epigenome not as an isolated mechanism, but as a central integrative link uniting:

- Genetic predisposition;
- Environmental exposure;
- Metabolic state;
- Immune activity;
- Age-related changes.

Epigenetic regulation ensures long-term cellular adaptation to chronic stress exposure. However, with prolonged and intense exposure, stable pathological gene activity is established, maintaining disease even when external causes act minimally.

Therefore, chronic disease can reasonably be regarded as the result of prolonged epigenetic reprogramming of cellular regulatory mechanisms.

Conclusion

Contemporary data convincingly demonstrate that epigenetic mechanisms occupy a central position in the pathophysiology of chronic diseases. DNA methylation, histone modifications, chromatin remodeling, and regulation by non-coding RNAs form the molecular basis of persistent restructuring of transcriptional networks under the influence of metabolic, inflammatory, and environmental factors. Chronic pathology develops not only due to ongoing damaging exposure but also as a result of consolidation of pathological programs at the chromatin level. Metabolic memory, trained immunity, and inflammatory aging illustrate mechanisms by which short-term stimuli are transformed into long-term alterations of cellular phenotype. The epigenome serves as an integrative platform uniting genetic predisposition, metabolic state, immune activation, and environmental factors. This explains interindividual variability in disease course, differences in therapeutic response, and persistence of complications even after correction of traditional risk factors. Clinical application of epigenetic approaches is in active development. At present, the most realistic direction is the use of epigenetic markers for risk stratification and prognosis, whereas targeted epigenetic therapy requires further validation and safety evaluation. Thus, understanding epigenetic mechanisms deepens the pathophysiological model of chronic diseases and opens prospects for personalized prevention and treatment based on correction of stable regulatory disturbances.

REFERENCES

[1] E. Stylianou, "Epigenetics of chronic inflammatory diseases," *J. Inflamm. Res.*, vol. 11, pp. 1–14, 2018.

[2] S. Alipour *et al.*, "Epigenetic alterations in chronic disease focusing on Behçet's disease: Review," *Biomed. Pharmacother.*, vol. 91, pp. 526–533, 2017.

[3] F. Ramzan, M. H. Vickers, and R. F. Mithen, "Epigenetics, microRNA and Metabolic Syndrome: A Comprehensive Review," *Int. J. Mol. Sci.*, vol. 22, no. 9, p. 5047, 2021.

[4] B. R. Joubert *et al.*, "DNA methylation in newborns and maternal smoking in pregnancy," *Am. J. Hum. Genet.*, vol. 98, no. 4, pp. 680–696, 2016.

[5] L. Zhang, Q. Lu, and C. Chang, "Epigenetics in Health and Disease," in *Advances in Experimental Medicine and Biology*, vol. 1253, pp. 3–55, 2020.

[6] E. M. Small and E. N. Olson, "Pervasive roles of microRNAs in cardiovascular biology," *Nature*, vol. 469, pp. 336–342, 2011.

[7] R. Jaenisch and A. Bird, "Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals," *Nat. Genet.*, vol. 33, pp. 245–254, 2003.

[8] J. Lambert and H. F. Jørgensen, "Epigenetic regulation of vascular smooth muscle cell phenotypes in atherosclerosis," *Circ. Res.*, vol. 117, pp. 1100–1112, 2015.

[9] P. A. Jones, "Functions of DNA methylation: islands, start sites, gene bodies and beyond," *Nat. Rev. Genet.*, vol. 13, pp. 484–492, 2012.

[10] N. Acevedo *et al.*, "Perinatal and early-life nutrition, epigenetics, and allergy," *Nutrients*, vol. 13, no. 3, p. 724, 2021.

[11] P. Ntontsi *et al.*, "Genetics and epigenetics in asthma," *Int. J. Mol. Sci.*, vol. 22, no. 5, p. 2412, 2021.

[12] A. Bird, "DNA methylation patterns and epigenetic memory," *Genes Dev.*, vol. 16, pp. 6–21, 2002.

[13] C. D. Allis and T. Jenuwein, "The molecular hallmarks of epigenetic control," *Nat. Rev. Genet.*, vol. 17, pp. 487–500, 2016.

[14] A. P. Feinberg, "The key role of epigenetics in human disease prevention and mitigation," *N. Engl. J. Med.*, vol. 379, pp. 400–401, 2018.

[15] P. W. Laird, "Principles and challenges of genome-wide DNA methylation analysis," *Nat. Rev. Genet.*, vol. 11, pp. 191–203, 2010.

[16] A. Portela and M. Esteller, "Epigenetic modifications and human disease," *Nat. Biotechnol.*, vol. 28, pp. 1057–1068, 2010.

[17] C. López-Otín *et al.*, "The hallmarks of aging," *Cell*, vol. 153, pp. 1194–1217, 2013.

[18] K. D. Robertson, "DNA methylation and human disease," *Nat. Rev. Genet.*, vol. 6, pp. 597–610, 2005.

[19] S. Horvath, "DNA methylation age of human tissues and cell types," *Genome Biol.*, vol. 14, p. R115, 2013.
[20] M. E. Levine *et al.*, "An epigenetic biomarker of aging for lifespan and healthspan," *Aging (Albany NY)*, vol. 10, pp. 573–591, 2018.
[21] C. Franceschi *et al.*, "Inflammaging: A new immune-metabolic viewpoint for age-related diseases," *Nat. Rev. Immunol.*, vol. 18, pp. 576–590, 2018.
[22] H. Cedar and Y. Bergman, "Epigenetics of haematopoietic cell development," *Nat. Rev. Immunol.*, vol. 11, pp. 478–488, 2011.
[23] H. Wu and Y. Zhang, "Reversing DNA methylation: mechanisms, genomics, and biological functions," *Cell*, vol. 156, pp. 45–68, 2014.
[24] J. Gräff and L.-H. Tsai, "Histone acetylation: molecular mnemonics on the chromatin," *Nat. Rev. Neurosci.*, vol. 14, pp. 97–111, 2013.
[25] A. Bird, "Perceptions of epigenetics," *Nature*, vol. 447, pp. 396–398, 2007.
[26] D. R. Donohoe *et al.*, "The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon," *Cell Metab.*, vol. 16, pp. 400–413, 2012.
[27] A. Koh *et al.*, "From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites," *Cell*, vol. 165, pp. 1332–1345, 2016.
[28] I. Tabas and K. E. Bornfeldt, "Macrophage phenotype and function in different stages of atherosclerosis," *Nat. Rev. Immunol.*, vol. 16, pp. 517–529, 2016.
[29] M. A. Reddy and R. Natarajan, "Epigenetic mechanisms in diabetic complications and metabolic memory," *Nat. Rev. Nephrol.*, vol. 7, pp. 675–688, 2011.
[30] P. Chi, C. D. Allis, and G. G. Wang, "Covalent histone modifications—miswritten, misinterpreted and mis-erased in human cancers," *Nat. Rev. Cancer*, vol. 10, pp. 457–469, 2010.