ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

The research progress on the mechanisms and therapeutic targets of ferroptosis and epigenetic modifications in diabetic complications

Junyu Meng[1,2,a], Guihong Huang[1,2,3,b,*]

[1]Department of Pharmacy, The Second Affiliated Hospital of Guilin Medical University; Lingui Clinical College of Guilin Medical University, Guilin, Guangxi, (541199), China
[2]Guangxi Key Laboratory of Drug Discovery and Optimization, Guangxi Engineering Research Center for Pharmaceutical Molecular Screening and Druggability Evaluation, School of Pharmacy, Guilin Medical University, Guilin, Guangxi, (541199), China
[3]Guangxi Key Laboratory of Metabolic Reprogramming and Intelligent Medical Engineering for Chronic Diseases, Guangxi Key Laboratory of Diabetic Systems Medicine, Guilin, Guangxi, (541199), China
[a]1183035692@qq.com, [b]guihonghuang666@163.com
**Corresponding author*

Abstract: *Diabetes, as a prevalent chronic metabolic disease, imposes a heavy medical burden and economic pressure on society. The long-term dysregulation of glucose metabolism leads to multi-system (including cardiovascular, renal, neurological, etc.) damage, which constitutes the core pathological features of diabetic complications. In recent years, ferroptosis and epigenetic regulation have emerged as new research directions, gradually becoming a burgeoning field of study. Increasing evidence suggests that epigenetics may play a significant role in regulating the relationship between ferroptosis and diabetic complications. Notably, the epigenetics of certain key iron metabolism genes may influence the epigenetic "switch" of the ferroptosis pathway. This article systematically reviews the molecular mechanisms of ferroptosis and epigenetics in diabetic microvascular complications, neuropathy, and other related conditions, while exploring potential therapeutic targets based on epigenetic regulation to provide a theoretical basis for the treatment of diabetic complications.*

Keywords: *Ferroptosis, Diabetes, Epigenetics, Diabetic Complications*

1. Introduction

Diabetes Mellitus (DM) is a systemic metabolic disease characterized primarily by insufficient insulin secretion, insulin resistance, and chronic hyperglycemia [1]. According to statistics [2], by 2021, the number of people with diabetes globally is expected to exceed 536.6 million, and this number may rise to 783.2 million by 2045. This data indicates that diabetes has become a serious public health issue worldwide, significantly increasing the burden of diabetes-related healthcare expenditures in various countries. Most diabetes patients experience at least one complication [3], which includes microvascular complications such as diabetic nephropathy, diabetic neuropathy, and retinopathy, as well as macrovascular complications like diabetic cardiovascular disease [4]. These complications severely impact the quality of life of patients and significantly increase mortality rates. Therefore, studying the underlying mechanisms of diabetic complications and developing potential therapeutic targets has become an important issue that urgently needs to be addressed in clinical practice, which is especially critical for improving the health status of diabetes patients.

Ferroptosis is a novel mode of cell death primarily triggered by the accumulation of lipid peroxides (such as ROS) caused by iron overload, which subsequently induces mitochondrial damage and oxidative stress, ultimately leading to cell death [5]. Dysregulation of glucose and lipid metabolism may be driven by ferroptosis [6], while chronic hyperglycemic conditions induce iron overload, triggering oxidative stress responses that result in ferroptosis [7]. Therefore, targeting ferroptosis holds promise as an effective strategy for treating various metabolic disorders, including type 2 diabetes [8][9]. Research indicates a close relationship between iron homeostasis imbalance and diabetes along with a series of related complications, which include diabetic kidney injury, endothelial dysfunction, and osteoporosis [10]. Therapeutic strategies targeting ferroptosis not only open new avenues for diabetes treatment but also

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

provide novel therapeutic targets for the intervention of diabetic complications.

Epigenetics refers to the biological processes that regulate gene expression patterns and affect cellular functions without altering the DNA sequence. The primary regulatory mechanisms include DNA methylation, histone modifications, and non-coding RNA regulation [11]. Recent studies have suggested that the pathogenesis of diabetic complications may involve the interaction between epigenetics and ferroptosis. Epigenetic modifications may mediate hyperglycemia-induced ferroptosis by regulating the transcriptional activity of key ferroptosis marker genes. This article systematically reviews the latest research findings in this field, revealing the potential value of the epigenetic regulatory network of ferroptosis as a novel therapeutic target, thus providing important reference for treatment strategies of diabetic complications.

2. Mechanisms of ferroptosis and its role in diabetic complications

2.1. Ferroptosis and Its Core Regulatory Pathways

In 2012, Dixon et al. [12] discovered a new form of cell death and confirmed that it has a unique molecular mechanism: its occurrence relies on the accumulation of reactive oxygen species (ROS) and lipid peroxidation generated by the Fenton reaction mediated by intracellular iron ions, and it can be specifically blocked by inhibitors such as ferrostatin-1 [13]. Notably, ferroptosis exhibits significant morphological changes, typically characterized by abnormal phenomena such as reduced mitochondrial volume, increased membrane density, and degradation or even disappearance of mitochondrial cristae [14]. These characteristic changes cannot be reversed by inhibitors of other types of cell death, such as apoptosis or necrosis [15]. Iron overload is a key factor that triggers ferroptosis. Excess iron catalyzes the conversion of hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals through the Fenton reaction, which subsequently induces non-enzymatic lipid peroxidation, ultimately leading to damage to the cell membrane system [16]. The molecular regulatory network of ferroptosis mainly involves the following core components: the Xc^- system, the glutathione (GSH) biosynthesis pathway, the regulatory pathway of glutathione peroxidase 4 (GPX4) activity, as well as the dynamic balance between iron metabolism and lipid peroxidation metabolism [17]. In recent years, several studies have systematically elucidated the key signaling pathways regulating ferroptosis and their mechanisms of action, including prominent regulatory axes such as the p53-SLC7A11 axis, the KEAP1-NRF2 antioxidant stress pathway, and the Hippo-YAP/TAZ axis [18]. These pathways collectively form the regulatory network of ferroptosis by modulating key biological processes such as redox homeostasis, iron ion transport, and polyunsaturated fatty acid metabolism.

2.2. Ferroptosis and Diabetic Complications

Diabetic kidney disease (DKD), as the most common microvascular complication of diabetes, has become a major cause of end-stage renal disease, with its global prevalence continuing to rise [19]. Research indicates that programmed cell death is involved in the pathological processes of DKD, in which ferroptosis, a form of cell death driven by iron-dependent lipid peroxidation, plays a significant role in the pathogenesis of DKD [20]. Podocyte ferroptosis has been confirmed as a critical link in the progression of DKD. Pei et al. [21] found that Hirsutine significantly alleviates podocyte ferroptosis by activating the P53/GPX4 pathway. The epigenetic regulator PRDM16 has a protective effect against DKD. Zheng et al. [22] discovered that PRDM16 inhibits ferroptosis in glomerular epithelial cells and improves DKD by activating the NRF2/GPX4 axis or directly regulating GPX4 expression. Diabetic retinopathy (DR), another significant microvascular complication, is a major cause of vision impairment and blindness in adults [23]. Research by Wang et al. [24] indicated that resveratrol effectively inhibits ferroptosis in DR by regulating the Nrf2/GPX4 pathway. Luo et al. [25] further found that Piperine affects GPX4 expression by regulating the YAP-mediated Hippo signaling pathway, thereby inhibiting ferroptosis and alleviating DR. Regarding diabetic cardiomyopathy (DCM), Wang et al. [26] confirmed that fibroblast growth factor 21 (FGF21) plays a critical protective role in DCM by inhibiting cardiomyocyte ferroptosis through binding with FTH1 and FTL. The above studies indicate a significant relationship between ferroptosis and various diabetic complications. By directly or indirectly regulating key targets in the ferroptosis pathway, there is potential to provide new strategies for the treatment of diabetic complications.

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

3. Epigenetic Regulatory Mechanisms of Ferroptosis in Diabetes Complications

3.1. Introduction to Epigenetics

3.1.1. DNA Methylation

DNA methylation is the earliest discovered and most extensively studied mechanism, specifically referring to the covalent modification of cytosine at the 5-position carbon atom catalyzed by DNA methyltransferases (DNMTs) [27]. This modification primarily occurs in regions rich in CpG dinucleotides known as "CpG islands" [28]. Research indicates that high methylation levels in CpG islands typically lead to gene silencing, while low methylation levels help maintain an open chromatin state, thereby promoting gene transcription activation [29]. In mammals, the DNMTs family comprises five members: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L, among which only DNMT1, DNMT3a, and DNMT3b possess methyltransferase activity [30]. DNMT1 is the most abundant DNA methyltransferase, primarily responsible for maintaining methylation, whereas DNMT3a and DNMT3b are mainly involved in de novo methylation [31].

3.1.2. m6A Methylation

N6-methyladenosine (m6A) methylation is a reversible RNA modification process mediated by a methyltransferase complex, defined as the selective addition of methyl groups to the N6 position of the adenine base in RNA [32]. As the most prevalent type of RNA epigenetic modification, m6A is widely found in various RNA molecules [33]. This modification process is regulated by three classes of regulatory proteins: methyltransferases (often referred to as "writer" proteins, such as METTL3 and METTL14), demethylases (called "eraser" proteins, including FTO and ALKBH5), and recognition proteins (termed "reader" proteins, such as YTHDC1/2, YTHDF1/2, and IGF2BP1) [34].

3.1.3. Long non-coding RNAs

Long non-coding RNAs (lncRNAs) are a class of RNA molecules that do not possess protein-coding capabilities but play crucial regulatory roles. This group includes microRNAs (miRNAs), lncRNAs, and circular RNAs (circRNAs) [35]. These molecules participate in regulating key biological processes such as cell proliferation, differentiation, and apoptosis through various mechanisms, including epigenetic regulation, transcriptional regulation, and post-transcriptional modifications [36].

3.1.4. Histone Modifications

Core histones (H2A, H2B, H3, and H4) assemble precisely with DNA to form the fundamental structural unit of chromatin [37]. The N-terminal tails of these histones can undergo a variety of post-translational modifications, including classical modifications like methylation and acetylation, as well as non-classical modifications recently discovered through high-resolution mass spectrometry, such as butyrylation (Kbu), crotonylation (Kcr), β-hydroxybutyrylation (Kbhb), succinylation (Ksucc), and lactylation (Kla) [38]. These dynamic modification networks play a critical role in epigenetic regulation.

3.2. Epigenetic Modifications Intervening in Ferroptosis Affecting Diabetic Complications

3.2.1. DNA Methylation Intervention in Ferroptosis Affecting Diabetic Complications

Research indicates that DNA methylation plays a significant role in the complications of diabetes by influencing key genes associated with ferroptosis-related diseases. KLF4 is a critical gene mediating diabetic nephropathy and is essential for maintaining normal kidney function, its downregulation is closely correlated with the onset of diabetic nephropathy [39]. A study by Cai et al. [40] found that berberine may inhibit ferroptosis and improve the progression of diabetic nephropathy by suppressing the hypermethylation of the KLF4 promoter region. Additionally, the Clusterin gene is essential for spermatogenesis in mammals [41], and its downregulation can lead to the activation of the AMPK and Nrf2 pathways [42]. Research by Xiao et al. [43] showed that DNMT3a is recruited to the Clusterin promoter, resulting in the downregulation of Clusterin, which ultimately impacts the AMPK pathway, exacerbating ferroptosis and inducing testicular damage caused by diabetes.

On the other hand, DNA methylation may also directly affect ferroptosis marker genes, thereby mediating the ferroptosis pathway. GPX4, as a core regulatory factor, converts lipid peroxides into non-toxic alcohols through reduction, thereby inhibiting ferroptosis, suppression of GPX4 expression is regarded as a hallmark of ferroptosis occurrence [44][45]. Some studies suggest that GPX4 expression may be regulated by DNA methylation [46]. In a diabetic osteoporosis (DOP) model, astragaloside VI may

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

influence GPX4 and modulate osteoblast ferroptosis by inhibiting the abnormal elevation of DNMT1 and DNMT3A in DOP mice [47]. Therefore, the mediating role of DNA methylation in ferroptosis, along with its mechanisms and therapeutic targets affecting diabetic complications, requires further exploration and research.

3.2.2. m6A Methylation Intervenes in Ferroptosis Affecting Diabetic Complications

m6A methylation modification may play a significant role in the occurrence and development of diabetic complications by regulating the ferroptosis pathway [48]. For instance, ZHX2, a key liver transcription factor, maintains hepatic homeostasis by regulating liver-specific gene expression. In studies of diabetic liver injury [49], Meng et al. [50] revealed the important role of the ZHX2-YTHDF2-ferroptosis axis. It was found that in a diabetic liver injury model, silencing ZHX2 inhibits the transcriptional expression of YTHDF2 by binding to the promoter region, and the downregulation of YTHDF2 further promotes ferroptosis by decreasing the expression of GPX4 and SLC7A11. In addition, Lin et al. discovered in a model of diabetic bone loss that the specific knockout of METTL3 significantly reduced the m6A methylation level of ASK1 in osteoblasts, thereby inhibiting the activation of the METTL3/ASK1/p38 signaling pathway and ultimately exerting an anti-ferroptotic effect [51]. These findings provide new theoretical evidence for the participation of m6A methylation in diabetic complications through the ferroptosis pathway.

3.2.3. Non-coding RNAs Influence Diabetic Complications by Intervening in Ferroptosis

Non-coding RNAs (ncRNAs) are closely related to the occurrence and development of various diseases, such as cancer [52] and diabetic complications [53]. Recent studies suggest that they may play a role in the pathological processes of diabetic complications by regulating ferroptosis [54]. In-depth research on the specific molecular mechanisms by which ncRNAs influence diabetic complications through ferroptosis may provide new molecular targets and intervention strategies for clinical treatment, offering significant theoretical and clinical value. p53 is an important transcription factor involved in the regulation of ferroptosis, and it has been confirmed to promote ferroptosis by inhibiting the expression of SLC7A11 [55]. Fang et al. [56] found that in high-glucose-induced retinal injury cells and mouse models, miR-214-3p influences the SLC7A11/GPX4 signaling pathway by regulating the expression of p53, thereby promoting ferroptosis, suggesting that miR-214-3p may be a potential therapeutic target for diabetic retinopathy. miR-93 is associated with a high risk of diabetic retinopathy [57]. Zhan et al. [58] discovered that vitamin D could downregulate the expression of miR-93 in retinal microvascular endothelial cells under high-glucose conditions, thereby alleviating oxidative stress and ferroptosis. Regarding LncRNA regulation, SNHG1, as a LncRNA, has been shown to influence the pathological process of liver cancer by regulating ferroptosis-related genes [59]. In addition, in diabetic nephropathy, the knockout of LncRNA SNHG1 can restore its expression by interacting with miR-16-5p, thereby downregulating the key ferroptosis gene ASCL4 and exerting an anti-ferroptotic and kidney-protective effect [60]. Ni et al. found that in a diabetic cardiomyopathy mouse model, the expression of LncRNA ZFAS1 was significantly upregulated, and it could promote ferroptosis by binding to miR-150-5p to regulate the expression of CCND2, suggesting that targeting ZFAS1 may be a potential strategy for treating diabetic cardiomyopathy [61]. Furthermore, Jin et al. [62] identified a novel circular RNA (mmu_circRNA_0000309) that can upregulate GPX4 expression by competitively binding to miR-188-3p, inhibiting ferroptosis and improving diabetic nephropathy. In summary, non-coding RNAs can play important roles in the occurrence and development of diabetic complications by directly regulating key ferroptosis genes or interacting with other RNA molecules to influence the ferroptosis signaling pathway. Targeting these non-coding RNAs may provide new intervention strategies for the treatment of diabetic complications.

3.2.4. Histone Modifications Intervene in Ferroptosis Affecting Diabetic Complications

Histone modifications play a crucial role in regulating ferroptosis and intervening in the occurrence and development of diabetic complications. Lysine acetyltransferase 2A (KAT2A), as an important acetyltransferase, regulates gene transcription by promoting histone acetylation [63]. Research by Zhen et al. [64] indicates that KAT2A enhances the enrichment of H3K27ac and H3K9ac in the promoter regions of target genes, leading to the upregulation of ferroptosis-related factors Tfrc and Hmox1, which ultimately promotes the ferroptosis process. Li et al. [65] found that elevated levels of histone H3K27 butyrylation in a high-glucose environment suppress SQSTM1 gene transcription, resulting in reduced autophagy levels. This suppression of autophagy is associated with the upregulation of ASCL4 expression, while the activation of the ferroptosis core gene ASCL4 promotes ferroptosis and subsequently affects the wound healing process. However, inhibiting H3K27 butyrylation can restore SQSTM1 expression and downregulate ASCL4 levels, thereby effectively suppressing ferroptosis. In

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

vitro studies have shown that knockdown of the histone methyltransferase EZH2 in HK-2 cells induced by high glucose can alleviate ferroptosis, suggesting that EZH2 may serve as a potential therapeutic target for diabetic nephropathy [66]. The molecular mechanisms by which histone modifications regulate ferroptosis and subsequently intervene in diabetic complications remain to be further explored.

4. Conclusions

This article systematically reviews the epigenetic regulatory mechanisms of ferroptosis and its pathological role in diabetic complications. Ferroptosis, a novel iron-dependent form of programmed cell death, has been confirmed to be closely associated with various pathological processes, including cancer and neurodegenerative diseases, and has received increasing attention in the field of diabetic complications in recent years. This review integrates and analyzes, from an epigenetic perspective, the regulatory networks of DNA methylation modifications, histone modifications, and non-coding RNA regulation in ferroptosis for the first time, elucidating how these epigenetic mechanisms influence the pathological processes of complications such as diabetic nephropathy, retinal lesions, and peripheral neuropathy. Although current research has revealed some associations between epigenetic regulation and key ferroptosis genes (such as GPX4, ACSL4, and SLC7A11), the targeted development of epigenetic drugs is still in the exploratory phase. Future research should build intervention strategies based on the epigenetic-ferroptosis axis and promote the clinical translation of related drugs, providing new targets and ideas for the prevention and treatment of diabetic complications.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NO.82160701), the Guangxi Natural Science Foundation (No.2018GXNSFAA281168; NO.2025GXNSFAA069059), the Guilin scientific research and technology development plan project (NO.202102275).

References

[1] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2011 Jan;34 Suppl 1(Suppl 1): S62-9.

[2] Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022 Jan; 183:109119.

[3] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018 Feb;14(2):88-98.

[4] Abel ED, Gloyn AL, Evans-Molina C, Joseph JJ, Misra S, Pajvani UB, Simcox J, Susztak K, Drucker DJ. Diabetes mellitus-Progress and opportunities in the evolving epidemic. Cell. 2024 Jul 25;187(15):3789-3820.

[5] Jin EJ, Jo Y, Wei S, Rizzo M, Ryu D, Gariani K. Ferroptosis and iron metabolism in diabetes: Pathogenesis, associated complications, and therapeutic implications. Front Endocrinol (Lausanne). 2024 Aug 30; 15:1447148.

[6] Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021 Apr;22(4):266-282.

[7] Musheshe N, Oun A, Sabogal-Guáqueta AM, Trombetta-Lima M, Mitchel SC, Adzemovic A, Speek O, Morra F, van der Veen CHJT, Lezoualc'h F, Cheng X, Schmidt M, Dolga AM. Pharmacological Inhibition of Epac1 Averts Ferroptosis Cell Death by Preserving Mitochondrial Integrity. Antioxidants (Basel). 2022 Feb 4;11(2):314.

[8] Zhang Z, Li L, Fu W, Fu Z, Si M, Wu S, Shou Y, Pei X, Yan X, Zhang C, Wang T, Liu F. Therapeutic effects of natural compounds against diabetic complications via targeted modulation of ferroptosis. Front Pharmacol. 2024 Sep 18; 15:1425955.

[9] Zhou D, Lu P, Mo X, Yang B, Chen T, Yao Y, Xiong T, Yue L, Yang X. Ferroptosis and metabolic syndrome and complications: association, mechanism, and translational applications. Front Endocrinol (Lausanne). 2024 Jan 8; 14:1248934.

[10] Miao R, Fang X, Zhang Y, et al. Iron metabolism and ferroptosis in typediabetes mellitus and complications: mechanisms and therapeutic oppoties. Cell Death Dis. 2023 Mar 8;14(3):186.

[11] Ling C, Rönn T. Epigenetics in Human Obesity and Type 2 Diabetes. Cell Metab. 2019 May

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

7;29(5):1028-1044.
[12] Christofferson DE, Yuan J. Necroptosis as an alternative form of programmed cell death. Curr Opin Cell Biol. 2010 Apr;22(2):263-8.
[13] Li J, Zhou Y, Wang H, Lou J, Lenahan C, Gao S, Wang X, Deng Y, Chen H, Shao A. Oxidative Stress-Induced Ferroptosis in Cardiovascular Diseases and Epigenetic Mechanisms. Front Cell Dev Biol. 2021 Aug 19; 9:685775.
[14] Jacquemyn J, Ralhan I, Ioannou MS. Driving factors of neuronal ferroptosis. Trends Cell Biol. 2024 Jul;34(7):535-546.
[15] Yang M, Luo H, Yi X, Wei X, Jiang DS. The epigenetic regulatory mechanisms of ferroptosis and its implications for biological processes and diseases. MedComm (2020). 2023 May 22;4(3): e267.
[16] Wu J, Zhu S, Wang P, Wang J, Huang J, Wang T, Guo L, Liang D, Meng Q, Pan H. Regulators of epigenetic change in ferroptosis-associated cancer (Review). Oncol Rep. 2022 Dec;48(6):215.
[17] He J, Li Z, Xia P, Shi A, FuChen X, Zhang J, Yu P. Ferroptosis and ferritinophagy in diabetes complications. Mol Metab. 2022 Jun; 60:101470.
[18] Pei Y, Qian Y, Wang H, Tan L. Epigenetic Regulation of Ferroptosis-Associated Genes and Its Implication in Cancer Therapy. Front Oncol. 2022 Jan 31; 12:771870.
[19] DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol. 2021 May;17(5):319-334.
[20] Wang X, Li Q, Sui B, Xu M, Pu Z, Qiu T. Schisandrin A from Schisandra chinensis Attenuates Ferroptosis and NLRP3 Inflammasome-Mediated Pyroptosis in Diabetic Nephropathy through Mitochondrial Damage by AdipoR1 Ubiquitination. Oxid Med Cell Longev. 2022 Aug 11; 2022:5411462.
[21] Pei Z, Chen Y, Zhang Y, Zhang S, Wen Z, Chang R, Ni B, Ni Q. Hirsutine mitigates ferroptosis in podocytes of diabetic kidney disease by downregulating the p53/GPX4 signaling pathway. Eur J Pharmacol. 2025 Mar 15; 991:177289.
[22] Zheng Q, Xing J, Li X, Tang X, Zhang D. PRDM16 suppresses ferroptosis to protect against sepsis-associated acute kidney injury by targeting the NRF2/GPX4 axis. Redox Biol. 2024 Dec; 78:103417.
[23] Li SY, Zhao N, Wei D, Pu N, Hao XN, Huang JM, Peng GH, Tao Y. Ferroptosis in the ageing retina: A malevolent fire of diabetic retinopathy. Ageing Res Rev. 2024 Jan; 93:102142.
[24] Wang Y, Song SY, Song Y, Wang Y, Wan ZW, Sun P, Yu XM, Deng B, Zeng KH. Resveratrol Protects Müller Cells Against Ferroptosis in the Early Stage of Diabetic Retinopathy by Regulating the Nrf2/GPx4/PTGS2 Pathway. Mol Neurobiol. 2025 Mar;62(3):3412-3427.
[25] Luo L, Cai Y, Jiang Y, Gong Y, Cai C, Lai D, Jin X, Guan Z, Qiu Q. Pipecolic acid mitigates ferroptosis in diabetic retinopathy by regulating GPX4-YAP signaling. Biomed Pharmacother. 2023 Dec 31; 169:115895.
[26] Wang R, Zhang X, Ye H, Yang X, Zhao Y, Wu L, Liu H, Wen Y, Wang J, Wang Y, Yu M, Ma C, Wang L. Fibroblast growth factor 21 improves diabetic cardiomyopathy by inhibiting ferroptosis via ferritin pathway. Cardiovasc Diabetol. 2024 Nov 2;23(1):394.
[27] Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013 Jan;38(1):23-38.
[28] Ahmed SAH, Ansari SA, Mensah-Brown EPK, Emerald BS. The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clin Epigenetics. 2020 Jul 11;12(1):104.
[29] Kesharwani D, Kumar A, Rizvi A, Datta M. miR-539-5p regulates Srebf1 transcription in the skeletal muscle of diabetic mice by targeting DNA methyltransferase 3b. Mol Ther Nucleic Acids. 2022 Aug 13; 29:718-732.
[30] Tóth DM, Szeri F, Ashaber M, Muazu M, Székvölgyi L, Arányi T. Tissue-specific roles of de novo DNA methyltransferases. Epigenetics Chromatin. 2025 Jan 17;18(1):5.
[31] Gowher H, Jeltsch A. Mammalian DNA methyltransferases: new discoveries and open questions[J]. Biochem Soc Trans, 2018, 46(5): 1191-1202.
[32] Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, Yi C, Lindahl T, Pan T, Yang YG, He C. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol. 2011 Oct 16;7(12):885-7.
[33] Deng X, Su R, Feng X, Wei M, Chen J. Role of N6-methyladenosine modification in cancer. Curr Opin Genet Dev. 2018 Feb; 48:1-7.
[34] Huang W, Chen TQ, Fang K, Zeng ZC, Ye H, Chen YQ. N6-methyladenosine methyltransferases: functions, regulation, and clinical potential. J Hematol Oncol. 2021 Jul 27;14(1):117.
[35] Zhang G, Wu K, Jiang X, Gao Y, Ding D, Wang H, Yu C, Wang X, Jia N, Zhu L. The role of ferroptosis-related non-coding RNA in liver fibrosis. Front Cell Dev Biol. 2024 Dec 9; 12:1517401.
[36] Wang J, Samuels DC, Zhao S, Xiang Y, Zhao YY, Guo Y. Current Research on Non-Coding Ribonucleic Acid (RNA). Genes (Basel). 2017 Dec 5;8(12):366.
[37] Jiang Y, Song S, Liu J, Zhang L, Guo X, Lu J, Li L, Yang C, Fu Q, Zeng B. Epigenetic regulation of

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

programmed cell death in hypoxia-induced pulmonary arterial hypertension. Front Immunol. 2023 Sep 11; 14:1206452.
[38] Ji Y, Liu S, Zhang Y, Min Y, Wei L, Guan C, Yu H, Zhang Z. Lysine crotonylation in disease: mechanisms, biological functions and therapeutic targets. Epigenetics Chromatin. 2025 Mar 22;18(1):13.
[39] Mallipattu SK, Estrada CC, He JC. The critical role of Krüppel-like factors in kidney disease. Am J Physiol Renal Physiol. 2017 Feb 1;312(2): F259-F265.
[40] Cai S, Zhu H, Chen L, Yu C, Su L, Chen K, Li Y. Berberine Inhibits KLF4 Promoter Methylation and Ferroptosis to Ameliorate Diabetic Nephropathy in Mice. Chem Res Toxicol. 2024 Oct 21;37(10):1728-1737.
[41] Wang H, Zhao R, Guo C, Jiang S, Yang J, Xu Y, Liu Y, Fan L, Xiong W, Ma J, Peng S, Zeng Z, Zhou Y, Li X, Li Z, Li X, Schmitt DC, Tan M, Li G, Zhou M. Knockout of BRD7 results in impaired spermatogenesis and male infertility. Sci Rep. 2016 Feb 16; 6:21776.
[42] Hernández-Herrador M, Marilina GA, Luisa Hortas M, Carrillo-Lucena S, Caracuel Z, Castilla-Alcalá JA, Martín-García D, Redondo M. Clusterin expression and distribution in spermatozoa as predictor of male fertility. Mol Reprod Dev. 2024 Jul;91(7): e23764.
[43] Xiao Y, Liang Z, Qiao J, Zhu Z, Liu B, Tian Y. BRD7 facilitates ferroptosis via modulating clusterin promoter hypermethylation and suppressing AMPK signaling in diabetes-induced testicular damage. Mol Med. 2024 Jul 12;30(1):100.
[44] Stoyanovsky DA, Tyurina YY, Shrivastava I, Bahar I, Tyurin VA, Protchenko O, Jadhav S, Bolevich SB, Kozlov AV, Vladimirov YA, Shvedova AA, Philpott CC, Bayir H, Kagan VE. Iron catalysis of lipid peroxidation in ferroptosis: Regulated enzymatic or random free radical reaction? Free Radic Biol Med. 2019 Mar; 133:153-161.
[45] Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, Fulda S, Gascón S, Hatzios SK, Kagan VE, Noel K, Jiang X, Linkermann A, Murphy ME, Overholtzer M, Oyagi A, Pagnussat GC, Park J, Ran Q, Rosenfeld CS, Salnikow K, Tang D, Torti FM, Torti SV, Toyokuni S, Woerpel KA, Zhang DD. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. Cell. 2017 Oct 5;171(2):273-285.
[46] Zhang X, Huang Z, Xie Z, Chen Y, Zheng Z, Wei X, Huang B, Shan Z, Liu J, Fan S, Chen J, Zhao F. Homocysteine induces oxidative stress and ferroptosis of nucleus pulposus via enhancing methylation of GPX4. Free Radic Biol Med. 2020 Nov 20; 160:552-565.
[47] Wei F, Ruan B, Dong J, Yang B, Zhang G, Kelvin Yeung WK, Wang H, Cao W, Wang Y. Asperosaponin VI inhibition of DNMT alleviates GPX4 suppression-mediated osteoblast ferroptosis and diabetic osteoporosis. J Adv Res. 2024 Dec 6: S2090-1232(24)00554-X.
[48] Wang Y, Zou J, Zhou H. N6-methyladenine RNA methylation epigenetic modification and diabetic microvascular complications. Front Endocrinol (Lausanne). 2024 Sep 4; 15:1462146.
[49] Luan F, Liu P, Ma H, Yue X, Liu J, Gao L, Liang X, Ma C. Reduced nucleic ZHX2 involves in oncogenic activation of glypican 3 in human hepatocellular carcinoma. Int J Biochem Cell Biol. 2014 Oct; 55:129-35.
[50] Meng W, Li L. ZHX2 inhibits diabetes-induced liver injury and ferroptosis by epigenetic silence of YTHDF2. Nutr Diabetes. 2025 Feb 22;15(1):6.
[51] Lin Y, Shen X, Ke Y, Lan C, Chen X, Liang B, Zhang Y, Yan S. Activation of osteoblast ferroptosis via the METTL3/ASK1-p38 signaling pathway in high glucose and high fat (HGHF)-induced diabetic bone loss. FASEB J. 2022 Mar;36(3): e22147.
[52] Balihodzic A, Prinz F, Dengler MA, Calin GA, Jost PJ, Pichler M. Non-coding RNAs and ferroptosis: potential implications for cancer therapy. Cell Death Differ. 2022 Jun;29(6):1094-1106.
[53] Xiao J, Xu Z. Roles of noncoding RNAs in diabetic retinopathy: Mechanisms and therapeutic implications. Life Sci. 2024 Nov 15; 357:123092.
[54] Loganathan T, Doss C GP. Non-coding RNAs in human health and disease: potential function as biomarkers and therapeutic targets. Funct Integr Genomics. 2023 Jan 10;23(1):33.
[55] Tarangelo A, Magtanong L, Bieging-Rolett KT, Li Y, Ye J, Attardi LD, Dixon SJ. p53 Suppresses Metabolic Stress-Induced Ferroptosis in Cancer Cells. Cell Rep. 2018 Jan 16;22(3):569-575.
[56] Yuan F, Han S, Li Y, Li S, Li D, Tian Q, Feng R, Shao Y, Liang X, Wang J, Lei H, Li X, Duan Y. miR-214-3p attenuates ferroptosis-induced cellular damage in a mouse model of diabetic retinopathy through the p53/SLC7A11/GPX4 axis. Exp Eye Res. 2025 Apr; 253:110299.
[57] Zou HL, Wang Y, Gang Q, Zhang Y, Sun Y. Plasma level of miR-93 is associated with higher risk to develop type 2 diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2017 Jun;255(6):1159-1166.
[58] Zhan D, Zhao J, Shi Q, Lou J, Wang W. 25-hydroxyvitamin D3 inhibits oxidative stress and ferroptosis in retinal microvascular endothelial cells induced by high glucose through down-regulation of miR-93. BMC Ophthalmol. 2023 Jan 13;23(1):22.

ISSN 2618-1584 Vol. 7, Issue 2: 138-145, DOI: 10.25236/FMSR.2025.070220

[59] Chen E, Yi J, Jiang J, Zou Z, Mo Y, Ren Q, Lin Z, Lu Y, Zhang J, Liu J. Identification and validation of a fatty acid metabolism-related lncRNA signature as a predictor for prognosis and immunotherapy in patients with liver cancer. BMC Cancer. 2022 Oct 4;22(1):1037.
[60] Fang X, Song J, Chen Y, Zhu S, Tu W, Ke B, Wu L. LncRNA SNHG1 knockdown inhibits hyperglycemia induced ferroptosis via miR-16-5p/ACSL4 axis to alleviate diabetic nephropathy. J Diabetes Investig. 2023 Sep;14(9):1056-1069.
[61] Ni T, Huang X, Pan S, Lu Z. Inhibition of the long non-coding RNA ZFAS1 attenuates ferroptosis by sponging miR-150-5p and activates CCND2 against diabetic cardiomyopathy. J Cell Mol Med. 2021 Nov;25(21):9995-10007.
[62] Jin J, Wang Y, Zheng D, Liang M, He Q. A Novel Identified Circular RNA, mmu_mmu_circRNA_0000309, Involves in Germacrone-Mediated Improvement of Diabetic Nephropathy Through Regulating Ferroptosis by Targeting miR-188-3p/GPX4 Signaling Axis. Antioxid Redox Signal. 2022 Apr;36(10-12):740-759.
[63] Haque ME, Jakaria M, Akther M, Cho DY, Kim IS, Choi DK. The GCN5: its biological functions and therapeutic potentials. Clin Sci (Lond). 2021 Jan 15;135(1):231-257.
[64] Zhen J, Sheng X, Chen T, Yu H. Histone acetyltransferase Kat2a regulates ferroptosis via enhancing Tfrc and Hmox1 expression in diabetic cardiomyopathy. Cell Death Dis. 2024 Jun 10;15(6):406.
[65] Li F, Ye H, Li L, Chen Q, Lan X, Wu L, Li B, Li L, Guo C, Ashrafizadeh M, Sethi G, Guo J, Wu L. Histone lysine crotonylation accelerates ACSL4-mediated ferroptosis of keratinocytes via modulating autophagy in diabetic wound healing. Pharmacol Res. 2025 Mar; 213:107632.
[66] Wang H, Wang J, Ran Q, Leng Y, Liu T, Xiong Z, Zou D, Yang W. Identification and functional analysis of the hub Ferroptosis-Related gene EZH2 in diabetic kidney disease. Int Immunopharmacol. 2024 May 30; 133:112138.