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REVIEW
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Epigenetics and Inflammation in Diabetic Nephropathy

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Diabetic nephropathy (DN) leads to high morbidity and disability. Inflammation plays a critical role in the pathogenesis of DN, which involves renal cells and immune cells, the microenvironment, as well as extrinsic factors, such as hyperglycemia, chemokines, cytokines, and growth factors. Epigenetic modifications usually regulate gene expression via DNA methylation, histone modification, and non-coding RNAs without altering the DNA sequence. During the past years, numerous studies have been published to reveal the mechanisms of epigenetic modifications that regulate inflammation in DN. This review aimed to summarize the latest evidence on the interplay of epigenetics and inflammation in DN, and highlight the potential targets for treatment and diagnosis of DN.

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

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INTRODUCTION

The latest Diabetes Atlas by the International Diabetes Federation indicates that the current number of patients with diabetes mellitus (DM) is 463 million in 2019, which is estimated to increase to 578 million by 2030 and to 700 million by 2045 (International Diabetes Federation, 2019). DM and its complications seriously affect patients' quality of life and result in tremendous socioeconomic burdens (GBD, 2017 Disease and injury incidence and prevalence collaborators, 2018; Lin et al., 2020b). Diabetic nephropathy (DN), one of the most common microvascular complications of DM, is the major contributor to chronic kidney disease (CKD) and end-stage renal disease (Ruiz-Ortega et al., 2020). Approximately 30–40% of DM patients gradually develop DN (Lim, 2014). Current therapies, including intensive glucose control and the treatment of hypertension through renin-angiotensin-aldosterone system (RAAS) blockers, only slow down the progression of DN and fail to reverse or stop it (Sanz et al., 2019; Ruiz-Ortega et al., 2020). Therefore, early diagnosis and novel treatment for DN are of great significance while recognizing its etiology remains urgent.

The biologist Conrad Waddington firstly introduced 'epigenetics' which describes a phenomenon of inheritance that is independent of DNA sequence (Russo et al., 1996; Goldberg et al., 2007). This concept has become one of the frontiers of genetic research over the years. Epigenetic modifications modulate gene expressions through DNA methylation, histone modification, and non-coding RNAs involving in the pathogenesis of DN (Keating and El-Osta, 2013; Reddy et al., 2015). Studies have also shown that the modifications are reversible indicating potential therapeutic value for DN (Hotamisligil, 2017; Kato and Natarajan, 2019). Low grade chronic inflammation is a major characteristic in the pathogenesis of DN, but the pathophysiological relevance between epigenetics and inflammation has not been

fully summarized. In this review, we highlighted recent epigenetic modifications relevant to inflammation and its signaling pathways in DN. The prespecified search strategies were shown in the **Supplementary Material 1**.

INFLAMMATION IN THE PROGRESSION OF DN

The Role of Renal Resident and Immune Cells in the Inflammatory Response

Hyperglycemia and glucose metabolites such as advanced glycation end products (AGEs) have long been regarded as initial factors of DN which promote the loss of podocytes, the hyperfiltration of endothelial cells, the expansion of mesangial cells and the thickening of glomerular basement membrane, and finally result in the deposition of extracellular matrix in the glomerulus (Schena and Gesualdo, 2005; Grabias and Konstantopoulos, 2014). The injured resident cells in kidney release chemokines and cytokines to attract the infiltration of immune cells (e.g., monocytes, macrophages, dendritic cells, and lymphocytes) (Tang and Yiu, 2020). Macrophages/monocytes are found to be the most predominant immune cells through both clinical and experimental studies. Previous study shows that macrophages are positively associated with pathological lesions in DN (Chow et al., 2004). A recent study of single cell RNA sequencing (scRNA-seq) indicates proportions of endothelial cells and immune cells are significantly increased while mesangial cells and podocytes are decreased in the glomerular cells in diabetic mouse kidney (Fu et al., 2019a). Among of immune cells in this study, macrophages are predominant, particularly M1 phenotype macrophages (Fu et al., 2019a). It has been also demonstrated that infiltration of macrophages in the glomeruli and tubulointerstitial tissues was increased in renal biopsies of patients (Klessens et al., 2017). In addition, the depletion of macrophages significantly reduces proteinuria and glomerular pathological changes in diabetic mice (You et al., 2013). The scRNA-seq analysis of kidney cortex from diabetic (n = 3) and non-diabetic patients (n = 3) shows patients in early diabetic nephropathy have 78 folds of leukocytes, including T cells, B cells, monocytes and plasma cells, compared to non-diabetic patients (Wilson et al., 2019). Few macrophages are observed in early diabetic kidneys (Wilson et al., 2019). Proportions of kidney cells and immune cells, and their roles at different stages of DN needed to be further studies. Epigenetic modifications in diabetic kidneys are shown in **Figure 1**.

The infiltration of macrophages is promoted by chemokines and adhesion molecules which are released from resident cells under the stimulation of high glucose and AGEs (Hickey and Martin, 2013). Notably, MCP-1 is an important mediator in the infiltration of macrophages and the progression of inflammation (Chow et al., 2006). The deletion of MCP-1 in mice and inhibition of MCP-1 in type 2 diabetic patients have been shown to improve renal function (Chow et al., 2006). Previous studies have shown that an increase in M1 macrophages is negatively associated with renal function (Wang et al., 2017), while the induction of M2 macrophages has been shown to attenuate renal damage in DN mouse model (Sun et al., 2015). High glucose and AGEs promote macrophages to M1 polarization and the release of inflammatory cytokines, such as tumor necrosis factor (TNF), contributing to pathogenesis in the early stage of diabetes (Webster et al., 1997). Additionally, macrophages can also act as myofibroblasts through the process of macrophage-myofibroblast transition (MMT) to deteriorate renal fibrosis, replace parenchyma tissue with (Tang et al., 2020b) extracellular matrix (ECM), and also contribute to the production of reactive oxygen species (ROS) and proteases (Meng et al., 2014; Torres et al., 2020). Orchestrated by TGF-β/Smad signaling pathway, MMT is a newly known fibrosis process which has been rarely found neither in acute inflammation, nor in normal kidney, indicating that chronic inflammation was the principle contributor to fibrosis (Meng et al., 2016; Tang et al., 2019). A recent study has found that brain-specific transcription factor POU4F1 is the only transcription factor taking part in the TGF-β1/Smad3-driven MMT and thus could be a new therapeutic target in chronic inflammation induced MMT fibrosis (Tang et al., 2020b). The proto-oncogene tyrosine protein kinase *SRC* presents as a direct SMAD3 target gene and is also essential for MMT in macrophages (Tang et al., 2018b). In general, the accumulation of macrophage are not only related to the degree of inflammation and kidney function, but also correlated to glomerulosclersis and the degree of interstitial fibrosis (Tang et al., 2019). Studies have shown that aberrant intrarenal infiltration and activation of T cells are involved in the pathogenesis of DN in both clinical samples and streptozotocin (STZ)-induced diabetes mice (Moon et al., 2012). Clinical findings show that T cell immunity and TNF-α signaling pathway are activated during the early development of DN in patients (Moon et al., 2012; Lampropoulou et al., 2020). The proportions of T helper cells (Th1, Th2, Th17 and regulatory T (Treg) cells) in DN are altered with the increased levels of Th1 and Th17, and the decreased level of Treg (Zhang et al., 2014). Adoptive transfer of CD4 + Foxp3 + Treg cells in mice have been found to ameliorate diabetic kidney injuries and insulin resistance by inhibiting inflammation (Eller et al., 2011).

The Role of Inflammatory Mediators and Signaling Pathways in DN

Several signaling pathways contribute to the inflammation and the release of inflammatory cytokines (**Figure 2**; Newton and Dixit, 2012). Interleukins (ILs) play critical roles in the regulation of the immune system. Studies have shown that the circulating level of IL-6 is positively correlated with the progression of DN in patients (Saraheimo et al., 2003), and IL-1β, IL-18, and IL-17A are associated with the occurrence and development of DN (Cortvrindt et al., 2017; Lemos et al., 2018; Lin et al., 2020a). TNF-α is involved in the development of various diseases, such as psoriasis, rheumatoid arthritis, and CKD (Elliott et al., 1994; Pina et al., 2016). Studies have demonstrated that macrophages are the main source of renal TNF-α (Awad et al., 2015). In diabetic mice, the inhibition of TNF-α leads to decreased urinary albumin excretion, and in a clinical trial where DN patients were treated with pentoxifylline,

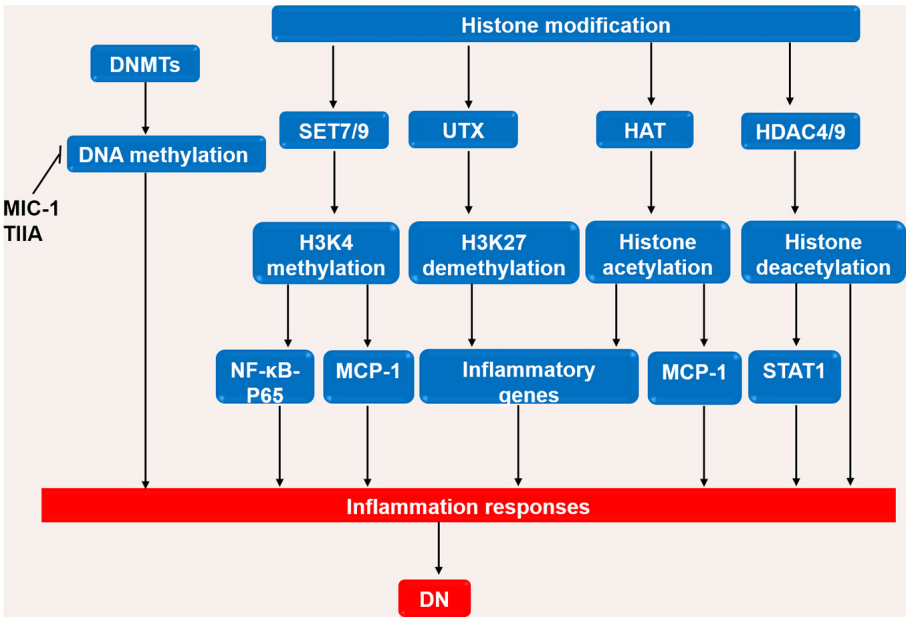

FIGURE 1 | Interaction of immune cells, kidney intrinsic cells and epigenetic modifications. DNA methylation, histone modifications, and non-coding RNA modifications activate inflammatory pathways by interactions of immune cells and kidney intrinsic cells. OS, oxidative stress; ROS, reactive oxygen species; HG, high glucose; Ang II, angiotensin II; AGE-RAGE, advanced glycation end-products-receptor for advanced glycation end products; IL, interleukin; TNF, tumor necrosis factor; MCP-1, monocyte chemoattractant protein 1; NF-κB, nuclear factor-κB; JAK-STAT, Janus kinase/signal transducer and activator of transcription; NRF2, Nuclear Factor-2 Erythroid Related Factor; NLRP, NOD-like receptor pyrin domain-containing protein.

a methylxanthine derivative with anti-inflammatory function, the reduction in urinary TNF-α concentration was directly correlated with the change in albuminuria, suggesting the role of TNF-α in the pathogenesis of DN (Moriwaki et al., 2007; Navarro-González et al., 2015).

Nuclear factor-κB (NF-κB) is the basic transcription factor that plays a pivotal role in inflammation in DN patients. Activated by upstream signals such as AGEs, angiotensin II, and oxidative stress (OS), NF-κB dissociates from its inhibitor IκB proteins and is transferred into the nucleus to regulate the expression of inflammatory gene including cytokines, chemokines, and adhesion molecules such as IL-6, TNF-α, and MCP-1 (Wada and Makino, 2016; Mikuda et al., 2018). One of the upstream signal pathways stimulated by AGEs is called the p38 mitogen-activated protein kinase (MAPK) pathway (Wu et al., 2002). The p38 MAPK pathway induces the activation of NF-κB in the infiltrating macrophages of DN (Adhikary et al., 2004). In turn, in renal parenchymal cells, elevated IL-1 and TNF-α have been shown to promote the phosphorylation of p38 MAPK, demonstrating their inflammatory roles in DN (Adhikary et al., 2004). Similarly, PI3K/AKT/mTOR is a widely studied signaling pathway that mediates the phenotype and injury of podocytes in DN. Stimulated by AGEs, PI3K/AKT can also promote NF-κB and aggravate inflammation (Ahmad et al., 2013; Hong et al., 2017). Recently, C-reactive protein (CRP) has been found to trigger a novel NF-κB-involved signaling pathway in the progression of DN, more narrowly, in human CRP transfected-db/db mice and cultured renal tubular epithelial cells, CRP is proved to promote inflammation via the evoking and dimerization of dipeptidyl peptidase-4 (DPP4) through DPP4/CD32b/NF-kB signaling circuit. The blockage of the circuit by the DPP4 inhibitor, linagliptin, attenuates DN, suggesting the potential therapeutic effect for DN (Tang et al., 2021).

TGF-β/SMAD signaling pathway plays a criticial role in diabetic kidney injuries (Chen et al., 2011, 2014a; Liu et al., 2011; Lan, 2012; Zhong et al., 2013; Li et al., 2014; Zhang et al., 2019b; Xu et al., 2020a; Yang et al., 2020). In the diabetic kidney, high glucose and AGEs enhance the phosphorylation of SMAD3 and decrease the phosphorylation SMAD7. SMAD3 deficiency prevents renal inflammation and fibrosis in SMAD3-db/db mice via regulations of lncRNA Erbb4-IR.transcription and miR-29b (Xu et al., 2020a). SMAD3 deficiency protects against diabetes-associated beta cell dysfunction and loss in DN mice (Sheng et al., 2021). SMAD3 also promotes autophagy dysregulation and kidney injury (Yang et al., 2020). SMAD7 inhibits IκBα, an NF-κB inhibitor, suppressing the activation of NF-κB pathway (Chung et al., 2009). The deletion of SMAD7 significantly aggravates renal inflammation as evidenced by the upregulation of IL-1β, TNF-α, and MCP-1 in diabetic mice by crosstalk with NF-κB pathway, and the addition of SMAD7 attenuates the kidney injuries (Chen et al., 2011). Thus, TGF-β/SMAD and NF-κB crosstalk pathway may act as a novel prevention and therapeutic targets for diabetic nephropathy.

Activation of OS signaling pathways contributes to renal inflammation in DN. Nuclear factor-2 erythroid related factor (NRF2) is a protein that has the ability to alleviate inflammation and act as an antioxidant mediator in the process

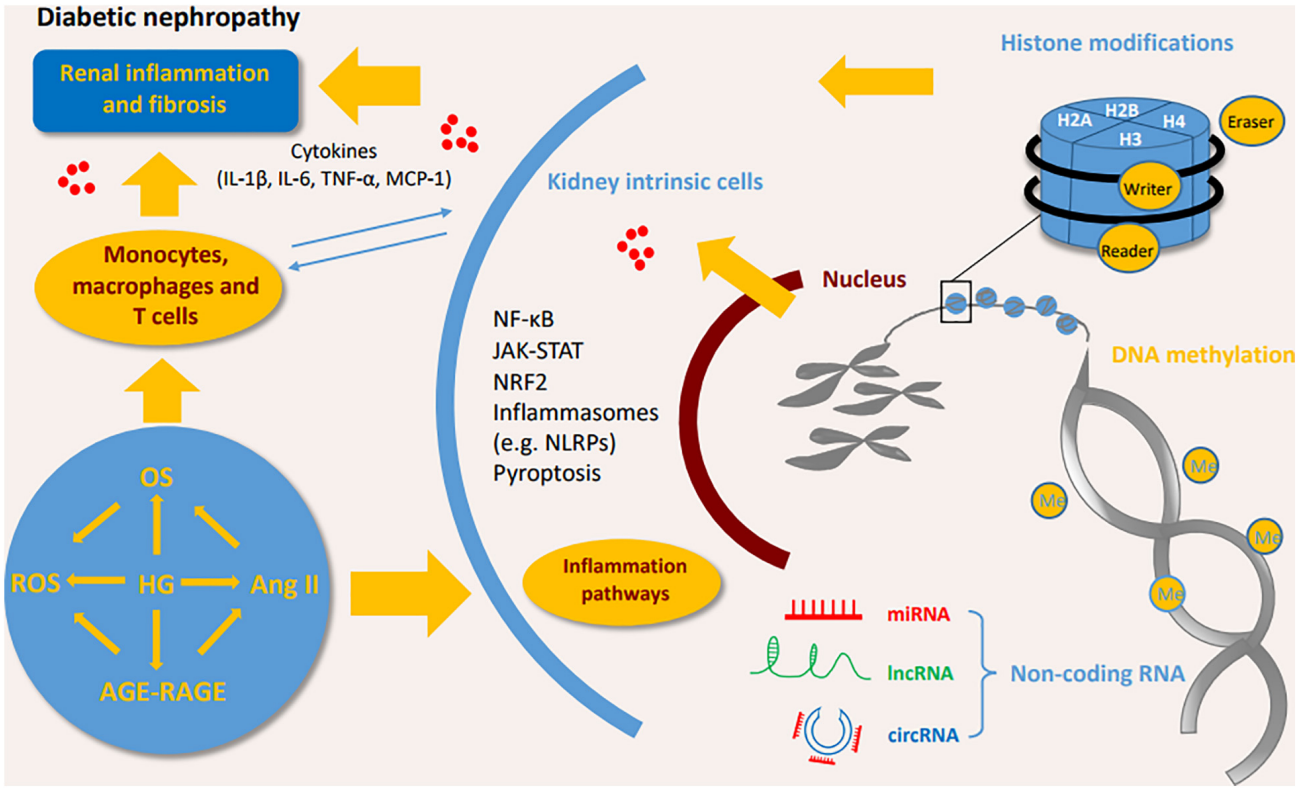

FIGURE 2 | The inflammatory pathways involved in the DN process. High glucose or stimulating factors cause the activation of multiple pathways, including P38/MAPK, PI3K/AKT, TLR4/NLRP3 and the novel CRP/DPP4/CD32b, which all further activate NF-κB pathway, and transcriptionally promote the expression of multiple inflammatory cytokines to enhance inflammation. SMAD7 can inhibit NF-κB activity. NRF2 has anti-inflammatory and antioxidant functions in DN. In addition, JAK/STAT pathway induces IL-6 to promote the inflammatory response in DN. DN, diabetic nephropathy; IL, interleukin; TNF, tumor necrosis factor; NF-κB, Nuclear factor-κB; MCP-1, monocyte chemoattractant protein-1; STAT, Signal transducer and activator of transcription; NRF2, Nuclear factor-2 erythroid related factor; NLRP3, NOD-like receptor protein 3; ROS, reactive oxygen species; DPP4, dipeptidyl peptidase-4; MAPK, mitogen-activated protein kinase; JAK2, Janus kinase; TLR4, Toll-like receptors 4; CRP, C-reactive protein; AGE, advanced glycation end product; RAGE, Receptor for advanced glycosylation end products; Ang II, angiotensin II; TGF, Transforming growth factor.

of OS. NRF2 reduces the infiltration of macrophages and proinflammatory cytokines by ameliorating oxidative overload. Clinical studies have demonstrated that the NRF2 activator, such as bardoxolone methyl, improves kidney function in diabetic patients (Pergola et al., 2011).

The nucleotide-binding oligomerization domain (NOD) family and NOD-like receptor pyrin domain-containing protein (NLRP) family are involved in DN. NOD2 promotes the endothelial-to-mesenchymal transition in DN (Shang et al., 2017). NLRP3 promotes the generation of IL-1β and IL-18 by activating the NLRP3-Caspase-1-IL-1β pathway in diabetic kidneys (Chi et al., 2020; Wang et al., 2020). NLRP3 has interactions with Toll-like receptors, ROS and NF-κB pathway to promote inflammation in DN (Shahzad et al., 2015; Wang et al., 2020).

The Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway is involved in processing extracellular signals (cytokines and chemokines) to the cell nucleus, resulting in gene expression (O'shea et al., 2013). The clinical findings show that JAK2 is increased in the podocytes of patients with early DN (Berthier et al., 2009). Podocyte-specific JAK2 overexpression in diabetic mice aggravates glomerulopathy while the inhibition of JAK1/2 attenuates the phenotypic changes of diabetic kidney (Zhang et al., 2017).

DN AND EPIGENETIC MODIFICATIONS INVOLVED IN INFLAMMATION

DNA Methylation Involved in Inflammation of DN

DNA methylation promotes inflammatory activation of immune cells in diabetic kidney disease and demethylating agents prevent the progressive kidney disease (Larkin et al., 2018; Chen et al., 2019b). DNA methylation is a process in which the methyl group of S-adenosylmethionine is transferred to the cytosine of DNA under the catalysis of DNA methyltransferases (DNMTs), resulting in down-regulation of the gene expression (Yagi et al., 2012). DNMTs mainly include DNMT1, DNMT3a, and DNMT3b. DNMT1 has been found to contribute to the maintenance of methylation and the other DNMTs are related

to *de novo* methylation (Hsieh, 1999). DNA methylation occurs specifically at the 5' site of the CpG dinucleotide cytosine residue, hindering the binding of transcription factors and promoters, subsequently inhibiting transcription (Yagi et al., 2012). The genome-wide DNA methylation analysis shows that DNA methylation is associated the kidney injuries and kidney inflammation in DN patients (VanderJagt et al., 2015; Park et al., 2019). *In vivo* study also indicates high-glucose induced high levels of methylation in kidney cells. It is found that there are 173 differentially methylated regions (DMRs) in high glucose (HG)-treated mesangial cells compared to the low-glucose (LG) treatment (Li et al., 2020d). Suppression of methylation by bioactive constituent extracted from plants, e.g., moringa isothiocyanate (MIC-1), potentially down-regulates expression of *TGF-β1*, and changes the *Nrf2, Col4a2, Tceal3, Ret, and Agt* expressions (Li et al., 2020d; Cheng et al., 2019).

Aberrant cytosine methylation of the upstream regulators of the mammalian target of rapamycin (mTOR) promotes inflammation by the upregulation of DNMT1 in DN (Chen et al., 2019b). Notably, DNA methylation is dynamic and can be altered by environmental factors. Studies have found that hyperglycemia in T2DM patients triggers a self-regulatory mechanism leading to the reduction of 5mC levels in the peripheral blood, which indicates that the DNA might undergo demethylation via the upregulation of ten-eleven-translocation 2 (TET2), a DNA demethylation enzyme (Yuan et al., 2019).

Histone Modifications Involved in Inflammation of DN

The nucleosome is the basic unit of chromatin consisting of DNA and wrapped histone proteins. The post-translational modifications (PTMs) on chromatin histone include acetylation, ubiquitination, phosphorylation, and methylation. Recently, the genome-wide analysis of chromatin binding proteins and histone modifications has been conducted through chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) or by microarrays. The modifications are mainly mediated by three types of enzymes: writer, eraser, and reader. Writers/erasers carry on the modifications by adding/removing methyl or acetyl groups at amino acid residues in histone, such as histone acetyltransferase, histone methyltransferase (HMT), histone deacetylase (HDAC) and histone demethylase (HDM) (Bhatt et al.). Readers are the effectors that can identify and interpret post-translational modifications. Histone acetylation promotes gene transcription, while histone methylation promotes or inhibits gene transcription (Kouzarides, 2007). Specifically, the methylation of histone mostly happens on the residues of lysine and arginine. There are three types of methylation in lysine, namely monomethylation, dimethylation and trimethylation, and all three types of methylation of H3 at lysine 4 (H3K4me1, H3K4me2 and H3K4me3, respectively) exert an active effect (Kato and Natarajan, 2019). Similarly, H3K36me2 and H3K36me3 are enriched at transcriptional activation genome regions (Kato and Natarajan, 2019). Conversely, the methylation of H3K9me3, H3K27me3 and H4K20me3 are associated with gene repression (Kato and Natarajan, 2019). These modifications usually happen at promoters, insulators, enhancers, and other cis-regulatory regions, and finally lead to aberrant gene expression (Barski et al., 2007; Heintzman et al., 2009; Pradeepa et al., 2016).

Histone PTMs are involved in the pathogenesis of DN (Kato and Natarajan, 2019). HG and other danger signals increase the expression of pro-inflammatory genes by histone PTMs (Kato and Natarajan, 2019). *TXNIP*, pro-inflammatory gene, has been demonstrated to play an important role in the development of DN (Chen et al., 2008). In hyperglycemia-induced DN mice, HG-induced *Txnip* expression is associated with the enrichment of activated histone marks H3K9ac, H3K4me3, H3K4me1, and the repressive histone mark H3K27me3 at the promoter region of the gene, which has also been proved in human mesanginal cells (De Marinis et al., 2016). Furthermore, histone methylation take part in the process of inflammation via the secretion of inflammatory cytokines in diabetes. Specifically, H3K4 methylation could be mediated by HMT SET7 (Cheng et al., 2005). It is reported that transient HG causes the recruitment of HMT SET7 and increases H3K4 methylation at the NF-κB -P65 promoter, which promotes the expression of P65, MCP-1 and VCAM-1 in endothelial cells (El-Osta et al., 2008). Meanwhile, in endoplasmic reticulum (ER) stress induced kidney model of db/db mice, the increased expression of *Mcp-1* is associated with the enrichment of H3K4me1 at *Mcp-1* promoters, and could be significantly attenuated by the methyltransferase SET7/9 gene silencing (Chen et al., 2014c). The other study indicates that SET7/9 modifies chromatin histone lysine at promoters of *MCP-1*and *TNF-α* which promotes the inflammation in THP-1 monocytes (Li et al., 2008). In contrast, UTX (ubiquitously transcribed tetratricopeptide repeat, X chromosome) is a histone demethylase that can remove di- and tri-methyl groups from H3K27 (Choi et al., 2015). Studies have reported that the expression of UTX is upregulated in podocytes, tubular and mesangial cells of DN patients *in vitro* and *in vivo* (Majumder et al., 2018). Moreover, the knockout of UTX or the treatment of UTX inhibitor, GSK-J4, can reduce palmitic acid-induced increase of inflammation and DNA damage (Chen et al., 2019c). Furthermore, one study demonstrated that the inhibition of UTX could inhibit hypertrophy, a key event in glomerular dysfunction (Jia et al., 2019). In parallel, TGF-β down-regulates Enhancer of Zeste homolog 2 (EZH2), a H3K27me3 methyltransferase, by inducing miR-101b, which targets the 3'-untranslated region (3'-UTR) of *EZH2*. Meanwhile, TGF-β up-regulates UTX, a key role for H3K27me3 demethylases in renal mesangial cells. TGF-β-induced the inhibition of H3K27me3 augments pathological genes via dysregulation of associated histone-modifying enzymes and miR-101b in DN (Jia et al., 2019). Another H3K27me3 demethylase JMJD3 regulates inflammatory genes in macrophages (De Santa et al., 2007). To conclude, these studies suggest that the inhibition of H3K27me3 augments the expression of inflammation genes and the progression of DN.

Similarly, acetylation and deacetylation of histones via histone acetyltransferases (HATs) and histone deacetylase (HDACs) contribute to the pathogenesis of DN. Hyperglycemia promotes chromatin histone acetylation at inflammatory genes promoter regions and enhances inflammatory gene expressions *in vivo*

(Miao et al., 2004). Levels of H3K9ac, H3K9ac/S10p, H3K18ac, H3K23ac and H3K56ac are increased in the kidneys of db/db mice (Huang et al., 2015). Furthermore, the expression of *Sirt6* (a histone deacetylase) is reduced in podocytes of STZ-induced mice which results high levels of H3K9ac at promoters of *Notch1* and *Notch4*, and exacerbates the inflammation in kidney (Liu et al., 2017). The silencing of HDAC9 attenuates renal injuries as demonstrated by the decrease in glomerulosclerosis, inflammatory cytokines, and alteration of podocyte apoptosis (Liu et al., 2016). The elevated HDAC4 in diabetic kidney exacerbates inflammation via suppressing STAT1 signaling and the silencing of HDAC4 is associated with the decreases of cytokines (TNF-α, TGF-β, IL-8, MCP-1) (Wang et al., 2014). The roles of DNA methylation and histone modification in the DN process are briefly shown in **Figure 3**.

Non-coding RNAs Involved in Inflammation of DN

Non-coding RNAs (ncRNAs) commonly include transfer RNA, ribosomal RNA, long ncRNA (lncRNA), small ncRNA (e.g., microRNA, piRNAs, snoRNA, snRNA, exRNA) and circular RNA (circRNA) (Storz, 2002; Yang, 2015). Roles of microRNA (miRNA), lncRNA and circRNA in DN have been recently studied (Loganathan et al., 2020; Zhou et al., 2021). MiRNA is the best characterized non-coding RNA for transcriptional gene regulation by targeting the 3′-UTR of a specific mRNA. Typically, miRNAs exert their inhibitory actions on the gene via RNA silencing and translational repression (Wilczynska and Bushell, 2015).

MiRNAs play significant roles in regulating inflammation in DN (Zhou et al., 2021). Recent studies involving models of DN podocytes have found that downregulation of the miR-17∼92 cluster ameliorates inflammation and podocyte injury by targeting ABCA1 (ATP-binding cassette transporter A1) (Fan et al., 2020). Similarly, the inhibition of miR-21-5p in a macrophage-derived extracellular vesicle model could also exert podocyte protective effect by the restraint of inflammasome activation (Ding et al., 2020). Moreover, miRNAs are also found to regulate inflammation in renal tubular epithelial cells. The overexpression of miR-199a-3p improves the injury in high glucose induced HK-2 cell damage model, following with decreased IL-1, IL-6 and TNF-α level, which is also consistent with the clinical finding that miR-199a-3p is negatively correlated with the progression of DN (Zhang et al., 2020b). The protective effects of miR-199a-3p is via suppressing miR-199a-3p mediated IKKβ/NF-κB pathway (Zhang et al., 2020b). *In vitro* experiments, the overexpression of miR-26a-5p significantly inhibits the bovine serum albumin (BSA)-induced IL-6 and TNF-α expression in HK2 cells while the inhibition of miR-26a-5p promotes the expression of inflammatory cytokines (Li et al., 2020c). MiR-26a-5p is also found to activate NF-κB pathway by targeting on *CHAC1* and *TLR4* genes (Zhong et al., 2018;

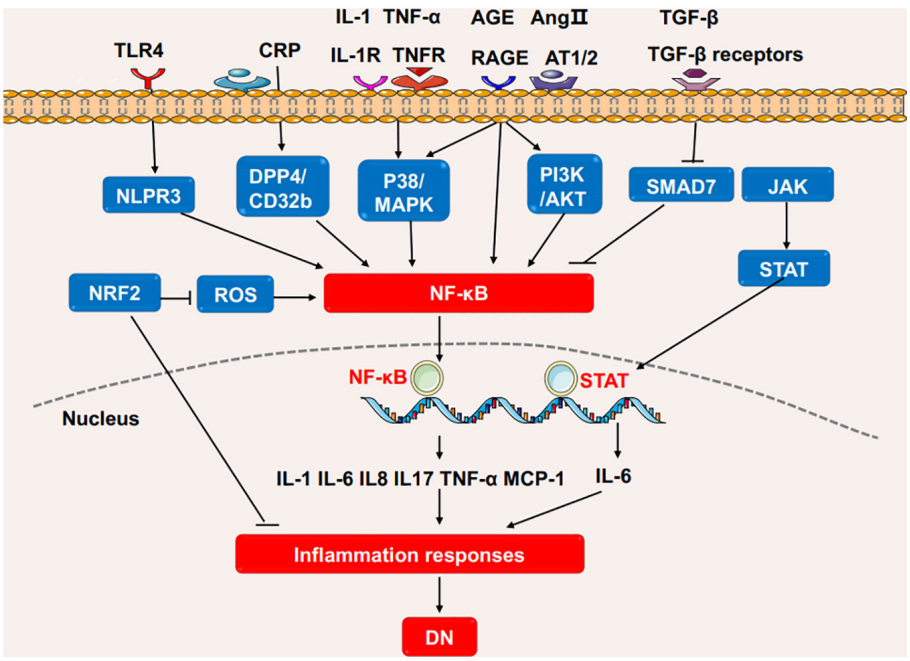

FIGURE 3 | The roles of DNA methylation and histone modification in the DN process. High glucose or stimulating factors cause DNA methylation and histone modification. DNA methylation is mainly regulated by DNMTs. MIC-1 and TIIA inhibits DNA methylation and reduces inflammation in DN. In the processes of histone modification, SET7/9 regulates H3K4 methylation, UTX regulates H3K27 demethylation, HAT promotes histone acetylation, and HDAC4/9 promotes histone deacetylation. The above processes regulate inflammatory genes, in turn affects the inflammatory response in DN. DN, diabetic nephropathy; DNMTs, DNA methyltransferases; UTX, ubiquitously transcribed tetratricopeptide repeat, X chromosome; HAT, histone acetyltransferases; HDAC, histone deacetylase; NF-κB, Nuclear factor-κB; MCP-1, monocyte chemoattractant protein-1; STAT1, Signal transducer and activator of transcription 1.

TABLE 1 | The target genes and potential mechanisms of miRNAs associated with inflammation in DN.

miR	Targeted Genes/Pathway	Inflammation Pathway/Related mediator	Sample	Model	Effect on Inflammation	References
miR-15b-5p	*Sema3A*	IL-1β, TNF-α, and IL-6.	Cells	Mouse podocytes	Alleviate	Fu et al., 2019b
miR-21	*Timp3*	Podocyte apoptosis	Rats	STZ-induced DN rats	Promote	Chen et al., 2018
			Cells	HG-treated podocytes		
miR-21	N/D	NF-κB	Mice	Db/db mice	Promote	Zhong et al., 2013
miR-29	*KEAP1*	SIRT1/NF-κB/microR-29/Keap1	Rats	STZ-induced DN rats	Alleviat	Zhou et al., 2015
			Cells	HG-induced injury in HK-2 cells		
miR-29b	*Sp1*	TNF-α, MCP-1/NF-κB	Mice	Db/db mice	Alleviate	Chen et al., 2014b
miR-31	N/D	The recruitment of leukocytes to vascular walls	Serum	DN patients	Alleviate	Rovira-Llopis et al., 2018
miR-126	*Vegf*	PI3K/AKT/mTOR IL-1β, IL-6, IL-18 and TNF-α	Rats	STZ-induced DN rats	Alleviate	Lou et al., 2020
			Cells	NRK52E		
miR-133	N/D	MAPK/ERK	Rats Cells	STZ-induced DN rats HG-induced injury in HK-2 cells	Promote	Shao et al., 2019
miR-140-5p	N/D	TLR4, NF-κB	Tissue	Kidney tissues from DN patients	Alleviate	Lou et al., 2020
			Cells	HG-induced injury in HK-2 cells		
miR-217	N/D	SIRT1/VEGF/HIF-1α	Serum	DN patients	Promote	Shao et al., 2017
miR-217	N/D	N/A	Cells	Rat glomerular mesangial cells	Promote	Shao et al., 2016
miR-218	N/D	NF-κB	Rats	Rat streptozotocin-induced model of DN	Alleviate	Li et al., 2020b
miR-218	*DACH1*	TNF-α and IL-1β	Cells	HG-induced injury in HK-2 cells	Peomote	Zhang et al., 2020c
miR-218	*GPRC5A*	N/A	Cells	HG-induced injury in HK-2 cells	Promote	Su et al., 2020
miR-325-3p	*CCL19*	N/A	Cells	HK-2 and human MC cells	Promote	Sun et al., 2020a
miR-328-3p	*Tlr4*	TLR4, NF-κB	Cells	MP5 cells	Alleviate	Duan et al., 2020
miR-34b	N/D	IL-6R/JAK2 /STAT3	Cells	HG-induced HK-2 cells	Promote	Lv et al., 2019
miR-451	*Lmp7*	NF-κB	Mice	Db/db mice	Alleviate	Sun et al., 2016
			Cells	HG-induced MCs		
miR-485	*NOX5*	N/A	Cells	Human MCs	Alleviate	Wu et al., 2020
miR-544	*Fasn*	NF-κB	Mice	Db/db mice	Alleviate	Sun et al., 2020b
miR-770-5p	*Timp3*	IL-1β, TNF-α	Cells	HG-induced mouse podocytes	Promote	Wang and Li, 2020
miR-874	N/D	TLR4	Rats	STZ-induced DN rats	Alleviate	Yao et al., 2019
			Cells	HG-induced podocytes		

N/D, not determined; N/A, not available; IL, interleukin; TNF, tumor necrosis factor; DN, diabetic nephropathy; STZ, streptozotocin; HG, High glucose; NF-κB, Nuclear factor-κB; SIRT1, Silent information regulator 1; KEAP1, Kelch-like ECH-associated protein 1; HK-2, human kidney 2; Sp1, specificity protein 1; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor; HIF-1α, hypoxia-inducible factor-1α; NRK52E, rat kidney tubular epithelial cells; MCs, mesangial cells; TLR4, Toll-like receptors 4; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; JAK2, Janus kinase 2; STAT3, Signal transducer and activator of transcription 3.

Li et al., 2020c). MiR-155 and miR-146a have also been found to be correlated with renal damage, possibly due to the increased expression of TNF-α, TGF-β1, and NF-κB, and their roles in inflammation-mediated glomerular endothelial damage (Huang et al., 2014). Moreover, miRNAs regulate inflammation by modulating macrophage polarization. As mentioned before, macrophage M1 polarization act as an inflammation driver. In miR-146a deficiency diabetic mice, the expression of M1 markers is increased while the M2 response is diminished which is in accordance with the upregulated pro-inflammatory cytokines, suggesting the anti-inflammatory proporities of miR-146a (Bhatt et al., 2016). M2 macrophages ameliorate podocyte injury is related to miR-25-3p (Huang et al., 2020). It is found that autophagy deficiency in diabetic mice increases macrophage infiltration in proximal tubules (Ma et al., 2020), and the induction of miR-214 enhances the autophagy impairment, thus aggravating renal inflammation (Li et al., 2011). MiR-214 in monocytes is upregulated by AGEs, which in turn impairs the expression of the phosphatase and tensin homolog (PTEN) and delays spontaneous apoptosis of monocytes (Li et al., 2011). Additionally, miR-27a is downregulated by an adipokine, omentin-1, which alleviates inflammation and OS by directly targeting the 3′-UTR of *Nrf2* (Song et al., 2018). MiR-29b attenuates podocyte injury by targeting the 3′-UTR of HADC4 in DN (Gondaliya et al., 2020). MiR-125b has been found to inhibit the chromatin histone H3K9

TABLE 2 | The target genes and potential mechanisms of lncRNAs associated with inflammation in DN.

lncRNA	Targeted Axis/ Inflammation Pathway	Sample	Model	Effect on Inflammation	References
XIST	miR-485/*PSMB8*	Human	DN patients	Promote	Wang, 2020
		Cells	Human MCs		
RPPH1	*Gal-3/Mek/Erk*	Mice	Db/db mice	Promote	Zhang et al., 2019a
		Cells	HG-induced MCs		
NEAT1	miR-34c/NLRP3- CASPASE-1-IL-1β	Rats	STZ-induced DN rats	Alleviate	Zhan et al., 2020
		Cells	HBZY-1		
MEG3	miR-181a/*Egr-1*/TLR4 pathway	Rats	DN rat models	Promote	Zha et al., 2019
KCNQ1OT1	miR-506-3p/NLRP3-CASPASE-1-IL-1β	Cells	HG-induced HK-2 cells	Promote	Li et al., 2017
MALAT1	miR-23c/NLRP3-CASPASE-1-IL-1β	Rats Cells	STZ-induced DN rats HG-induced HK-2 cells	Promote	Li et al., 2017
Gm4419	NF-κB/NLRP3 inflammasome	Cells	HG-induced MCs	Promote	Yi et al., 2017
NON-HSAG053901	*Egr-1/TGF*-β	Mice Cells	STZ-induced mice Mesangial cells	Promote	Peng et al., 2019
HOTTIP	miR-455-3p/*WNT-2B*	Cells	HG-inducedSV40-MES13 cells and HK-2 cells	Promote	Zhu et al., 2019
GAS5	miR-452-5p/NLRP3-CASPASE-1-IL-1β	Cells	HK-2 cells	Alleviate	Xie et al., 2019
UCA1	miRNA-206	Rats	DN rat models	Alleviate	Yu et al., 2019
		Cells	HK-2 cells		
LRNA9884	*Mcp-1/Smad3*	Mice	Db/db	Promote	Zhang et al., 2019b
		Cells	Mouse tubular epithelial cells		

PSMB8, proteasome subunit beta type-8; DN, diabetic nephropathy; MCs, mesangial cells; HG, high glucose; STZ, streptozotocin; NLRP3, NOD-like receptor protein 3; IL, interleukin; STZ, streptozotocin; HBZY-1, Rat glomerular mesangial cell line; TLR4, Toll-like receptors 4; Egr-1, Early growth response protein 1; HK-2, human kidney tubular epithelial cell 2; WNT-2B, a protein of the Wnt signaling pathway.

methyltransferase to regulate inflammatory genes in diabetic mice (Villeneuve et al., 2010). Hyperglycemia induces miR-101b, which targets the EZH2, leading to mesangial dysfunction in DN (Jia et al., 2019).

Moreover, accumulating evidence shows that a lot of miRNAs are involved in the regulation of inflammation in DN as shown in **Table 1**.

LncRNAs also contribute to the development and progression of DN. LncRNA myocardial infarction associated transcript (MIAT) promotes hyperglycemia-induced podocyte inflammation by sponging miR-130a-3p and the regulation of TLR4 (Zhang et al., 2020a). LncRNA 4930556M19Rik has been found to protect against HG-induced podocyte damage by downregulation miR-27a-3p (Fan and Zhang, 2020). Macrophage-specific lncRNA_7949 mediates macrophage-induced kidney inflammation by the controlling of MCP-1 transcription through TLR4/NF-κB pathway (Lv et al., 2015). TGF-β/Smad3 transits the miRNA profile and promotes renal diseases via regulating transcriptional levels of non-coding RNAs. SMAD3-dependent lncRNAs have been recently uncovered in kidney diseases (Tang et al., 2018a, 2020a). LncRNA Erbb4-IR is responsible for TGF-β/Smad3-regulated renal fibrosis by inhibiting SMAD7 (Feng et al., 2018). It has been reported that lncRNA Erbb4-IR enhances diabetic kidney injury by mediating miR-29b in db/db Mice. Deletion of SMAD3 could down-regulate the lncRNA Erbb4-IR transcription, and therefore protect against renal injury in db/db mice (Sun et al., 2018). LRNA9884, a novel SMAD3-dependent lncRNA, is not only involved into NF-κB-mediated inflammatory responses by activation of macrophage migration inhibitory factor (MIF) in AKI, but also enhances diabetic renal injury via promoting MCP-1-dependent renal inflammation in db/db mice (Zhang et al., 2019b, 2020d; Xu et al., 2020a). The lncRNAs involved in the inflammation of DN are shown in **Table 2**.

CircRNAs regulate gene expressions by acting as sponges of miRNA (Kristensen et al., 2019), and play an important role in renal diseases (Jin et al., 2020). As a sponge of miR-135a, circRNA_010383 is markedly decreased in the kidney of db/db mice and HG-induced kidney resident cells, and overexpression of circRNA_010383 in kidney protects kidney from proteinuria and fibrosis in DN (Peng et al., 2021). CircLRP6, as a sponge of miR-205, activates TLR4/NF-κB pathway and induces inflammation in high glucose treated mesangial cells (Chen et al., 2019a). CircACTR2 induces inflammation and pyroptosis in high glucose treated renal tubular cells (Wen et al., 2020). Circ_0003928 attenuates the high glucose-induced inflammation in HK-2 cells by targeting miR-151-3p/Anxa2 (An et al., 2020). CircWBSCR17 aggravates inflammation and fibrosis in high glucose-induced HK-2 cells via miR-185-5p/SOX6 axis (Li et al., 2020a). Circ0000285 enhances inflammation via sponging miR-654-3p in high glucose treated podocytes and diabetic mouse kidney (Yao et al., 2020).

DISCUSSION

The current evidence reveals epigenetics (methylation, acetylation, and non-coding RNA modification) modulate inflammation via intrinsic cells, immune cells, and numerous inflammatory pathways in the development of DN. Persistent inflammation in DN promotes the renal fibrosis, thus resulting in CKD and even end-stage renal disease (Tang et al., 2020a). Anti-inflammatory therapy has long been considered to have enormous benefits for either the alleviation or the prevention of DN (Barutta et al., 2015). In this review, we summarized the evidence linking epigenetic modifications and inflammation in DN. Thus, it may be an effective approach to target these modifications for DN treatment. As for histone modification, the inhibition of HATs/HDACs provides as a class of new agents or therapeutic targets for the treatment of DN. Most of agents are non-selective inhibitors hindering the clinical application (Wang et al., 2014). Valproic acid is a specific HDAC1 inhibitor, which attenuates proteinuria, fibrosis, and inflammatory effects and even acute pancreatitis (Van Beneden et al., 2011; Jain et al., 2019). However, effects of specific HDAC inhibitors for DN remain largely unexplored.

LncRNAs have been considered the novel markers as well as the potential therapeutic targets, and novel drug delivery vehicles (e.g., exosome-ncRNAs). Metformin has been found to protect against inflammation and ECM accumulation in mesangial cells via the H19/miR-143-3p/TGF-β1 axis, suggesting that the H19/miR-143-3p/TGF-β1 axis could be a potential therapeutic target for the management of DN (Xu et al., 2020b). The competing endogenous RNA (ceRNA) network analysis on human miRNA indicates that RP11-363E7.4/TTN-AS1/HOTAIRM1-hsa-miR-106b-5p-PTGER3 and LINC00960-hsa-miR-1237-3p-MMP-2 interaction pairs are significant in diabetic kidney (Yu et al., 2021). Drugs such as iloprost, treprostinil, and captopril that target PTGER3 and MMP-2 might benefit patients with DN (Yu et al., 2021).

Intriguingly, several studies show miRNA-192 is upregulated in diabetic patients with microalbuminuria, but downregulated in macroalbumnuria compared to normalbuminuria (Krupa et al., 2010; Jia et al., 2016). However, another study shows that miR-192 is increased in DN patients with over proteinuria (ACT >300 mg/g) compared to microalbuminuria (Chien et al., 2016). These studies indicate miRNA-mediated epigenetic modifications may have various roles in different stages of a disease.

Besides DNA methylation, histone modification and non-coding RNA, RNA methylation plays an important role in the mRNA post-translational modification. For example, N6-methyladenosine (m^6A) methylation is the most chemically modified form of eukaryotic messenger RNA (mRNA) which modifies the adenosine at the 3'-UTR and the stop codon of a mRNA (Fu et al., 2014; Roundtree et al., 2017). Roles of epigenetic modifications are not fully elucidated. Recently, single nucleus ATCT-seq integrated with snRNA-seq has been used to detect the cell-type-specific chromatin accessibility which enable to deep understanding of cell heterogeneity in kidney (Bansal et al., 2020; Muto et al., 2021). It may provide a new approach to understand the epigentic modifications in DN.

Collectively, further studies are warranted to reveal the precise regulatory mechanisms in the different stages of DN as well as potential therapeutic targets and diagnostic biomarkers for DN.

AUTHOR CONTRIBUTIONS

H-YC and X-MM conceived, revised and edited the manuscript. B-YS and S-FZ collected studies and drafted the manuscript. H-DL assisted in data extraction and revised the manuscript. All authors approved the final version of the manuscript for publication.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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