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REVIEW

Advances in the Epigenetic Mechanisms of Diabetic Nephropathy Pathogenesis

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Abstract: Diabetic nephropathy (DN) is one of the most severe microvascular complications of diabetes and a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). While traditional research has linked the onset of DN to factors such as metabolic dysregulation, inflammation, and oxidative stress, these mechanisms alone fail to fully explain the complex pathological features and individual variability of DN. In recent years, epigenetic research has provided new insights, revealing the critical roles of DNA methylation, histone modifications, and non-coding RNAs in the development of DN. DNA methylation regulates gene expression by altering methylation levels in promoter regions, affecting genes involved in inflammation and fibrosis. Histone modifications, including acetylation and methylation, influence gene transcription by altering chromatin structure. Additionally, non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play essential roles in gene expression networks. This review summarizes the latest advances in understanding these epigenetic mechanisms in DN pathogenesis, explores their roles in regulating inflammation, fibrosis, and cell damage, and discusses their potential applications in the diagnosis and treatment of DN. Further investigation into epigenetic modifications holds promise for identifying novel diagnostic markers and personalized therapeutic strategies for DN.

Keywords: diabetic nephropathy, epigenetics, DNA methylation, histone modifications, non-coding RNAs

Introduction

Diabetic nephropathy (DN) is one of the most common and severe microvascular complications of diabetes, and it is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1,2] Patients with DN typically exhibit abnormalities such as proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis, which lead to a progressive decline in kidney function. Ultimately, this can result in uremia, with patients needing dialysis or kidney transplantation to sustain life.[3] Over the past few decades, the global incidence of diabetic nephropathy (DN) has shown a marked increase, paralleling the rising prevalence of diabetes. According to recent data, there are approximately 529 million adults worldwide living with diabetes as of 2021, with projections indicating that this number could rise to 1.3 billion by 2050. In regions such as Asia, the surge in type 2 diabetes cases has particularly fueled the rise in DN cases. It is estimated that around 40% of diabetes patients may develop DN, significantly contributing to the global burden of chronic kidney disease and related complications.[4] Therefore, effective prevention and treatment of DN remains a major global medical challenge.

Historically, the pathogenesis of DN has been primarily attributed to the metabolic abnormalities caused by hyperglycemia. Hyperglycemia, the primary trigger for DN, initiates a cascade of harmful biochemical pathways. In the polyol pathway, excessive glucose is converted to sorbitol by aldose reductase, increasing intracellular osmotic pressure and causing cell swelling and damage. Hyperglycemia - induced PKC activation leads to abnormal regulation of cell growth, differentiation, and gene expression in renal cells, along with increased production of extracellular matrix components. Hyperglycemia also promotes the accumulation of AGEs. AGEs bind to their receptors (RAGEs) on cells,

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triggering oxidative stress and inflammatory responses. Oxidative stress further damages cellular components and activates inflammatory pathways. Collectively, these mechanisms induce cellular dysfunction, inflammation, and fibrosis, ultimately contributing to glomerular and tubulointerstitial injury, manifested as abnormal activation of inflammatory responses, extracellular matrix deposition, and glomerulosclerosis. In the progression of DN, inflammation and oxidative stress play critical roles, causing damage to mesangial cells and podocytes, further aggravating renal injury.[5,6]

However, while these traditional mechanisms explain certain pathological aspects of DN, they cannot fully account for the individual variability in disease onset and progression. For instance, patients with comparable glycemic control can exhibit vastly different severities of renal damage, and some may still experience kidney function decline despite effective blood glucose management. Therefore, exploring deeper mechanisms is crucial to uncover the true pathogenesis of DN.

The term "epigenetics" was coined by Conrad Waddington in 1942 to describe the phenomenon of phenotypic changes without alterations in the genotype, aiming to explain various aspects of development.[7] Approximately three-quarters of a century later, it was discovered that epigenetic mechanisms, which regulate gene expression patterns, do not rely on changes to the DNA sequence but instead operate through modifications to chromatin, which is the physiological form of genetic information. The key mechanisms of epigenetic regulation include DNA methylation, histone modifications (Figure 1 shows acetylation and methylation modifications), and regulation by non-coding RNAs. These epigenetic marks dynamically respond to environmental signals and "remember" external stimuli at the level of gene expression.[8] As such, epigenetics plays a vital role not only in development but also in metabolic responses, environmental adaptation, and disease pathogenesis.

In the pathological process of DN, environmental factors such as hyperglycemia, oxidative stress, and inflammatory mediators exert complex effects on gene expression. Epigenetic modifications can alter gene expression patterns, allowing the body to respond to pathological environmental stimuli either adaptively or maladaptively.[9] Recent studies have highlighted the significant roles of DNA methylation, histone modifications, and non-coding RNAs in the progression of DN.[10] Research has shown that genes associated with inflammation and fibrosis often exhibit abnormal DNA methylation and histone modification patterns in DN patients, which may promote the overexpression of pro-inflammatory and fibrotic factors, further exacerbating renal damage.[11] Additionally, certain microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are abnormally expressed in DN, and these non-coding RNAs may accelerate the

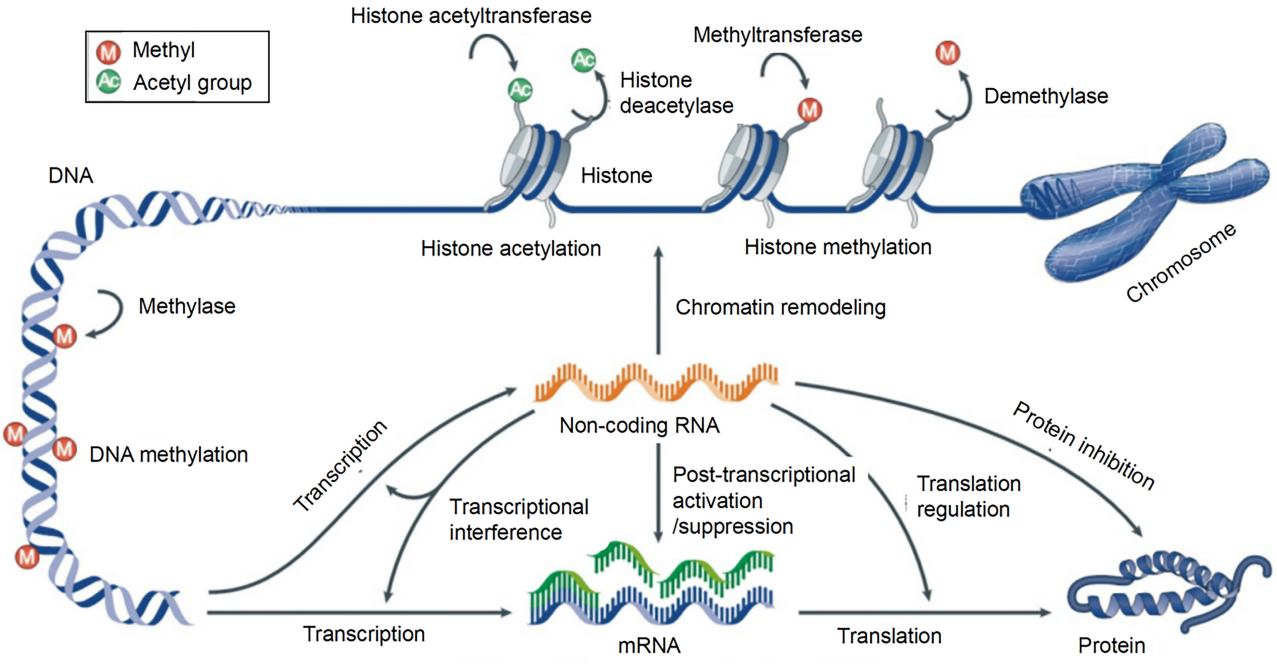

Figure 1 Epigenetic Regulation of Gene Expression.

pathological process by influencing the transcription and translation of target genes. These findings suggest that epigenetic regulation could be a central mechanism in the development of DN.[12,13]

In recent years, the application of epigenetics in DN research has become increasingly widespread. Studies on epigenetic modifications not only provide insights into the underlying mechanisms of DN but also offer new approaches for early diagnosis and therapeutic intervention. DNA methylation, histone modifications, and non-coding RNA regulation each play distinct roles in the progression of DN, sometimes interacting with each other, or acting independently, to offer new perspectives on the complex pathogenesis of DN. This review aims to summarize the latest advances in epigenetic research related to diabetic nephropathy, focusing on how DNA methylation, histone modifications, and non-coding RNAs regulate the onset and progression of DN, and explores their potential for future clinical applications. By systematically reviewing these studies, we hope to provide valuable insights for future research on the pathogenesis of DN and offer theoretical support for clinical applications.

DNA Methylation and Diabetic Nephropathy

Mechanism Overview

DNA methylation is a key epigenetic regulatory mechanism that involves the addition of a methyl group ($-CH_3$) to specific sites on the DNA molecule, such as CpG islands, to regulate gene expression (Molecular Mechanism of DNA Methylation as Shown in Figure 2).[14] This process is carried out by the DNA methyltransferase (DNMT) family of enzymes. DNMT1 is responsible for maintaining the methylation pattern after cell division, while DNMT3a and DNMT3b add new methyl groups during DNA replication, converting unmethylated cytosine into 5-methylcytosine. This division of labor suggests that in the context of hyperglycemia, DNMT3a/3b may initiate changes in the demethylation of inflammation- and fibrosis-related genes, while DNMT1 helps maintain these changes, thereby continuously regulating gene expression in diabetic nephropathy (DN).[15]

DNA methylation is a pivotal epigenetic mechanism in gene expression regulation, involving the transfer of a methyl group ($-CH_3$) to cytosine residues, primarily in CpG islands. This process, catalyzed by the DNA methyltransferase (DNMT) family of enzymes, influences chromatin structure and gene activity. DNMT1 maintains methylation patterns during DNA replication, while DNMT3a and DNMT3b establish de novo methylation during cellular differentiation and response to external stimuli such as hyperglycemia.[16]

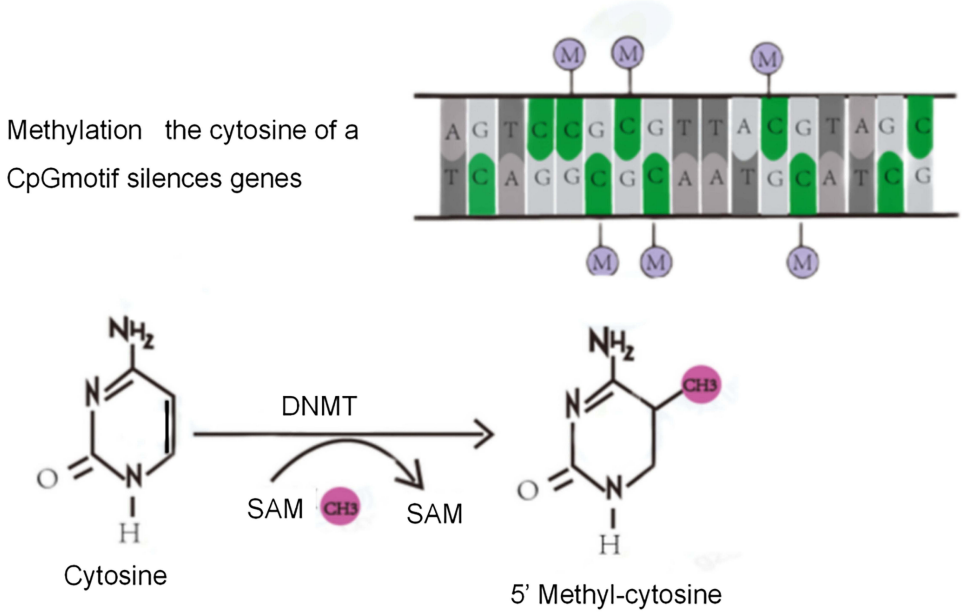

Figure 2 Molecular Mechanism of DNA Methylation.

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In diabetic nephropathy (DN), hyperglycemia induces epigenetic modifications that sustain pathological gene expression even after glucose levels normalize, a phenomenon known as "metabolic memory".[17] DNMT3a and DNMT3b initiate methylation changes in genes associated with inflammation and fibrosis, whereas DNMT1 perpetuates these methylation patterns, contributing to persistent gene dysregulation.[18] The precise role of DNA methylation in DN pathogenesis underscores the interplay between environmental factors and genetic regulation, amplifying tissue damage in renal structures.

Promoter Region DNA Methylation and Diabetic Nephropathy

In DN patients, abnormal methylation of CpG islands in the promoter regions is closely associated with the dysregulation of key gene expressions. The let - 7a - 3 miRNA gene is located on chromosome 9q22.32.[19] Research has shown that in DN patients, the promoter region of let - 7a - 3 is highly methylated, inhibiting the expression of this microRNA.[20] In a study using a mouse model of DN, it was demonstrated that the downregulation of let - 7a - 3 due to methylation led to an upregulation of fibrosis - and inflammation - related genes, directly contributing to the pathological progression of DN.[21] Given that let - 7a - 3 plays a critical role in regulating fibrosis and inflammation - related genes, its methylation - induced downregulation directly contributes to the pathological progression of DN. Additionally, in the glomerular tissue of DN patients, the methylation level of the connective tissue growth factor (CTGF) gene promoter is reduced, leading to increased CTGF expression and accelerating glomerular fibrosis.[22] The demethylation of these specific gene promoters may be linked to hyperglycemia - induced oxidative stress and inflammatory factor stimulation, further exacerbating the progression of DN. Investigating the demethylation pathways triggered by oxidative stress will help elucidate the critical role of promoter methylation changes in the pathogenesis of diabetic nephropathy.

Genome-Wide Methylation Abnormalities

The overall genomic methylation levels in DN patients are significantly elevated. High-performance liquid chromatography (RP-HPLC) analysis has shown that DN patients have higher levels of genomic methylation compared to individuals with diabetes alone. This global change may represent an adaptive response to the high-glucose environment and involves key genes in insulin signaling and inflammatory pathways. Differentially methylated regions (DMRs) are closely associated with the insulin signaling pathway and the mitogen-activated protein kinase (MAPK) signaling pathway. The persistent activation of these pathways and the silencing of gene expression further aggravate metabolic dysfunction and glomerular injury.[23] Further research on the genome-wide methylation landscape, particularly the methylation status of key signaling pathway genes, will help uncover the overall pathological regulation of genomic methylation in diabetic nephropathy.

DNA Methylation and Inflammatory Injury

In the inflammatory damage of diabetic nephropathy, the expression of inflammatory factors is closely related to methylation changes in the promoter regions. Studies have indicated that demethylation of the promoters of tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1B) leads to their overexpression, enhancing the inflammatory response around the glomerulus and renal tubules.[24] Research has also shown that the abnormal activation of the NF-κB signaling pathway in DN patients is associated with reduced methylation in its promoter region. Since NF-κB further promotes the expression of TNF-α and IL-1B, creating a positive feedback loop, these promoter demethylation events intensify the chronic inflammation state. Moreover, demethylation may impair the immunosuppressive function of regulatory T cells (Tregs), leading to immune dysregulation and persistent stimulation of the inflammatory response in DN.[25] Understanding the methylation regulation of these pro-inflammatory genes could help identify strategies to inhibit specific inflammatory signals and alleviate DN progression.

DNA Methylation and Oxidative Stress

Oxidative stress is a crucial pathogenic factor in diabetic nephropathy. The accumulation of reactive oxygen species (ROS) caused by high glucose levels directly damages glomerular cells while also affecting gene expression through changes in DNA methylation. Normally, thrombin-activated protein C helps alleviate oxidative stress and protects

glomerular cells; however, in DN patients, its levels are significantly reduced, which is closely linked to the demethylation of the p66Shc gene promoter. This leads to upregulated p66Shc expression, exacerbating oxidative stress damage. Sun et al[26] further suggested that reduced methylation of mitochondrial genes may result in mitochondrial dysfunction, eventually contributing to increased oxidative stress. A recent in - vitro study using renal cell lines demonstrated that by modulating the methylation status of oxidative stress - related genes, the level of oxidative stress in cells could be effectively regulated. Therefore, studying the methylation status of oxidative stress - related genes may provide valuable insights into the regulation of oxidative stress in DN, and further functional studies are needed to identify potential targets for blocking the oxidative stress response.

DNA Methylation and Renal Fibrosis

During the fibrotic process of diabetic nephropathy, DNA methylation regulates the expression of several fibrosis-related genes. Studies have shown that the methylation of the TGF-β1 gene promoter region is reduced in renal tubular cells of DN patients, leading to excessive expression of TGF-β1 and accelerating extracellular matrix (ECM) deposition, ultimately causing tubular fibrosis. The demethylation induced by high glucose may further exacerbate fibrosis by promoting epithelial-to-mesenchymal transition (EMT) of renal tubular epithelial cells.[27] Additionally, the demethylation of fibrosis-related genes such as FN1 and COL1A1 may increase their expression, driving the ongoing fibrosis process. Exploring how to block the demethylation of these key genes in the early stages of fibrosis could become an important strategy for delaying or reversing the progression of DN fibrosis.

Histone Modifications and Their Association with Diabetic Nephropathy

Histone modifications play a pivotal role in the pathogenesis and progression of DN. These modifications regulate gene expression related to renal function and contribute to key pathological features such as fibrosis, inflammation, and cell-cycle dysregulation in the kidneys of DN patients. Among various histone modifications, histone acetylation and methylation have been extensively studied and are closely associated with the onset and progression of DN.[28]

The core of chromatin structure consists of highly conserved histones, including H3, H4, H2A, H2B, and H1. These histones package and fold eukaryotic DNA into higher-order chromatin structures through nucleosomes, thereby regulating gene transcription.[29] The amino-terminal regions of histones are the primary sites for modification. More than 60 different types of modifications have been identified, with methylation and acetylation of lysine and arginine being the most widely studied.[30] Histone modifications, which are tightly regulated by various epigenetic enzymes, are reversible and represent potential therapeutic targets for diseases. In the context of epigenetic regulation, chemical modifications of histones play a crucial role in gene transcription and maintaining the dynamic balance of chromatin structure. The main types of modifications are acetylation and methylation, each influencing gene expression and chromatin structure in different ways. The three-dimensional structure of histones (Figure 3) shows that each histone has a small "tail" extending from its structure, known as the N-terminal tail.

Histone Acetylation

In diabetic nephropathy, histone acetylation has been increasingly recognized as a key factor in the dysregulation of gene expression related to the disease. An imbalance in histone acetylation can lead to abnormal activation or repression of genes involved in fibrosis, inflammation, and cell-cycle regulation in the kidney, thus promoting the development and progression of DN.[31]

Acetylation Process

Histone acetylation is a critical modification in epigenetics, primarily regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), which maintain a dynamic balance between acetylation and deacetylation. This process involves the addition or removal of acetyl groups (CH_3CO) at specific sites on histones, primarily at lysine residues, thereby modulating chromatin structure and gene expression.[32] HATs add acetyl groups to lysine residues, altering the positive charge of the histones and reducing the electrostatic interaction between histones and the negatively charged DNA. This results in a more relaxed chromatin structure, facilitating easier access for transcription factors and enhancing

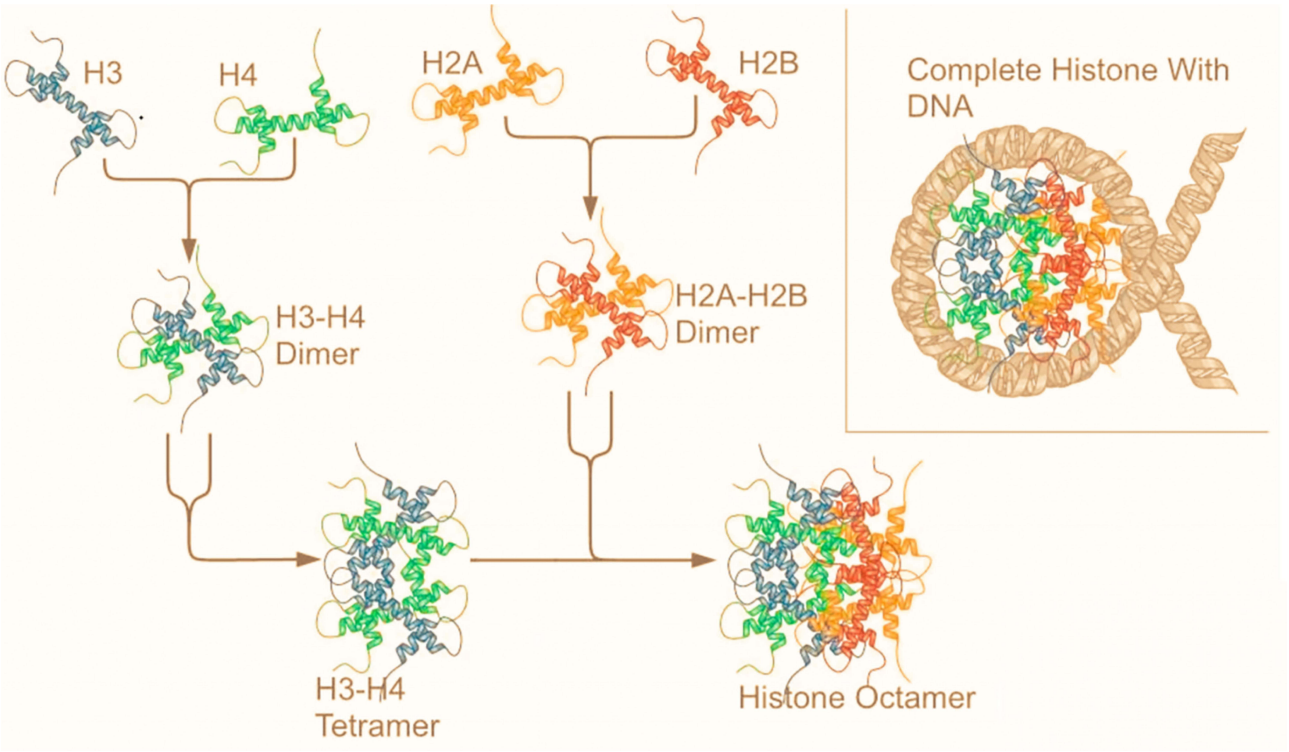

Figure 3 Three-dimensional Structure of Histones.

gene expression. Additionally, acetylated lysine residues in relaxed chromatin can serve as "recruitment platforms" for other co-activators, chromatin remodeling complexes, or specific transcription factors. This cooperative interaction further amplifies the transcriptional activation process.[33] Acetylation of lysine residues at H3K9ac and H3K14ac is commonly associated with transcriptionally active regions, and the acetylation at these sites not only affects chromatin structure but also regulates downstream gene expression by binding specific transcription factors. A study by Diallo et al[34] demonstrated that in diabetic kidney disease, there is an increase in histone acetylation at promoters of pro-fibrotic genes, leading to their upregulation and contributing to disease progression.

Function and Mechanism

Histone acetylation involves both acetylation and deacetylation of histones, regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. The acetylation pattern of histones is relatively straightforward, as acetylation is typically associated with gene activation. Acetylation neutralizes the positive charge of histones, making chromatin more accessible to transcription factors and their co-activators. In contrast, deacetylation generally leads to a more compact chromatin structure, resulting in transcriptional repression.[35] HATs are classified into two groups: Class A and Class B. Class A HATs, located primarily in the nucleus, are closely associated with gene transcription regulation, including well-known enzymes like CBP/p300 and PCAF. Class B HATs are mainly expressed in the cytoplasm and are responsible for acetylating newly synthesized histones, ensuring that these modifications are in place before nucleosome assembly. Research has shown that CBP/p300, key members of the HAT family, can add acetyl groups to histones H3 and H4, thereby activating various genes involved in cell proliferation and differentiation.[36]

HDACs remove acetyl groups from histones, leading to chromatin condensation and gene repression. The HDAC family is divided into four classes (I, II, III, and IV), each exhibiting specific functions in different cells and tissues. Class I HDACs primarily regulate gene expression in the nucleus, while Class II HDACs function both in the nucleus and cytoplasm. Class III HDACs, known as sirtuins, play significant roles in regulating cellular metabolism and aging. HDAC-mediated deacetylation not only contributes to gene silencing but also plays a role in processes such as cellular

stress responses and DNA repair.[37] A study by Xu highlighted the role of HDACs in diabetic nephropathy, showing that inhibition of HDACs can modulate gene expression and potentially ameliorate disease progression.[38]

Biological Significance of Acetylation

Histone acetylation predominantly occurs on the lysine residues of H3 and H4, and the degree of acetylation at these sites is a key determinant of gene activity. Acetylation marks are generally associated with gene activation and regulate gene expression patterns in cells, influencing processes such as cell differentiation, proliferation, apoptosis, and adaptive responses. Histone acetylation plays particularly important roles in physiological and pathological processes, such as embryonic development, cell fate determination, and stress responses. Acetylation promotes gene activation by enhancing the activity of promoters and enhancers, attracting transcription factors and co-activators, thereby increasing gene expression levels.[39] Additionally, acetylation marks can mediate "gene expression memory", where certain genes continue to be expressed even after the removal of transcription factors. This epigenetic memory mechanism is crucial for maintaining specific cellular phenotypes and cellular memory. Furthermore, histone acetylation regulates cellular stress responses, helping cells adapt to external stimuli such as oxidative stress and inflammation. In inflammatory responses, acetylation promotes the expression of inflammatory genes, aiding rapid immune responses. In the context of DN, histone acetylation - mediated gene activation can have both beneficial and detrimental effects. For example, while the acetylation - induced activation of some antioxidant - related genes may help counteract oxidative stress, the over - acetylation of pro - fibrotic genes can lead to excessive extracellular matrix deposition and glomerulosclerosis. A recent clinical study Agarwal[40] showed that the level of histone acetylation in renal biopsy samples from DN patients was positively correlated with the degree of renal fibrosis.

Role in Diabetic Nephropathy (DN)

An imbalance between acetylation and deacetylation can lead to abnormal chromatin structure and gene expression, contributing to the development and progression of various diseases. Excessive acetylation may result in the abnormal activation of genes, such as oncogenes in cancer, while excessive deacetylation can inhibit the expression of tumor suppressor genes. In the case of diabetic nephropathy, increased HAT activity raises the acetylation levels of pro-fibrotic genes, ultimately contributing to glomerulosclerosis and fibrosis. Additionally, HDAC inhibitors have been developed as therapeutic agents for various diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders. These inhibitors work by restoring or modulating the balance of histone acetylation, achieving therapeutic effects.[41]

Histone Methylation

Methylation Process

Histone methylation is a chemical modification catalyzed by histone methyltransferases (HMTs), where methyl groups are added to specific lysine or arginine residues on histones. Common methylation sites include H3K4, H3K9, and H3K27, and methylation can occur in single, double, or triple forms. Different methylation states have distinct regulatory effects on gene expression.

Function and Mechanism

Histone methylation typically occurs at specific lysine or arginine residues and is regulated by both histone methyltransferases and histone demethylases. Each lysine residue can undergo monomethylation, dimethylation, or trimethylation, while arginine can undergo monomethylation or symmetric/asymmetric dimethylation. These methylation modifications can either activate or repress gene expression. Generally, methylation at H3K4, H3K36, and H3K79 is associated with gene activation, while methylation at H3K9, H3K27, and H4K20 is linked to gene repression. Studies have shown that methylation of histone H3 plays a key role in gene regulation.

Monomethylation: The monomethylation of H3K4, catalyzed by the SET7 methyltransferase, plays a key role in diabetic atherosclerosis. Research indicates that short-term high glucose exposure significantly increases SET7 and H3K4me1 levels, which activates the expression of vascular cell adhesion molecules (VCAM-1) and chemokine MCP-1, triggering chronic inflammation. Similar studies have found that high glucose can induce increased expression of SET7 and H3K4me1 in mesangial cells of rat glomeruli, activating pro-inflammatory factors. This "epigenetic memory" effect

of short-term high glucose exposure may explain why complications in diabetes persist even after blood glucose levels are normalized.

Polymethylation: The expression of the trimethyltransferase SUV39H1 for H3K9 trimethylation shows dynamic changes under high glucose conditions. Early in hyperglycemia, SUV39H1 expression increases, leading to the accumulation of H3K9me3 at the promoters of inflammatory genes, thereby suppressing their expression. However, as diabetes progresses, SUV39H1 expression decreases, resulting in reduced H3K9me3 levels, which in turn activates inflammatory gene expression, aggravating the inflammation. Furthermore, H3K27 trimethylation (H3K27me3) plays a significant role in the progression of diabetic nephropathy. Studies have shown that the loss of H3K27me3 in diabetic mice accelerates podocyte dedifferentiation, glomerular inflammation, and fibrosis, while increased H3K27me3 levels help slow disease progression.[42] A recent study Wang et al[43] in a rat model of DN found that the modulation of SUV39H1 expression could significantly affect the methylation level of H3K9 in genes related to renal fibrosis. By increasing SUV39H1 expression, the H3K9me3 levels at the promoters of fibrotic genes were increased, which inhibited the expression of these genes and alleviated renal fibrosis.

Role in Diabetic Nephropathy (DN)

In the progression of diabetic nephropathy, histone methylation regulates the expression of pro-inflammatory and anti-inflammatory genes, playing a crucial role in the chronic inflammation response. Under hyperglycemic conditions, the upregulation of SET7, a histone H3K4 monomethyltransferase, leads to the activation of various pro-inflammatory factors, inducing sustained inflammation. Another key enzyme, SUV39H1, regulates H3K9 trimethylation and, in early hyperglycemia, suppresses inflammatory gene expression. However, as diabetes progresses, the downregulation of SUV39H1 leads to a reduction in H3K9me3, activating inflammatory genes and exacerbating kidney damage. Additionally, the reduction of H3K27me3 accelerates podocyte injury and dedifferentiation, contributing to the progression of diabetic nephropathy.

Non-Coding RNAs and Diabetic Nephropathy

The regulatory role of non-coding RNAs, particularly miRNAs and siRNAs, in diabetic nephropathy (DN) has garnered significant attention in recent years.[44] siRNAs can be synthetically produced and introduced into cells to pair with homologous mRNA sequences, thereby interfering with the expression of specific genes. miRNAs, as endogenous short-chain RNAs, have limited roles during early embryonic development but play crucial regulatory functions in various pathological conditions, such as diabetes, cancer, and metabolic disorders.[45] In the progression of DN, certain miRNAs have been found to be closely linked to the regulation of key genes involved in fibrosis and inflammation. For example, miR-192 has been shown to be upregulated in kidney biopsy samples from diabetic patients, and activation of the TGF-β signaling pathway induces increased expression of miR-192 in proximal tubular cells, which is significantly associated with glomerular fibrosis and renal dysfunction.[46] In mouse models, inhibiting miR-192 effectively reduces fibrosis and urinary protein excretion. Moreover, miR-21 has been shown to correlate positively with the severity of fibrosis and the decline in kidney function in DN patients, making it a potential biomarker for DN. TGF-β-induced miR-200b/c promotes mesangial cell proliferation in the glomerulus, while miR-200a may regulate the TGF-β pathway through negative feedback. The absence of miR-146a accelerates diabetic glomerular changes, while miR-29a protects podocyte function under high glucose conditions. In contrast, miR-29c is linked to fibrosis and podocyte apoptosis.[47] Other miRNAs, such as miR-34c, miR-26a, and miR-126, show differential regulatory effects on inflammation or fibrosis in DN patients, presenting potential diagnostic and prognostic value.[48] Current studies suggest that the abnormal expression of specific miRNAs contributes to the progression of fibrosis and inflammation in DN, offering new possibilities for early diagnosis, therapeutic targeting, and potential urinary biomarkers.[49]

Limitations Future Directions

Despite advances in the management of diabetic nephropathy, current therapeutic approaches primarily focus on controlling hyperglycemia, hypertension, and proteinuria. However, these interventions often fail to fully prevent or halt the progression of renal damage. Limitations include suboptimal efficacy in advanced stages of DN, potential side

effects of long-term treatments, and the inability to reverse established fibrosis and glomerulosclerosis. Additionally, individual variations in drug response and the lack of reliable biomarkers for early diagnosis hinder personalized treatment strategies. To address these challenges, future research must explore novel therapeutic approaches targeting the underlying epigenetic mechanisms of DN. Potential strategies include the development of RNA inhibitors, histone modification regulators, and DNA demethylating agents, which could enable more precise control of fibrosis and inflammation. The identification of stage-specific molecular targets and early biomarkers will be critical for timely intervention and improved outcomes. Personalized medicine approaches that account for patient-specific epigenetic landscapes may further enhance therapeutic efficacy while minimizing side effects.

Conclusion

In conclusion, the complex interplay of epigenetic mechanisms plays a pivotal role in the progression of diabetic nephropathy, offering promising avenues for innovative diagnostics and therapies. While significant progress has been made, further research is needed to fully realize the potential of epigenetic interventions and translate them into clinical practice. The development of comprehensive, stage-specific treatment strategies holds promise for transforming the management and outcomes of diabetic nephropathy.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics and Consent Statements

This study was approved by the ethics committee of Heilongjiang University of Chinese Medicine. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests in this work.

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