Epigenetic modifications associated to diabetic peripheral neuropathic pain (Review)

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Abstract. The present review aimed to provide an update on the scientific progress of the role of epigenetic modifications on diabetic peripheral neuropathic pain (DPNP). DPNP is a devastating and troublesome complication of diabetes mellitus (DM), which affects one third of patients with DM and causes severe hyperalgesia and allodynia, leading to challenges in the treatment of these patients. The pathophysiology of DPNP is multifactorial and is not yet fully understood and treatment options for this disease are currently unsatisfactory. The underlying mechanisms and pathophysiology of DPNP have largely been explored in animal models and a mechanism-derived approach might offer a potential therapeutic-target for attenuating certain phenotypes of DPNP. Altered gene expression levels within the peripheral or central nervous systems (CNS) are a crucial mechanism of DPNP, however, the transcriptional mechanisms of these genes have not been fully elucidated. Epigenetic modifications, such as DNA methylation and histone modifications (methylation, acetylation, or phosphorylation), can alter gene expression levels via chromatin remodeling. Moreover, it has been reported that altering gene expression via epigenetic modifications within the peripheral or CNS, contributes to the changes in both pain sensitivity and pharmacological efficacy in DPNP. Therefore, the present review summarized the findings of relevant literature on the epigenetic alterations in DPNP and the therapeutic potential for targeting these alterations in the future treatment of this disease.

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Contents

1. Introduction

Diabetes mellitus (DM) is a worldwide health issue that affects 463 million individuals globally (1). Diabetic peripheral neuropathic pain (DPNP) is a frequent and devastating complication of DM, affecting 25-30% of patients with DM (2,3). DPNP is characterized by spontaneous pain, mechanical allodynia, paresthesia and numbness in the terminal phase of DM and can lead to lower-limb amputation (4). However, the presentation of DPNP in patients is inconsistent. The clinical presentation of DPNP largely depends on the affected primary sensory fibers, although the symptoms of patients with large-fiber involvement typically manifest as numbness and loss of sensation, whereas those with small-fiber involvement more often present with pain and dysesthesia (5). The discovery of effective therapeutic-targets for DPNP is critical because of current lack of effective therapies and most current guidelines recommend the use of duloxetine, amitriptyline, gabapentin or pregabalin as initial analgesic for the treatment of DPNP, which are effective for symptomatic relief, but not for disease modification (6). Deeply understanding the pathogenesis of DPNP might help explore mechanism-based approach to deal with this difficult problem. Diabetes is a chronic metabolic disease and alterations in the internal environment might revise gene expression through epigenetic modifications in the occurrence of DPNP.

Epigenetics is the biological process of long-term heritable changes in gene expression that are influenced by the environment, which is able to inhibit or stimulate protein expression

at the transcriptional level (7). Epigenetic modifications that are involved in the regulation of chromatin structure and gene expression have been reported to serve a role in the progression of DPNP (7). One of the mechanisms considered to contribute to the development of DPNP may affect primary sensory neurons, causing altered genes expression, impaired trafficking and the abnormal functioning of receptors and ion channels (3,5). In addition, neuronal and glial cells, such as microglia and astrocytes, are also involved in DPNP through the production of powerful neuromodulators including pro-inflammatory cytokines and chemokines, which increase neuronal excitability. Abnormal expression levels of pro-inflammatory cytokines and chemokines, neuronal receptors or ion channels have been linked to epigenetic modifications involved in DPNP. These epigenetic modifications include DNA methylation, histone methylation and acetylation, non-coding RNA (ncRNA) and RNA modifications. A number of previous reviews have discussed the importance of epigenetics in the pathogenesis of neuropathic pain (NP) (8-12). However, studies of epigenetic mechanisms of pain are continuing and reports of epigenetic modifications on DPNP are currently lacking. Therefore, the present review aimed to comprehensively summarize the etiology and disease mechanisms of DPNP.

In the present review, recent studies on epigenetic modifications in DPNP were summarized. The downstream changes brought about by epigenetic modifications, including alterations in the expression levels of ion channels, altered pain-related receptors, unbalanced inhibitory effects, activation of glial cells and neuroinflammatory responses were exhaustively presented. Moreover, the present review assumed that an epigenetics-derived approach might provide potential diagnosis and therapeutic targets for DPNP.

2. Rodent models of DPNP

Rodent models of DM are the source of experimental evidence for the study and treatment of DPNP and a mechanism-derived approach might offer a potential therapeutic-target and an enhanced benefit in attenuating certain phenotypes of DPNP. The physiology of DPNP in animal models are similar to humans and the conclusions obtained from different DPNP animals were introduced in the present review to help understand the pathogenesis of DPNP and bring some beneficial ideas for the treatment of DPNP. In addition, as an entire system, animal models can be used to preliminarily screen a group of potential therapeutic targets to deal with DPNP and to measure the efficacy and toxicity of potential drugs. Some *in vitro* models have been used to explore specific molecular mechanisms involved in DPNP, including primary culture of dorsal root ganglion (DRG) neurons, neural tissue, Schwann cells and other specific cell lines. Results obtained using *in vitro* models for the mechanism of DPNP include, but are not limited to, mitochondrial events, apoptotic changes and the generation of reactive oxygen species (5). Although *in vitro* models are suitable for investigating molecular mechanisms of disease, they must ultimately be confirmed in a living system, that is, an *in vivo* animal model. Other aspects of DPNP pathophysiology, especially those involved in pain, demand the employment of an entire system, necessitating an animal model. All these rodent models exhibit the three key characteristics of DPNP in humans: Sensory loss, as measured by behavioral tests, nerve impairment, measured using electrophysiology and nerve fiber loss, as detected by the density of the intraepidermal nerve fiber (IENF). The current models for DPNP mainly include genetic rodents and streptozotocin (STZ) or diet-induced approaches.

Genetic models of type 1 diabetes (T_1DM) include the nonobese diabetic and B6Ins2^{Akita} rodents, while type 2 diabetes (T_2DM) models typically use animals which have a mutation in the leptin gene, known as db/db rodents. There is currently no sufficient evidence to conclude that these genetic models are superior to the STZ/diet-induced model in relation to DPNP (13). In previously published studies, the STZ/diet-induced model is more widely used compared with the genetic models. T_1DM occurs due to the destruction of pancreatic β-cells and accounts for ~5% of DM cases, and is typically associated with autoimmune issues and a complete insulin deficiency (5,13,14). The animal model of T_1DM is constructed using treatment with STZ, a cytotoxic methyl nitrosourea substance that can enter pancreatic β-cells through the glucose 2 transporter, where it leads to cell death by initiating DNA fragmentation (15). The death of pancreatic β-cells caused by STZ leads to insulin deficiency and results in the development of T_1DM. Multiple low-dose intraperitoneal injections of STZ are typically used to initiate a T1DM model in animals to avoid the toxicity induced by the administration of excessive levels of STZ. The symptoms of this model initially present as hyperalgesia in response to noxious stimuli and eventually develop hypoalgesia and spontaneous pain in the later stages of disease, which replicates the DPNP symptoms of humans (16). T_2DM can also be induced by either a high-fat diet alone or a high-fat diet combined with a single of low-dose STZ (25 mg/kg). Until mice are fed a high fat diet for 16 weeks, there are no changes in IENF density but tactile allodynia, thermal hypoalgesia and reduced nerve conduction velocities are observed (17). Similar characteristics to patients with prediabetes and obesity can be observed; however, the spontaneous pain associated with late-stage DPNP in humans has not been reported in the high-fat-diet induced animal models of DPNP. Although it may be challenging to fully replicate the clinical manifestations of human DPNP in rodent models, these studies are useful tools for studying the underlying mechanisms of DPNP.

3. DNA methylation and DPNP

DNA methylation is an epigenetic mechanism involving the transfer of a methyl group onto the C5 position of cytosine to form 5-methylcytosine (18). DNA methylation regulates gene expression by preventing the binding of transcription factors to DNA or through recruiting certain proteins involved in gene repression. DNA methylation is performed by DNA methyltransferases and demethylation by ten-eleven translocation methylcytosine dioxygenases.

A number of studies have explored the role of DNA methylation in NP, but there are few reports on the effect of DNA methylation in DPNP (19-23). In a murine model of DPNP, the whole-genome bisulfite sequencing of DRGs reveals an altered methylation pattern in the CpG sites in DNA promoter regions (24). Additionally, a total of 376 promoter regions

with hypermethylated CpG sites and 336 promoter regions with hypomethylated CpG sites were respectively detected. Furthermore, differentially methylated CpG sites genes have been reported to be involved in nervous sensory systems and contribute to the development diabetes or symptoms of pain. A previous study verified the involvement of one of the aforementioned genes in DPNP, as it was shown that P2X3R promotes DNA demethylation and increases interaction with p65, an active form of NF-κB, contributes to P2X3R sensitization and DPNP hypersensitivity (25). Similarity, the expression level of TET2 was increased in a murine model of DPNP, which resulted in activation of NLRP3 inflammasome and alleviation of pain sensitivity (26). DNA methylation participates in DPNP by regulating metabolism and the inflammatory response; however, there are few studies on the role of DNA methylation in channel sensitivity, neurodegeneration or dendritic spine remodeling, which are reported to serve a role in DPNP.

Thus, studies have suggested the potential role of DNA methylation in DPNP. As there are currently few reports on the involvement of DNA methylation in DPNP, further studies are required to elucidate the molecular mechanisms underlying these epigenetic alterations.

4. Histone modification and DPNP

The posttranslational modification of histone proteins is another method of regulation of chromatin structure. Accumulating evidence indicates that histone modifications contribute to the occurrence and persistence of NP (27). Histone modification refers to the process in which histones undergo methylation, acetylation, phosphorylation, adenylation, ubiquitination, ADP ribosylation and other modifications by certain enzymes (28,29). This can alter histone interactions with DNA and other nuclear proteins, cause the remodeling of chromatin structure and alter gene expression. Histone acetylation, catalyzed by histone acetyltransferases, results in the gene transcriptional activation of genes, whereas histone deacetylation, catalyzed by histone deacetylases (HDACs), leads to gene repression, which is associated with the development and maintenance of NP in terms of neuronal excitability and neuroinflammation in the latest review (30). The review comprehensively shows that HDACs regulate pivotal genes linked to neuronal activity, oxidative stress and mitochondrial function in a cell□specific manner in DRG, which leads to peripheral sensitization in NP and outlines the recent experimental evidence supporting the therapeutic potential of HDAC inhibitor in NP. Unlike acetylation, when acetylation of most histone subunits at any of several lysine residues can relax chromatin and enhance transcriptional activation, lysine methylation can cause different effects on gene expression, depending upon the methylation site (31). For instance, methylation at lysine 4 (K4), K36 and K79 of histone 3 (H3) promotes gene expression, whereas, methylation at K9 and K27 of H3 is associated with transcriptional repression (32).

Emerging evidence suggests that enhanced histone modifications of certain promoters is associated with increased expression levels of pain-related genes in DPNP. In a rat model of T_1DM, HDAC5 was aberrantly activated in spinal astrocytes, which promoted STAT3 deacetylation through direct protein-protein interactions, resulting in a decrease in the numbers of spinal astrocytes and consequently increasing pain hypersensitivity (33). Another histone deacetylase, Sirtuin3 (SIRT3) was also reported to inhibit oxidative stress and alleviate NP by deacetylating Forkhead box O3a in the spinal dorsal horn of a diabetic rat model (34). Conversely, reduction in the level of H3 acetylation in the PDX-1 promoter suppresses the expression of PDX-1 and inhibits insulin secretion, which may be a potential cause of both diabetes and DPNP (35). Treatment interventions targeting histone acetylation may be successful for the treatment of DPNP. A study reported that HDACs are increased in DPNP and suppression of HDAC with the HDAC inhibitor FK228 can alleviate diabetic nerve degeneration and pain (36). Furthermore, in a murine model of diabetes, valproate sodium serves a role in decreasing inflammation and pain through inhibition of spinal HDAC1 expression and glial reactivity (37). However, a clinical trial showed that the novel HDAC6-inhibitor ricolinostat used for the treatment of patients with DPNP patients was not associated with a reduction in NP when compared with placebo (38). Perhaps, despite being called an HDAC6-inhibitor, unlike other HDAC subtypes, it acts in the cytosol but not histone and is hypothesized to contribute to the pathophysiology of small fiber neuropathies in a dose-dependent manner.

Therefore, the aforementioned studies have highlighted the role of histone modifications in the pathophysiological process of DPNP and show that histone modifications may serve as potential treatment targets for the management of DPNP. However, despite the various forms of histone modification, currently, there exists reports only related histone acetylation modification on DPNP. Other histone modifications in DPNP such as methylation, phosphorylation, adenylation and ubiquitination and their potential role in DPNP have yet to be reported.

5. RNA modifications and DPNP

The 5' cap modification and the poly(A) tail of eukaryotic mRNA are gaining attention for their roles in mRNA metabolism. The most common internal mRNA modification is *N*6-methyladenosine (m6A) and identification of proteins that recognize, install and remove the marks have highlighted roles for mRNA modification in numerous aspects of the mRNA life cycle, as well as in various cellular, developmental and disease processes (39). The m^6A modification regulate mRNA stability, splicing and translation and targeting m^6A regulatory genes have potential role in alleviating the pathogenesis of a variety of human diseases.

Methyltransferases, known as m6A 'writers', increase the expression level of m6A. This family of proteins consists of methyltransferase-like (METTL) 3, METTL14 and Wilms' tumor 1 associated protein (40). Methyltransferases form a methyltransferase complex and function in conjunction with each other. These enzymes can be specifically identified by diverse m6A 'readers'. The m6A 'readers' consist of YTH domain family 2 and insulin like growth factor 2 mRNA binding proteins (41). Methylated mRNAs are recognized by these 'readers' and promote m6A methylation together

with methyltransferase. The 'readers' may affect NP through mRNA metabolism via splicing, transcription, subcellular localization, or degradation. Conversely, m6A-specific demethylases, AlkB homolog 5 (ALKBH5) and fat-mass and obesity-associated protein (FTO), can reverse m6A modification of RNA. The m6A RNA demethylase FTO or ALKBH5, m6A can be converted to adenosine, which indicates that the process of m6A modification is dynamically reversible. In addition, other RNA modification such as *N*4-Acetylcytidine and RNA-binding proteins (RBPs) serve diverse roles in the pathophysiology of pain that span RNA modification in terms of splicing, stability, translation and decay (42-44).

Previous *in vivo* and *in vitro* studies report that RNA modifications, particularly in m6A, serve crucial roles in the occurrence and maintenance of NP through regulation of gene expression, glial cell activation or channel sensitivity in pain-related areas (20,45-50). However, the direct research on RNA modification and DPNP is relatively limited. Similar reports have preliminarily demonstrated the role of RNA modifications in DPNP, as mRNA splicing alterations of vascular endothelial growth factor (VEGF) were linked to neuronal damage associated with DPNP in diabetic rats and humans and targeting alternative RNA splicing of VEGF could potentially serve as a new analgesic strategy for the treatment of diabetic neuropathy (51-54). However, the link between RNA modifications and mRNA splicing alterations and the mechanisms regulating mRNA splicing alterations of VEGF are currently unknown and need further exploration. Similarly, whether RNA modifications playing a role in DPNP through regulation of gene expression, glial cell activation or channel sensitivity as in NP is unclear.

Although DPNP, categorized as an NP, is a familiar complication of diabetes, DPNP has unique characteristics especially in terms of metabolic abnormalities and the conclusions obtained from different experimental models of NP may not be fully applicable to DPNP. Given the significant role of RNA modification in NP, studies on its potential effects in DPNP is worth further performed to clarify the molecular events underlying these epigenetic alterations.

6. ncRNA and DPNP

ncRNAs are a heterogeneous group of transcripts that typically do not encode detectable protein, but this does not mean they are useless or that ncRNAs do not contain information nor have a function. Compared with mRNAs, the functions of ncRNAs are more complex and much of the genome can be translated into ncRNAs. Previous studies have reported that ncRNAs regulate a diverse range of molecular and biological processes and the aberrant expression of ncRNAs may be involved with the procession of various human diseases, including NP (55-63). A total of three types of ncRNAs have been reported to serve roles in DPNP: Long non-coding RNA (lncRNA), microRNA (miRNA) and circular RNA (circRNA). The present review aimed to summarize the current literature reporting the role of these ncRNAs in DPNP. Understanding ncRNA expression profiles and their involvement in certain regulatory networks and the pathogenesis of DPNP may facilitate the discovery of effective treatments for this disease.

7. lncRNA and DPNP

lncRNA are a group of non-coding RNAs >200 nucleotides in length, which are defined as transcripts. lncRNAs are involved in regulating gene expression at epigenetic, transcriptional and post-transcriptional levels and their role in DPNP has been reported (63). lncRNAs may serve a role as scaffolds for transcriptional and epigenetic protein complexes, which combine with specific genomic loci to modulate gene transcription. and also involved in RNA processing through the direct targeting of mRNAs (64,65).

A microarray analysis with genome-wide expression patterns of lncRNAs in the spinal dorsal horn identified 1,481 differentially expressed lncRNAs in a murine model of DPNP (64). Functional analysis showed that calcium ion transport was the second most significant biological process of differentially expressed lncRNAs. A total of 289 neighboring and 57 overlapping lncRNA-mRNA pairs, such as ENSMUST00000150952-Mbp and AK081017-Usp15, may contribute to DPNP pathogenesis.

In vivo evidence shows certain alleviation of DPNP with the intervention of specific lncRNAs, which are involved in epigenetic modifications through affecting purinergic signaling in the ganglia of diabetic rats (65). In addition, uc.48+ short interfering (si)RNA treatment in DRG alleviates DPNP by inhibiting the excitatory transmission mediated by the P2X3 receptor, a member of an ATP-gated ion channel family (65). Similarly, lncRNA.NONRATT021972 siRNA treatment can repress the upregulated expression and activation of the P2X3 receptor in DRG and reduce the hyperalgesia potentiated by the pro-inflammatory cytokine TNF-α in rats with T_2DM (66). lncRNA-uc.25+ short hairpin (sh)RNA decreases the expression of the pro-inflammatory P2Y14 receptor, inhibits the release of inflammatory factors and diminishes the p38 MAPK phosphorylation (67). DPNP rats treated with shRNA targeting MSTRG.81401 show an increased mechanical withdrawal threshold (MWT) and thermal withdrawal latency (TWL), which is accompanied by decreased expression levels of the P2X4 receptor, TNF-α and interleukin (IL)-1β in the hippocampus and spinal cord (68). A previous study reports that administration of shRNA targeting lncRNA MSTRG.81401 relieves the hyperalgesia in rats with DPNP (69). NONRATT021972 siRNA treatment inhibits the expression of P2X7, reduces the release of inflammatory factors (TNF-α), suppresses the activation of satellite glial cells (SGCs) in the DRG of rats with T_2DM, restores the excitability of DRG neurons and ameliorates mechanical and thermal hyperalgesia (70). Another study reports that P2X7 receptor is expressed in SGCs and is involved in hypersensitivity of DPNP, which is mediated by TRPV1 (71). Rats treated with STZ and siRNA targeting lncRNA BC168687 show increased MWT and TWL, a decreased expression level of TRPV1 receptors in DRG and reduced levels of TNF-α and IL-1β in serum (72). Intrathecal nerve injury-specific lncRNA antisense oligonucleotides also mitigate increases in nociceptive hypersensitivity caused by diabetic neuropathy (73).

In addition, a clinical trial is currently underway to investigate the role of lncRNA in DPNP. A significantly increased concentration of lncRNA NONRATT021972 is reported in the blood and increased severe symptoms of NP are demonstrated

in patients with D2TM (74). lncRNA NONRATT021972 is positively associated with the severity of DPNP. In addition, siRNA targeting lncRNA NONRATT021972 attenuates inflammation through decreasing levels of TNF-α and alleviating DPNP in a murine model.

In summary, there are increasing reports that suggest the involvement of lncRNAs in DPNP. However, current studies on lncRNA and its association with DPNP lack depth. Current reports mainly focus on the mechanism of action of the lncRNA/miRNA/target axis or treatments targeting lncRNAs. However, lncRNAs may directly bind to ligands, receptors or enzymes and be involved in the pathogenesis of DPNP (75).

8. miRNA and DPNP

miRNAs are endogenous, single-stranded RNAs ranging from 21-25 nucleotides in length. miRNAs regulate gene expression and >60% of genes are targeted by miRNAs (76). The aberrant activity of miRNAs contributes to various complications in diabetes, including nephropathy, retinopathy and DPNP. miRNAs regulate various processes involved in diabetic complications related to inflammation, provoking pain and metabolic syndrome pathways (77). Furthermore, a number of miRNAs are implicated in the process of DPNP (78). Therefore, various miRNAs and their targets may serve as potential biomarkers for the diagnosis, prognosis and therapeutic interventions of DPNP.

RNA sequencing of a DPNP rodents model show alterations in miRNA expression levels and their regulatory networks. An miRNA array profile of DRGs of mice with T_1DM shows that miRNA (miR)-33 and miR-380 expressed in nociceptive neurons are critical determinants of diabetic pain and miR-124-1 is an important mediator for physiological nociception (79). Further functional analyses identified variant functional roles for four miRNAs that are prominently dysregulated in DPNP, namely that overexpression of i) pre-miR-33 alleviates mechanical hypersensitivity, ii) pre-miR-380 enhances mechanical hypersensitivity, iii) pre-miR-124 increases basal mechanical sensitivity without involving in diabetes-induced mechanical hypersensitivity and iv) pre-miRNA-335 serves no role in either basal or diabetes-induced mechanical hypersensitivity. However, another study reports that miR-122 is the most notably upregulated miRNA as determined by sequencing analysis of STZ-induced mice (80) There is an association between miR-122 and NP (81); however, whether miR-122 is involved in DPNP remains unclear and requires further exploration.

The expression levels of certain miRNAs in different models of DPNP and their targets are inconsistent. The expression levels of some miRNAs are negatively correlated with the occurrence and persistence of DPNP. miR-193a expression is decreased in the lumbar spinal dorsal horn of STZ-induced diabetic mice and overexpression of miR-193a alleviates DPNP through the inhibition of HMGB1 expression (82). miR-184-5p expression is decreased in spinal dorsal in diabetic mice, while intrathecal injection of miR-184-5p agomir attenuates DPNP; by contrast, intrathecal miR-184-5p antagomir exacerbates pain-associated behaviors (83). Low concentrations of bupivacaine inhibits microglial inflammation and attenuates diabetic neuropathy through downregulating PDE4B via activating miR-23a expression, indicating the presence of a negative relationship between pain and miRNA-23a expression (84). miR-96 expression, reversed by participating in swimming exercises, alleviates pain associated with diabetes by inhibiting the expression of $Na_V1.3$ in rats with T_2DM, indicating the analgesic potential of miR-96 in DPNP (85). miR-145 expression precludes the development of mechanical hyperalgesia via suppression of Nav1.8 in diabetic rats (86). Furthermore, the expression level of miR-590-3p is decreased in mice with DPNP and miR-590-3p agomir ameliorates pain-related behavior, reduces expression of the inflammatory cytokines TNF-α, IL-1β and IL-6 and suppresses neural infiltration by immune cells in db/db mice (87). Similarly, miR-497 alleviates DPNP, which is associated with suppression of USP15, a reported target of miR-497 (88). miR-503-5p alleviates peripheral neuropathy-induced pain in T_2DM mice by regulating SEPT9 expression (89). Glucose-induced astrocytes exhibit a decrease in miR-125a-5p expression levels and administration of the miR-125a-5p mimic in db/db mice attenuated DPNP (90). In a number of clinical trials, the expression levels of miR-1-3p and miR-199a-3p were decreased and increased, respectively, in whole blood samples from patients with diabetic neuropathy compared with the healthy controls, suggesting their diverse and potential relationship with progression of DPNP (91,92).

By contrast, the expression of some miRNAs are positively associated with the occurrence and persistence of DPNP. Inhibition of miR-221 can reduce pain and decrease expression of inflammatory factors by targeting SOCS3 in DPNP (93). In a rat model of DM, miR-133a-3p antagomir administration alleviates DPNP and downregulates p-p38 phosphorylation and overexpression of miR-133a-3p in sciatic nerve induced pain (94). miR-155 targets and suppresses Nrf2 expression in DPNP and miR-155 silencing improves angiogenesis and alleviates inflammation and sciatic nerve injury in DPNP rats (95). Subcutaneous injection of the miRNA-expressing HSV vector targeting $Na_V\alpha$ subunits into the feet of a diabetic rats models to transduce DRG leads to a decrease in the expression of $Na_V\alpha$ subunits 1 in DRG neurons, which was associated with an alleviation of symptoms such as cold allodynia, thermal hyperalgesia and mechanical hyperalgesia (96).

Therefore, manipulation of miRNA expression levels is an emerging diagnostic and therapeutic approach in which to screen and identify nerve-specific targets or successful drug delivery systems. This will be vital to ensure suitable safety profiles that could facilitate the translation of this technology to future clinical use.

9. circRNA and DPNP

Inconsistent with linear RNAs, circular (circ)RNAs are circular molecules with covalently closed loop structures that are exempted from exonucleases. These stable characteristics of circRNAs enable them to be highly expressed in both cells and extracellular vesicles and they are expressed at different levels during the process of diseases (97). As a type of ncRNA, circRNAs exert biological functions by acting as transcriptional regulators, protein templates and miRNA sponges that thereby affect the expression levels of miRNAs and their target genes, circRNAs also serve as decoys or sponges of RNA-binding proteins that influence the expression and function of coding

Table I. Non-coding RNA related to diabetic peripheral neuropathic pain.

Epigenetic modifications	Epigenetic effect	Region	Target	Result	(Refs.)
lncRNA	lncRNA uc.48+	DRG	P2X3, ERK1/2	Mechanical allodynia and thermal hyperalgesia	(65)
	lncRNA NONRATT021972 ↑	DRG	P2X3, ERK1/2	Mechanical allodynia and thermal hyperalgesia	(66)
	lncRNA-UC.25 + ↑	Spinal cord	STAT1, P2Y14 receptor	Activation of microglia, increasing the expression of inflammatory factors and the level of p38 mitogen-activated protein kinase phosphorylation	(67)
	lncRNA MSTRG.81401 ↑	Hippocampus, spinal cord	P2X4 receptor, ERK1/2, P2X7 receptor	TNF-α, and IL-1β, mechanical allodynia and thermal hyperalgesia, depression-like behaviors	(68, 69)
	lncRNA NONRATT021972 ↑	DRG	P2X7 receptor	TNF-α expression, mechanical allodynia and thermal hyperalgesia	(70)
	lncRNA BC168687 ↑	DRG	TRPV1	Mechanical allodynia and thermal hyperalgesia	(72)
	NIS-lncRNA/	DRG	CCL2	Nociceptive hypersensitivity	(73)
	lncRNA NONRATT021972 ↑	Blood	TNF-α	Mechanical allodynia and thermal hyperalgesia	(74)
miRNA	miR-33 ↑ miR-380 ↑ miR-124 ↑	DRG	A set of mRNAs	Mechanical hypersensitivity	(79)
	miR-122 ↑	Spinal cord	A set of mRNAs	Neuropathic pain	(80)
	miR-193a ↓	Spinal dorsal horn	HMGB1	Peripheral neuroinflammation, neuropathic pain	(82)
	miR-184-5p ↓	Spinal dorsal horn	CCL1	Mechanical hypersensitivity	(83)
	miR-23a ↓	Spinal cord	PDE4B	inflammatory cytokines, mechanical allodynia and thermal hyperalgesia	(84)
	miR-96 ↓	Sciatic nerve	$Na_V1.3$	Thermal hyperalgesia	(85)
	miR-145 ↓	DRG	Nav1.8	Mechanical hyperalgesia	(86)
	miR-590-3p ↓	DRG	RAP1A	T cells proliferation and migration, mechanical allodynia and thermal hyperalgesia	(87)
	miR-497 ↓	DRG	USP15	G6PD expression, mechanical allodynia and thermal hyperalgesia	(88)
	miR-503-5p ↓	Spinal cord	SEPT9	Astrocyte activation, mechanical allodynia and thermal hyperalgesia	(89)
	miR-125a-5p ↓	Sciatic nerve	TRAF6	Astrocyte activation, mechanical allodynia and thermal hyperalgesia	(90)
	miR-1-3p ↓	Blood mononuclear cells	CXCR4	Patients' diabetic neuropathy	(91)
	miR-199a-3p ↑	Lower limb skin tissues, plasma of peripheral blood	SerpinE2	Patients' diabetic neuropathy	(92)
	miR-221 ↑	Serum exosomes	SOCS3	Expression of inflammatory factors, mechanical allodynia and thermal hyperalgesia	(93)
	miR-133a-3p ↑	Sciatic nerve	p38	Mechanical allodynia, p-p38 MAPK activation	(94)
	miR-155 ↑	Sciatic nerve	Nrf2	Sciatic nerve injury, inflammation	(95)
cicRNA	circRNA.4614 ↑ other 11 circRNAs ↑	DRG	A set of mRNAs	Sciatic nerve injury, mechanical allodynia and thermal hyperalgesia	(98)

Table I. Continued.

Epigenetic modifications	Epigenetic effect	Region	Target	Result	(Refs.)
	64 circRNAs ↑ 71 circRNAs ↓	Spinal cord	/	Mechanical allodynia and thermal hyperalgesia	(80)
	circHIPK3 ↑	Serum (patients) DRG (rats)	miR-124	Neuroinflammation, mechanical allodynia and thermal hyperalgesia	(100)

DRG, dorsal root ganglion; NIS-lncRNA, nerve injury-specific long non-coding RNA; HMGB1, high mobility group box 1 protein; CCL2, Chemokine CC motif ligand 2; PDE4B, phosphodiesterase 4 B; RAP1A, Ras-associated protein 1A; TRAF6, tumor necrosis factor receptor associated factor 6; CXCR4, C-X-C motif chemokine receptor 4; SerpinE2, serine protease inhibitor E2; SOCS3, suppressors of cytokine signaling; Nrf2, nuclear factor erythroid 2; lncRNA, long non-coding RNA; miR, microRNA; circ, circularRNA.

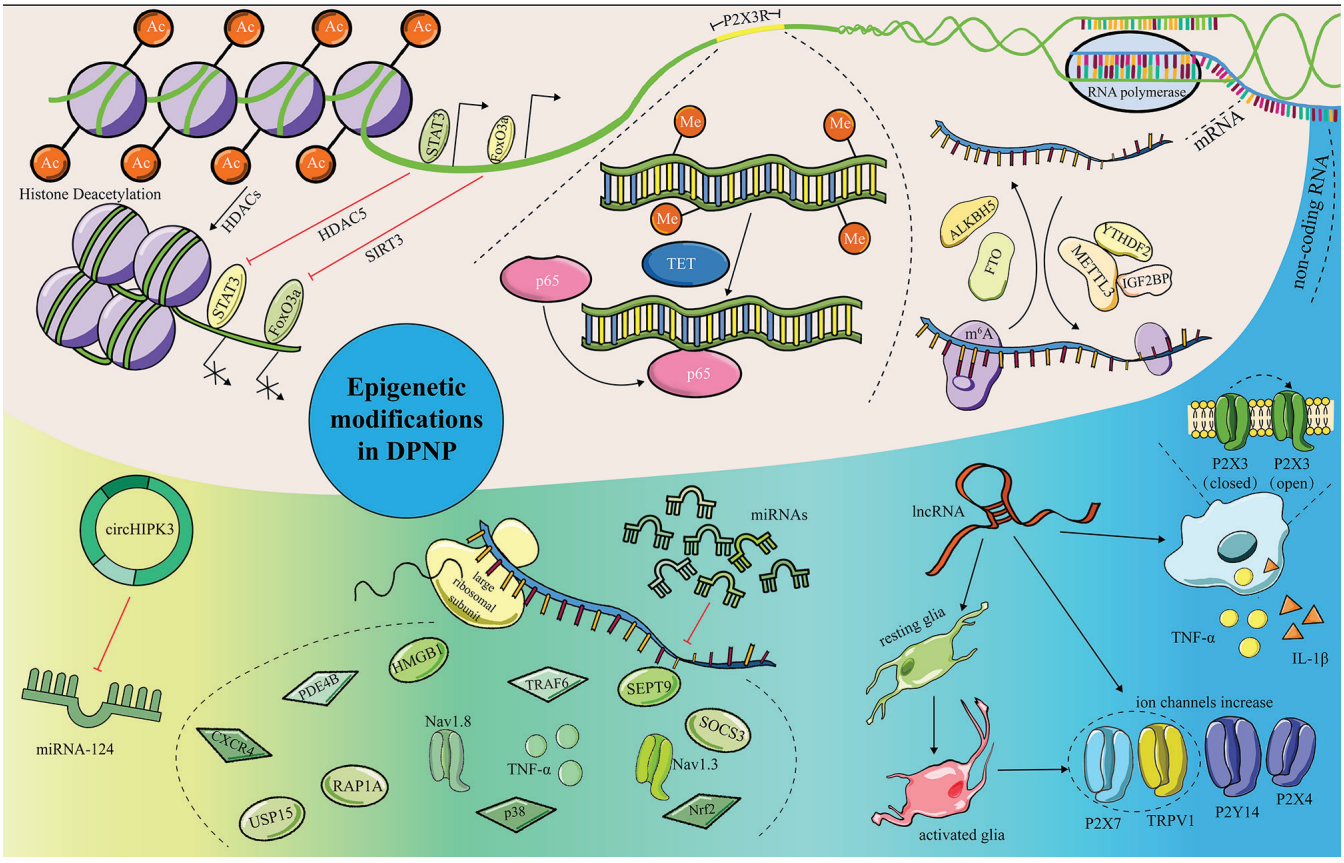

Figure 1. Epigenetic modifications and their regulatory mechanism in DPNP. Epigenetic modifications can participate in pain regulation through various mechanisms. Some common and key mechanisms mainly include pain-related signaling pathways; pain-related receptors and targets; regulation of cytokines release; and targeting ion channels related to pain. Epigenetic modifications that are involved in the regulation of DPNP include (A) Histone modification, causing the remodeling of chromatin structure and alter gene expression, (B) DNA methylation, regulating gene expression, (C) RNA modification, involving in mRNA metabolism and (D) ncRNA, serving diverse roles in pain. DPNP, diabetic peripheral neuropathic pain; HDAC, histone deacetylase; TETs, methylcytosine dioxygenases; ALKBH5, AlkB homolog 5; FTO, fat-mass and obesity-associated protein; METTL3, methyltransferase-like 3; YTHDF2, YTH domain family 2; IGF2BP, insulin like growth factor 2 mRNA binding proteins; miRNA, microRNA; circ, circularRNA; FoxO3a, Forkhead box O3a; SIRT3, Sirtuin3; IL, interleukin.

mRNAs and are associated with various biological processes including NP (98,99).

There are currently few reports which evaluate the role and mechanisms of circRNAs in DPNP. An analysis of high-throughput RNA sequencing data of DRGs comparing wild-type mice and mice with diabetic neuropathy shows that 11 circRNAs and 14 mRNAs have a significant correlation and the expression of circRNA.4614 is clearly upregulated, suggesting that such dysregulated circular RNAs may be involved in the initiation and progression of DPNP (98). Another sequencing analysis identifies 135 different expression circRNAs (64 upregulated and 71 downregulated) in spinal cord between the

DPNP and control group, but with no further functional verification (80). circHIPK3 is highly expressed in serum samples obtained from diabetes patients with DPNP and in DRG from STZ-induced diabetic rats (100). Additionally, the expression level of circHIPK3 is positively associated with the grade of NP in patients with T_2DM. In diabetic rats, downregulating circHIPK3 attenuates NP. Further study demonstrates that circHIPK3 target miRNA-124 and suppress its expression level to reverse the inhibitory effects of miRNA-124 on neuroinflammation. The aforementioned *in vivo* and clinical study suggests that circRNA HIPK3 may act as a potential target for the treatment of DPNP. However, further studies are required to explore the therapeutic potential for targeting dysregulated circRNAs to treat DPNP.

In conclusion, ncRNAs may serve as a promising biomolecule for treatment of DPNP as epigenetic modifications of ncRNAs contributes to the pathophysiology of this condition (Table I). A number of dysregulated ncRNAs have been reported in the serum of patients with DPNP, which can be considered as potential biomarkers for early diagnosis of this condition. As certain ncRNAs have shown promise for alleviating DPNP in *in vivo* experiments, treatment targeting these ncRNAs may be a promising therapeutic approach for patients with DPNP in the future.

10. Conclusions and future perspectives

The present review identified the role of epigenetic modifications in DPNP. The roles of different forms of epigenetic modifications, including DNA methylation, histone modification, RNA modification and ncRNA, were summarized to demonstrate their potential effects on regulating the occurrence and maintenance of DPNP (Fig. 1). The experimental approach of targeting these epigenetic modifications shows potential for the alleviation of DPNP in diabetic models. Despite current evidence highlighting the role of epigenetic modifications in NP, there are limited reports on a number of forms of the epigenetic modifications involved in DPNP, particularly RNA modifications, which need to be further studied and requires more evidence in the future to verify the role of RNA modification in DPNP. In addition, there are too few studies on the effect of epigenetic modifications on the neural circuit to draw solid conclusions. Activating certain neural circuits can alleviate pain and its associated comorbidities, such as depression and anxiety, while activating other circuits can exacerbate these conditions (101-103). An increasing number of studies research the role of neural circuits in pain; however, the relationship between neural circuits and epigenetic modifications in DPNP is currently ambiguous and requires further exploration. Additionally, the mechanisms of action of epigenetic modifications in DPNP have mainly been derived from rodent studies and few of the conclusions drawn from such studies have been verified and applied in a clinical setting. Finally, the upstream mechanisms of epigenetic modifications are unclear at present. For example, whether the changes in the internal homeostatic environment in DM will promote the epigenetic alterations through post-translational modifications, namely O-GlcNAcylation, to regulate the development of DPNP, remains to be further studied. Further research will be required to develop the results of mechanistic studies into clinically available treatments.

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Authors' contributions

TG and JL wrote the manuscript. HY designed and wrote the manuscript. JF and GG revised the manuscript and drew the table and figure. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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