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Review

Hyperglycaemia-induced metabolic stress and epigenetic imprinting in the inflammatory pathogenesis of diabetic neuropathy

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ABSTRACT

Diabetic neuropathy (DN), a major microvascular complication of diabetes mellitus, results from a complex interplay among oxidative stress, inflammation, and persistent epigenetic modifications. Hyperglycemia-induced mitochondrial dysfunction increases reactive oxygen species (ROS), which activate redox-sensitive inflammatory cascades, including NF-κB, JAK/STAT, and the NLRP3 inflammasome. These pathways amplify cytokine release and neuronal sensitisation, while reciprocal feedback between ROS and inflammation mediated by Nrf2 suppression further perpetuates nerve damage. Damage-associated molecular patterns (DAMPs), including HMGB1, S100A8/A9, mitochondrial DNA, and extracellular ATP, act as key amplifiers of neuroinflammation. By engaging receptors such as RAGE, Toll-like receptors (TLRs), and NOD-like receptors (NLRs), particularly NLRP3, these DAMPs trigger glial activation and nociceptive signalling, contributing to axonal degeneration and pain hypersensitivity in DN. Epigenetic dysregulation, including DNA methylation drift, histone modification imbalance, and aberrant non-coding RNA expression, constitutes a critical mechanism underlying metabolic memory, wherein prior hyperglycemic exposure leaves lasting molecular imprints. Persistent histone acetylation (H3K9ac), altered methylation (H3K4me1/Set7, H3K9me3/SUV39H1), and stable 5-methylcytosine patterns sustain inflammatory and oxidative pathways, even after glucose normalisation. Therapeutically, DNMT and HDAC inhibitors, miRNA modulators, and agents targeting RAGE/TLR4/NLRP3 pathways show promise in reversing these molecular imprints. Antioxidants and anti-inflammatory compounds with epigenetic effects further represent potential disease-modifying strategies. Future research must focus on longitudinal human studies, nerve-specific epigenomics, and multi-omics integration to enable personalised, mechanism-based therapy for DN. Understanding the interdependence of ROS, DAMPs, and epigenetic memory is key to breaking the cycle of chronic neuroinflammation and neuronal injury.

1. Introduction

Diabetes mellitus (DM), a complex metabolic disorder marked by persistent hyperglycemia, triggers early cellular stress responses, namely oxidative stress and low-grade chronic inflammation, which are primary drivers of diabetic neuropathy (DN), affecting nearly 50% of diabetic individuals [1]. These stressors also release damage-associated molecular patterns (DAMPs) such as high-mobility group box 1 (HMGB1), S100 proteins, adenosine triphosphate (ATP), and mitochondrial DNA (mtDNA). DAMPs engage pattern recognition receptors (PRRs) like toll-like receptors (TLRs), receptor for advanced glycation end products (RAGE), and also C-X-C chemokine receptor type 4 (CXCR4) (via HMGB1-CXCL12 complexes), thereby activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and prolonging neuroinflammation in peripheral nerves [2].

Such inflammation and oxidative stress reshape the epigenetic landscape through DNA methylation, histone modifications, and non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), resulting in durable alterations in gene expression even after glycemic normalisation, a phenomenon termed metabolic memory [3,4]. For instance, oxidative damage leads to DNA methylation changes at the promoters of antioxidant genes, such as nuclear factor erythroid 2-related factor 2 (Nrf2) and superoxide dismutase 2 (SOD2), while histone marks (e.g., H3K4me1, H3K9ac,

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H3K27me3) alter chromatin accessibility at inflammatory gene loci. Moreover, emerging evidence reveals that DAMPs such as HMGB1, once released extracellularly, can feed back to regulate chromatin-modifying enzymes such as DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs), further entrenching inflammatory and neurodegenerative gene expression programs [3].

Complementing this, ncRNAs like miR-146a, miR-155, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), and maternally expressed gene 3 (MEG3) coordinate these responses by targeting transcripts involved in neuroinflammation, oxidative defence, and neuronal repair pathways. These epigenetic signatures, maintained or reinforced by DAMP signalling, constitute a vicious cycle that sustains nerve damage long after glucose levels normalise. [5] Importantly, epigenetic modifications are potentially reversible. Understanding the crosstalk between oxidative stress, DAMP release, inflammatory signalling, and chromatin remodelling offers promising therapeutic avenues. Targeting epigenetic regulators (DNMTs, HDACs, ncRNAs) may thus help break this cycle and restore nerve function.

This review examines the interplay between oxidative stress, DAMP signalling, inflammation, and epigenetic regulation in diabetic neuropathy. We examine the roles of DNA methylation, histone modifications, and non-coding RNAs, analyse how HMGB1 and other DAMPs influence these, and propose potential epigenetic-targeted strategies for future diagnostic and therapeutic approaches.

2. Oxidative stress and inflammatory pathways in diabetic neuropathy

2.1. Reactive oxygen species (ROS) generation and mitochondrial dysfunction in diabetic nerves

In diabetic neuropathy, hyperglycemia-driven ROS generation and mitochondrial dysfunction form a self-reinforcing cycle that damages peripheral neurons. Elevated glucose levels intensify mitochondrial oxidative metabolism, particularly at complexes I and III of the electron transport chain, resulting in excessive mitochondrial superoxide production. This process impairs mitochondrial membrane potential ($\Delta\Psi m$) and ATP synthesis, contributing directly to axonal energy deficits and nerve conduction failure [1]. Recent studies have shed light on the role of impaired mitophagy in this context. Yang *et al.* (2024) [6] showed in a painful diabetic neuropathy rat model that reduced sirtuin 3 (SIRT3) expression in dorsal root ganglion (DRG) neurons leads to accumulation of fragmented, damaged mitochondria and elevated ROS due to defective forkhead box O3a (FoxO3a), PTEN-induced kinase 1 (PINK1), and Parkin mitophagy. Restoring SIRT3 activity improved mitochondrial integrity and reduced oxidative stress [6]. Moreover, a 2024 review highlights how mitochondrial dysfunction in diabetic neuropathy triggers the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome, linking oxidative stress to neuroinflammatory injury [7]. In additional mechanistic detail, hyperglycemia shifts mitochondrial dynamics toward excessive fission, mediated by proteins such as dynamin-related protein 1 (Drp1), and suppresses fusion proteins, including mitofusin 2 (Mfn2). This fragmentation not only impairs bioenergetics but further increases ROS production and mitochondrial damage [8].

2.2. Chronic inflammation and activation of NF-κB, JAK/STAT, and inflammasomes

Persistent low-grade inflammation is a hallmark of DN, driven by complex signalling networks that interconnect oxidative stress, metabolism, and immune responses. Three central pathways underlie neuroinflammatory processes in DN: the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, and inflammasome activation primarily via NLRP3 [9].

2.2.1. NF-κB pathway

Hyperglycemia, advanced glycation end products (AGEs), and mitochondrial ROS activate IκB kinase (IKK), leading to phosphorylation and degradation of IκBα and nuclear translocation of NF-κB. NF-κB promotes transcription of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), enzymes (COX-2, iNOS), and adhesion molecules (ICAM-1, VCAM-1) in neurons, Schwann cells, and microvascular endothelium [10,11]. These changes drive immune cell infiltration, microvascular dysfunction, demyelination, and pain hypersensitivity (Fig. 1). Pharmacological inhibition of NF-κB (e.g., BAY 11–7082) reduces neuroinflammation and attenuates neuropathic pain [11].

2.2.2. JAK/STAT signalling

The JAK/STAT cascade is activated by cytokines, such as IL-6, in the diabetic milieu, leading to JAK-mediated phosphorylation of STAT3. Activated STAT3 then induces transcription of pro-inflammatory and apoptotic genes within neurons and Schwann cells. IL–6-JAK2-STAT3 activation sustains a feedforward inflammatory loop that perpetuates neuropathic injury. Though much of the literature focuses on diabetic nephropathy and systemic inflammation, the pathway is implicated in neuroinflammatory processes in DN (Fig. 1). It represents a promising therapeutic target supported by data on JAK inhibitors in related metabolic disorders [9].

2.2.3. NLRP3 inflammasome activation

Mitochondrial ROS, mtDNA release, AGEs, and Thioredoxin-interacting protein (TXNIP) upregulation activate the cytosolic NLRP3 inflammasome. Activated NLRP3 recruits ASC and pro-caspase-1, leading to caspase-1 activation. Caspase-1 then mediates two downstream events: (1) cleavage of pro-IL-1β and pro-IL-18 into their active cytokine forms and (2) cleavage of gasdermin D, triggering pyroptotic cell death [12]. In diabetic neuropathy, elevated NLRP3 expression correlates with neuroinflammation, neuronal apoptosis, and pain hypersensitivity. ROS further primes NLRP3 by dissociating TXNIP from thioredoxin, directly binding NLRP3, and amplifying inflammatory signaling [13,14]. Inhibition of this pathway, for example via TXNIP silencing or natural compounds, confers neuroprotection in preclinical models [13].

2.3. Feedback loops between oxidative stress and inflammation

In diabetic neuropathy, oxidative stress and inflammation reinforce one another in tightly interwoven feedback loops, driving progressive neuronal damage, hyperalgesia, and impaired nerve function. Here, we examine how these cycles operate mechanistically and evaluate emerging strategies to interrupt them.

2.3.1. Ros-driven inflammatory activation

Hyperglycemia increases mitochondrial ROS production via electron transport chain overload. These ROS act as signals, activating sensors such as NF–κB and NLRP3 inflammasomes in neurons, Schwann cells, and microglia. Once activated, NF-κB promotes the expression of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and COX-2, as well as adhesion molecules such as ICAM-1/VCAM-1, leading to immune cell infiltration and microvascular dysfunction in peripheral nerves [10]. Activated inflammasomes, particularly NLRP3, process pro-IL-1β and pro-IL-18 into their mature forms, further amplifying inflammatory signals and prompting pyroptotic neuronal death. ROS itself primes and activates NLRP3 by disengaging TXNIP from thioredoxin (TRX) and binding to NLRP3 [14].

2.3.2. Inflammation-Induced oxidant amplification

Hyperglycemia-induced ROS act as upstream signals linking mitochondrial dysfunction to inflammatory pathways. In addition to NF-κB activation, ROS stimulate NLRP3 inflammasome assembly, resulting in

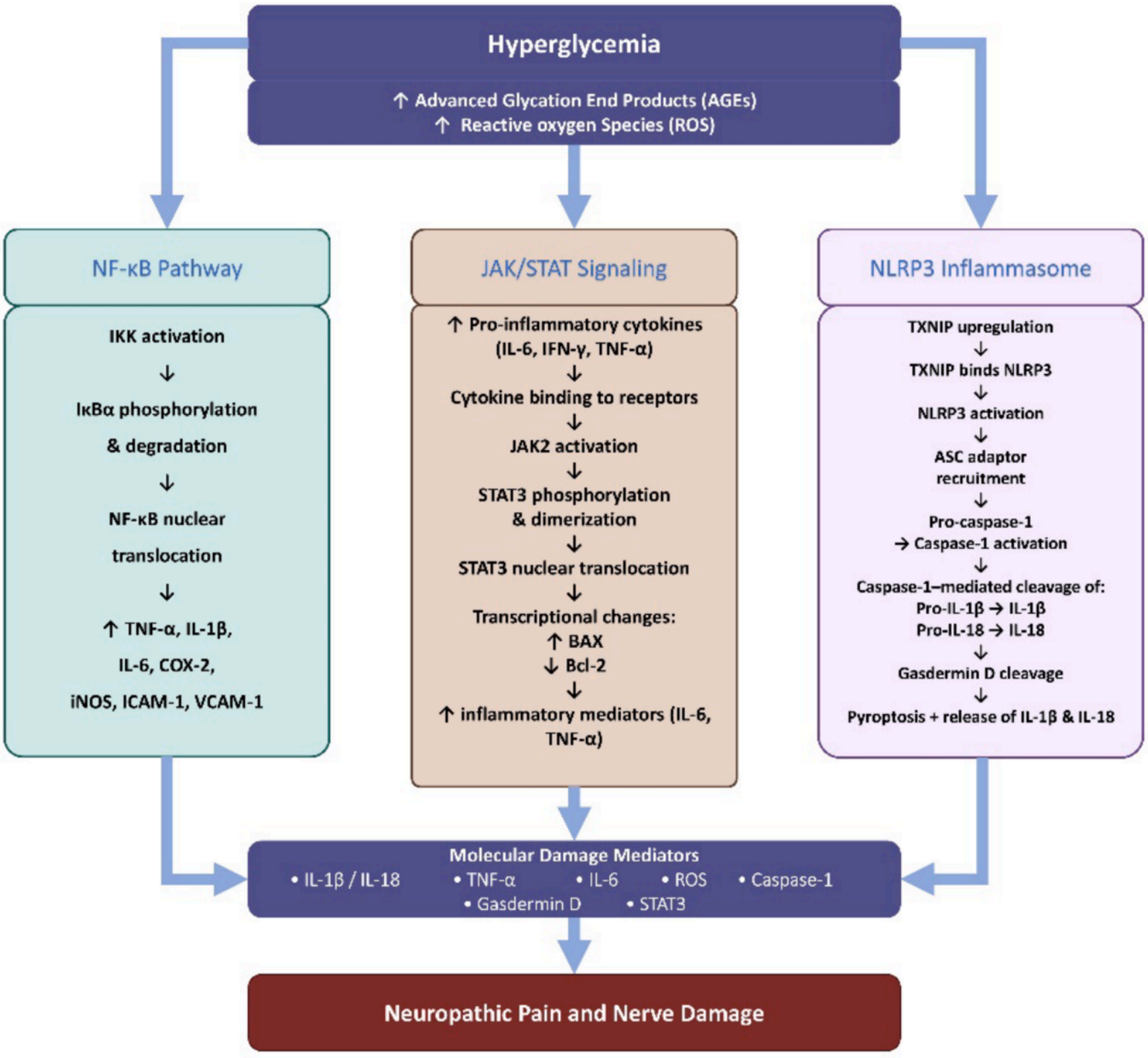

Fig. 1. Hyperglycemia-driven inflammatory pathways in diabetic neuropathy. Chronic hyperglycemia activates three pro-inflammatory cascades in peripheral nerves: (1) the NF-κB pathway (inducing neuroinflammation and demyelination); (2) the JAK/STAT pathway (amplifying neuronal injury via a feedforward loop); and (3) the NLRP3 inflammasome (where active caspase-1 independently matures pro-IL-1β/pro-IL-18 and triggers gasdermin D-mediated pyroptosis). These pathways collectively drive neuropathic pain and nerve damage. Abbreviations: JAK/STAT, Janus kinase/signal transducer and activator of transcription; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein.

cytokine release and pyroptotic neuronal death. The combined activation of these pathways creates a feed-forward loop, where oxidative stress and neuroinflammation exacerbate peripheral nerve damage in diabetic neuropathy [10,14,15].

2.3.3. *Nrf2 Suppression as a central Node*

The redox-sensitive transcription factor Nrf2 orchestrates antioxidant defences. However, in diabetes, persistent inflammation via the NF-κB and mitogen-activated protein kinase (MAPK) pathways suppresses Nrf2, reducing the expression of detoxifying enzymes (e.g., SOD, catalase, HO-1) [10]. This loss of Nrf2-mediated protection exacerbates ROS accumulation and further inflammatory signalling, a detrimental feed-forward cycle [10].

2.3.4. *Structural and functional Consequences*

The ROS-inflammation feedback loops cause structural and functional nerve damage, including demyelination, axonal degeneration, altered ion channel function, microvascular ischemia, and fibrosis, leading to neuropathic pain and sensory deficits. Persistent oxidative-inflammation interactions underpin the metabolic memory observed in diabetic neuropathy, where damage continues even after hyperglycemia is controlled [16].

2.3.5. *Therapeutic Intersections and strategies*

Strategies aimed at disrupting these feedback loops have demonstrated prevention or reversal of neuropathic changes in preclinical studies: Nrf2 activators (e.g., sulforaphane, bardoxolone methyl) restore

antioxidant defences and block NF–κB-driven inflammation [16]. NADPH oxidase inhibitors reduce ROS, thereby attenuating NLRP3 activation and downstream inflammatory responses [14]. NLRP3 inflammasome inhibitors (e.g., TXNIP silencing, echinacoside, loganin) prevent IL-1β maturation, decrease pyroptosis, and reduce neuroinflammation [14]. NF–κB pathway blockers (e.g., BAY 11–7082, dexmedetomidine) reduce the expression of inflammatory mediators and improve nerve conduction [16].

3. Damage-Associated molecular patterns (DAMPs): Amplifiers of inflammation in DN

3.1. Definition and Types of DAMPs relevant to diabetic neuropathy

DAMPs are endogenous molecules released by stressed, injured, or dying cells. In DN, chronic hyperglycemia, oxidative damage, and mitochondrial dysfunction lead to enhanced release of DAMPs such as HMGB1, S100A8/A9 (calprotectin), mitochondrial DNA (mtDNA), and extracellular ATP. These DAMPs bind to pattern recognition receptors (PRRs), including TLR2, TLR4, and TLR9, as well as RAGE and P2X7, activating inflammatory cascades such as NF-κB, the NLRP3 inflammasome, and MAPKs, thereby exacerbating neuroinflammation, neuronal damage, and neuropathic pain.

3.1.1. High-Mobility group box 1 (HMGB1)

HMGB1 is a nuclear protein that functions as a DAMP when released extracellularly under hyperglycemic or oxidative stress conditions. In rodent models of type 2 diabetes, HMGB1 is markedly upregulated in the DRG and spinal cord, accompanied by increased expression of the receptor for advanced glycation end-products (RAGE), Toll-like receptor 4 (TLR4), and NLRP3 inflammasome components [1].

3.1.2. S100A8/A9 (Calprotectin)

S100A8 and S100A9 are calcium-binding proteins released by activated myeloid cells, acting as key DAMPs. In a study involving 59 type 1 diabetic patients with neuropathy, S100A8 and S100A9 gene expression was significantly elevated compared to diabetic patients without complications [2,17].

3.1.3. Mitochondrial DNA (mtDNA)

Diabetic neuropathy is associated with mitochondrial damage and the release of mtDNA (Fig. 2). Recent work has shown that mtDNA activates the NLRP3 inflammasome in DN, promoting the release of IL-1β and IL-18, as well as neuroinflammation and neuropathic pain [3].

3.1.4. Extracellular ATP

Although specific studies on diabetic neuropathy are emerging, stressed neurons release extracellular ATP, which activates glia, in turn activating inflammasome-mediated inflammation via P2X7 receptors (Fig. 2). In other neuropathy models, blocking P2X7 reduces IL-1β production and alleviates pain, suggesting potential relevance to DN [18].

3.2. DAMP Receptors: RAGE, Toll-Like receptors (TLRs), and NOD-Like receptors (NLRs)

DAMPs released from injured peripheral neurons in diabetic neuropathy exert their deleterious effects primarily by binding to specific pattern recognition receptors (PRRs). Here, we describe major receptor classes RAGE, TLRs, and NLRs that are central to DAMP-mediated

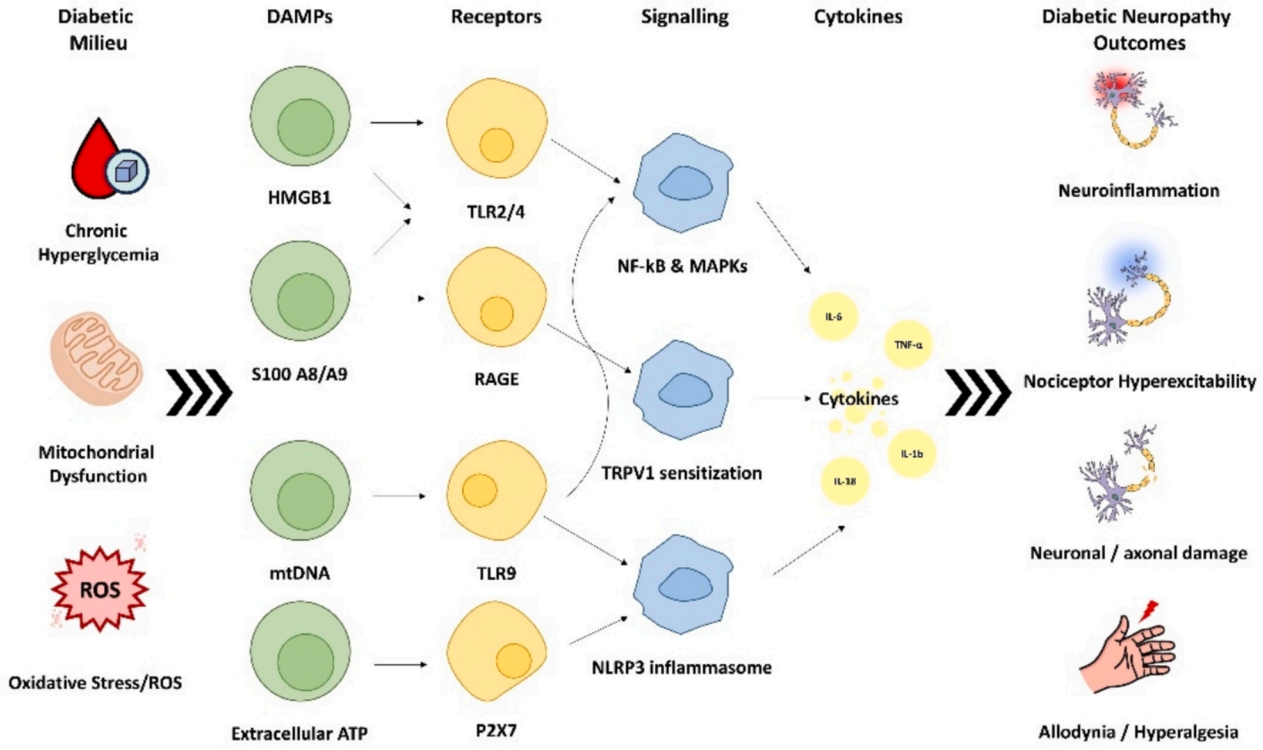

Fig. 2. DAMP-mediated signalling pathways in diabetic neuropathy. Chronic hyperglycemia, mitochondrial dysfunction, and ROS (the diabetic milieu) release DAMPs (HMGB1, S100A8/A9, mtDNA, ATP). These bind receptors (TLR2/4, TLR9, RAGE, P2X7) to activate NF-κB/MAPKs (pro-inflammatory cytokine transcription), TRPV1 sensitisation (nerve hyperexcitability), and the NLRP3 inflammasome (mature IL-1β/IL-18 production). These outputs drive diabetic neuropathy outcomes: neuroinflammation, nerve damage, and pain (allodynia/hyperalgesia). Abbreviations: ATP, adenosine triphosphate; DAMP, damage-associated molecular pattern; HMGB1, high-mobility group box 1; IL, interleukin; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TLR, toll-like receptor; TRPV1, transient receptor potential vanilloid 1.

neuroinflammation in DN [19,20].

3.2.1. RAGE (Receptor for advanced glycation End-products)

RAGE is a pattern recognition receptor broadly expressed on neurons, Schwann cells, endothelial cells, and macrophages. It binds multiple DAMPs characteristic of DN, including HMGB1, S100A8/A9, and AGEs. Upon ligand binding, RAGE activates downstream signalling cascades such as MAPKs (primarily p38 MAPK and ERK1/2), CDC42/Rac, and NF-κB, leading to ROS generation and expression of pro-inflammatory genes (e.g., TNF–α, IL–6, VCAM–1) [10]. Functional studies in neuropathic pain models show that oxidised HMGB1 (the all-thiol form) selectively activates neuronal RAGE, leading to DRG sensitisation and mechanical hyperalgesia, without engagement of TLR4 [6]. Specifically, in diabetic rat DRG, upregulated RAGE augmented transient receptor potential vanilloid 1 (TRPV1) mediated calcium influx under high-glucose conditions; this was reversed by vascular endothelial growth factor isoform A165b (VEGF-A165b), demonstrating the clinical relevance of RAGE as a pain mediator in DN [7].

3.2.2. TLRs (Toll-Like Receptors)

TLRs, particularly TLR2, TLR4, and TLR9, are expressed on DRG neurons, Schwann cells, microglia, and infiltrating macrophages in diabetic nerves. They recognise DAMPs, including HMGB1, S100 proteins, and extracellular mtDNA. Activation of TLRs leads to recruitment of adaptor proteins (MyD88, TRIF), triggering NF-κB, MAPK, and IRF signalling pathways that result in pro-inflammatory cytokine release (TNF–α, IL–1β, IL–6) [10]. Expression profiling shows high basal levels of TLR2 and TLR4 in Schwann cells, with further upregulation following HMGB1 stimulation. This enhances both TLR and RAGE signalling, amplifying inflammatory responses [11]. In diabetic patients and rodent models, elevated TLR2/4 expression correlates with increased NF-κB activity, cytokine levels, and neuropathic symptoms. TLR4 blockade alleviates pain by suppressing the NICD1-TLR4-NF-κB pathways in DRG [14].

3.2.3. NLRs (NOD-Like Receptors) – focus on NLRP3

NLRs, particularly NLRP3, form intracellular inflammasome complexes when triggered by DAMPs such as oxidised mtDNA, ROS, and extracellular ATP. Activation of NLRP3 leads to the assembly of NLRP3 with ASC and pro-caspase-1, resulting in the activation and maturation of caspase-1, which in turn activates the maturation of IL-1β and IL-18. In diabetic nerves, increased NLRP3 expression has been observed in DRG and sciatic nerve tissues, and its inhibition, either via genetic silencing or pharmacological agents, reduces neuropathic pain and protects neuronal integrity [10]. While mtDNA primarily engages NLRP3, extracellular ATP signals via P2X7 receptors to activate NLRP3, further enhancing inflammatory cascades in DN indirectly.

3.3. DAMP–Mediated neuroinflammation and nociceptive sensitisation in diabetic neuropathy

DAMPs, released from stressed neurons and glia under diabetic conditions, significantly contribute to neuroinflammation and heightened pain sensitivity, key features of DN [21,22].

3.3.1. HMGB1 and RAGE/TLR4-Mediated sensitization

Extracellular HMGB1 is released either passively from damaged neurons or actively from stressed cells, and it engages RAGE and TLR4 on sensory neurons, microglia, and macrophages. This interaction triggers downstream signalling cascades that sensitize neurons, in part by enhancing TRPV1-mediated calcium influx, thereby increasing neuronal excitability under hyperglycemic conditions [7,23]. HMGB1 also amplifies neuroinflammation by promoting NF-κB activation and NLRP3 inflammasome assembly, leading to cytokine release and pyroptotic neuronal death. Together, these mechanisms create a feed-forward loop linking oxidative stress, receptor-mediated sensitization, and inflammation in diabetic neuropathy [7].

3.3.2. TLR4 & NLRP3 inflammasome activation

High HMGB1 also activates microglial TLR4, which primes and activates the NLRP3 inflammasome, leading to the release of IL-1β/IL-18. These cytokines exacerbate neuroinflammation and nociceptor hypersensitivity. In diabetic rats, increased spinal ROS, NLRP3, TXNIP, and pro-inflammatory cytokines were observed; however, the use of ROS scavengers or TXNIP knockdown reduced pain responses [7].

3.3.3. ATP-P2X7 axis in nociceptor Excitation

Although direct evidence in DN remains limited, extracellular ATP released under neuronal stress activates P2X7 receptors, which further trigger NLRP3 pathways and IL-1β release. In non-diabetic neuropathic models, P2X7 blockade attenuated mechanical allodynia, suggesting potential relevance for DN [15].

3.4. Clinical and experimental evidence of DAMP elevation in diabetic neuropathy

3.4.1. HMGB1 in painful diabetic neuropathy

HMGB1 is a nuclear protein released into the extracellular environment during cellular stress or injury, where it functions as a key DAMP. Preclinical evidence from rodent models of type 2 diabetes reveals that HMGB1 is significantly upregulated in DRG and spinal cord during hyperglycemia. This elevation is associated with increased expression of receptors such as RAGE and TLR4, as well as components of the NLRP3 inflammasome. Functionally, upregulated HMGB1 correlates with increased pain sensitivity. Notably, pharmacological inhibition of HMGB1 using glycyrrhizin reduces HMGB1, TLR4, and NLRP3 expression and attenuates mechanical and thermal hyperalgesia, highlighting HMGB1′s central role in neuroinflammation and nociceptive sensitisation in DN [2].

3.4.2. S100A8/A9 levels in human diabetic neuropathy

S100A8 and S100A9, collectively known as calprotectin, are calcium-binding proteins released mainly by activated myeloid cells. Clinical studies demonstrate that serum S100A8/A9 concentrations are significantly elevated in patients with type 2 diabetes who have neuropathy and other microvascular complications compared to those without these complications. This association underscores the potential of S100A8/A9 both as biomarkers and as active players in the inflammatory milieu contributing to diabetic neuropathy [24].

3.4.3. mtDNA-NLRP3 pathway in experimental models

Mitochondrial dysfunction, a hallmark of diabetic metabolic stress, leads to the cytosolic release of oxidised mitochondrial DNA (mtDNA), a potent DAMP. Experimental studies in diabetic rodent models show that released mtDNA activates the NLRP3 inflammasome in DRG neurons and peripheral nerves, promoting caspase–1 activation and subsequent production of proinflammatory cytokines such as IL-1β and IL-18 (Fig. 2). Genetic or pharmacological inhibition of the NLRP3 inflammasome results in reduced cytokine levels and alleviated neuropathic pain behaviours, emphasising the pathogenic significance of the mtDNA-NLRP3 axis in DN [25].

4. Epigenetic Regulation: Mechanisms and Diabetes-Induced alterations

Epigenetic regulation controls transcriptional output by altering chromatin accessibility and RNA stability without changing DNA sequence. In diabetes, hyperglycemia, ROS, and inflammatory signalling remodel epigenetic writers, erasers, and readers, producing durable chromatin states that can persist after glycemic normalisation (metabolic memory) (Fig. 3). These stable states bias cells toward chronic oxidative stress, inflammation, and impaired repair processes, which are

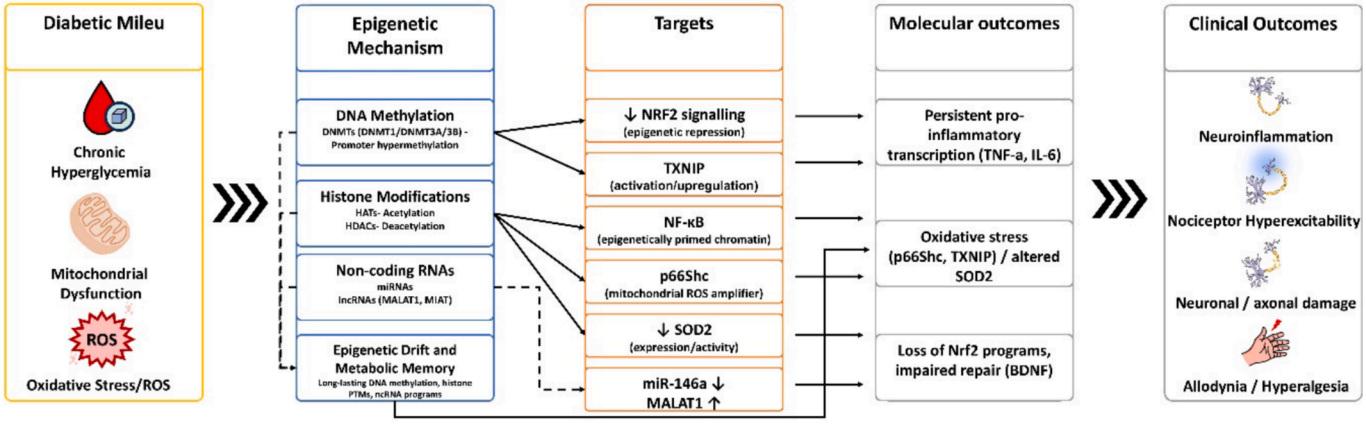

Fig. 3. Epigenetic mechanisms linking diabetes to neuropathic pain. Chronic hyperglycemia induces mitochondrial dysfunction and oxidative stress, leading to epigenetic modifications that sustain inflammatory and redox-imbalanced transcriptional programs. Persistent repression of antioxidant pathways and activation of pro-inflammatory signalling contribute to neuroinflammation, neuronal damage, and pain hypersensitivity. Dashed arrows indicate indirect or long-lasting effects associated with epigenetic drift and metabolic memory. Abbreviations: BDNF, brain-derived neurotrophic factor; DNMTs, DNA methyltransferases; HATs, histone acetyltransferases; HDACs, histone deacetylases; IL-6, interleukin-6; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; miRNA, microRNA; NF-κB, nuclear factor kappa B; NRF2 (Nrf2), nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SOD2, superoxide dismutase 2; TNF-α, tumour necrosis factor alpha; TXNIP, thioredoxin-interacting protein.

central to microvascular disease and are increasingly implicated in diabetic neuropathy [26,27].

A key concept is that diabetes does not create a single uniform epigenetic signature; rather, it produces (i) locus-specific hypermethylation or repressive chromatin at protective genes (e.g., antioxidant and neurotrophic pathways), alongside (ii) persistent activation marks at inflammatory loci, sometimes occurring concurrently with - global hypomethylation. This pattern reflects selective pressure from stress-responsive transcription factors (e.g., NF-κB) acting in concert with chromatin-modifying enzymes, creating self-reinforcing feedback loops [28–32].

4.1. Overview of epigenetic Mechanisms: DNA Methylation, histone Modifications, and non-coding RNAs

Epigenetic information is encoded through three interconnected layers: DNA methylation, histone post-translational modifications (PTMs), and ncRNAs. These layers are mechanistically interdependent; for example, ncRNAs can recruit DNMTs or Polycomb complexes, histone marks can guide DNMT localisation, and DNA methylation can alter transcription factor binding and nucleosome positioning. In diabetes, this coupling enables transient metabolic stress to become a long-lasting transcriptional bias [5,31,33,34].

Importantly, these three layers rarely act in isolation. Diabetic stress activates transcription factors (e.g., NF-κB) that physically recruit HATs and histone methyltransferases to specific loci, while ncRNAs can tether these enzymes to chromatin and simultaneously tune enzyme abundance by targeting their mRNAs. This creates locus-specific chromatin remodelling on a background of generalised methylome instability, explaining how diabetes can produce both global drift and selective silencing/activation of key protective and pathogenic pathways [31,33,34].

4.1.1. DNA methylation

DNA methyltransferases DNMT1, DNMT3A, and DNMT3B catalyse methylation at CpG dinucleotides. Promoter CpG methylation often reduces transcription by limiting transcription-factor binding and recruiting methyl-binding proteins, while gene-body methylation can correlate with active transcription depending on context. In diabetes, hyperglycemia and ROS are associated with locus-specific methylation changes in stress-response genes, including hypermethylation of antioxidant pathways such as NFE2L2 (Nrf2) and SOD2, which contribute to sustained oxidative stress and support a metabolic-memory phenotype [28–30].

4.1.2. Histone modifications

Histone PTMs regulate chromatin compaction and transcription by modifying charge, nucleosome dynamics, and recruitment of reader proteins. Key PTMs include acetylation by HATs such as p300/CBP (generally activating) and deacetylation by HDACs (often repressive), as well as methylation marks such as H3K4me (activating), H3K9me3 and H3K27me3 (repressive), and context-dependent marks (e.g., H3K4me1 at enhancers). Under diabetic conditions, increased recruitment of SET7/9 (SETD7) and p300/CBP to NF-κB responsive loci enriches activating marks (e.g., H3K4me1, H3K9ac, H3K27ac), while reduced SUV39H1 activity contributes to the loss of repressive H3K9me3, reinforcing chronic inflammatory transcription [31,32].

4.1.3. Non-coding RNAs (ncRNAs)

ncRNAs shape gene expression through post-transcriptional regulation and chromatin remodelling. miRNAs (~22 nt) typically repress translation or promote mRNA degradation, whereas lncRNAs (>200 nt) can act as scaffolds for chromatin regulators (DNMTs, HDACs, histone methyltransferases), guide them to specific loci, or sponge miRNAs. In diabetes, lncRNAs such as MALAT1 and MIAT are upregulated and interact with epigenetic machinery, including EZH2 and DNMT3B, supporting persistent pro-inflammatory and pro-oxidant programs in endothelial and neuronal contexts [5,33,34].

4.2. Epigenetic drift and metabolic memory in diabetes

Epigenetic drift refers to progressive, cumulative deviation of epigenetic marks (DNA methylation, histone PTMs, ncRNA expression) from baseline. Diabetes accelerates drift by increasing ROS, inflammatory cytokines, and metabolic intermediates that alter chromatin enzyme activity and targeting. Once established, these marks can persist through cell division (in proliferative cells) or through long-lived chromatin states (in post-mitotic cells), maintaining pathological gene expression even when glycemia improves [26,27]. Landmark clinical trials (DCCT/EDIC, UKPDS) demonstrate that early intensive glycemic control confers long-term protection against complications, despite later glycemic deterioration, consistent with early epigenetic programming of vascular and immune pathways that later become relatively autonomous of glucose levels [27,35].

Metabolic memory is best viewed as a set of reinforcing feedback loops rather than a single mark. Once inflammatory enhancers gain acetylation and H3K4 methylation, transcription is more readily reinitiated, leading to increased cytokines/ROS that further perturb chromatin enzymes and sustain the open state. In parallel, miRNAs that suppress repressive writers (e.g., SUV39H1) reduce the cell's capacity to restore heterochromatin, making the off switch progressively weaker over time [28,31].

4.2.1. DNA methylation drift and durable stress signalling

In type 1 diabetes, transient hyperglycemia can produce persistent methylation changes at loci such as TXNIP, sustaining oxidative stress and inflammatory signalling after glucose normalisation. Mechanistically, methylation drift may both (i) repress protective genes (antioxidant, repair) and (ii) lock in permissive states at stress-response genes, depending on genomic context and transcription-factor occupancy [29,35].

4.2.2. Histone PTM Drift: A Canonical Metabolic-Memory Module

In primary human endothelial cells, transient high glucose induces persistent chromatin changes at promoters including p66Shc, SOD2, and NF-κB p65, characterised by increased histone acetylation and H3K4 monomethylation (e.g., at p66Shc) and reduced repressive marks such as H3K9me3 (e.g., at SOD2), sustaining oxidative stress after return to normoglycemia [32]. Enzymes such as SET7/9 and LSD1 contribute to establishing and maintaining these signatures [32].

4.2.3. ncRNAs as Engines of persistence (Beyond transient post-transcriptional Effects)

miRNAs can stabilise long-term chromatin states indirectly by targeting epigenetic enzymes. In endothelial cells exposed to transient hyperglycemia, sustained upregulation of miR-125b, miR-29a-3p, and -miR-146a-5p suppresses chromatin regulators, including SUV39H1 and DNMT3B, promoting loss of the repressive H3K9me3 mark and altering DNA methylation at inflammatory and oxidative stress-responsive loci [36]. These ncRNA-mediated feedback loops can prevent full chromatin resetting after glucose normalisation, thereby enforcing long-term activation of inflammatory programs and/or repression of protective programs, depending on the targets engaged [36].

4.3. Epigenetic alterations as stable drivers of diabetic neuropathy (DN)

Although metabolic-memory mechanisms are best characterised in vascular and immune cells, accumulating evidence suggests analogous epigenetic persistence in DN, where chronic oxidative stress, neuroinflammation, microvascular dysfunction, and impaired axonal repair coexist. In DN, stable epigenetic changes can (i) sustain inflammatory and oxidative pathways that damage nerves and Schwann cells, and (ii) suppress regeneration and neurotrophic support, limiting recovery even when glycemia improves [37,38]. In DN, cell-type specificity matters: endothelial and immune metabolic memory can maintain a pro-inflammatory milieu, while neuronal and Schwann cell epigenetic changes directly impair axonal transport, mitochondrial resilience, myelination programs, and regeneration capacity. Thus, neuropathy likely reflects convergence of (i) persistent extrinsic injury signals (vascular/immune) and (ii) intrinsic failure of repair programs (neuronal/Schwann), both stabilised by epigenetic remodelling [37,38].

4.3.1. DNA methylation signatures Predicting DN risk

Prospective human data support a role for DNA methylation beyond a passive disease marker. In the Pittsburgh Epidemiology of Diabetes Complications cohort, hypermethylation at CpG sites in PKNOX1, CACNA1B, and CHMP6 predicted future distal peripheral neuropathy, consistent with methylation patterns functioning as early risk indicators and potentially contributing to causal pathways [39,40]. Because these methylation signals precede clinical neuropathy, they may represent either causal programming or stable biomarkers of early, subclinical injury. Discriminating these possibilities will require mapping methylation to gene expression (eQTM analyses), cell-type deconvolution of blood signals, and functional perturbation in relevant neural cell models [39,40].

4.3.2. DN-relevant histone Programs: Chronic inflammation and oxidative stress

Hyperglycemia induces persistent histone acetylation and H3K4 methylation at NF-κB target promoters via recruitment of CBP/p300 and SET7/SETD7, while reducing repressive H3K9me2/3. These alterations can persist after restoration of normoglycemia, maintaining inflammatory gene expression [41]. Given the neuroimmune component of DN, such chromatin programs in immune cells and endoneurial microvascular cells may propagate cytokine exposure and oxidative injury to axons and Schwann cells, thereby linking vascular metabolic memory to neural pathology [37,38,41].

4.3.3. Histone methylation as a Long-Lived Lock: SUV39H1/H3K9me3 axis

Repressive H3K9me3 and activating H3K4me signatures represent durable epigenetic marks in diabetic complications. In smooth muscle cells from diabetic mice, loss of H3K9me3 at inflammatory loci persists in vitro and is linked to increased miR-125b and reduced SUV39H1, illustrating a stable, self-reinforcing memory circuit [28]. Similar persistence of altered histone methylation (e.g., H4K20me3 at SOD2 -promoter in retinal cells) indicates that writer/eraser imbalance can be conserved across tissues, supporting the plausibility of analogous locking mechanisms in DN-relevant cells [28].

4.3.4. ncRNAs in DN: Functional Reinforcement of regeneration failure

In DN models, sensory neurons exhibit persistent miRNA dysregulation, including decreased let-7i and increased miR-341 (Table 1), both of which suppress neuronal regeneration programs. Importantly, intranasal delivery of let-7i or anti-miR-341 partially reversed sensorimotor deficits, providing functional evidence that ncRNA alterations can be causal and therapeutically tractable rather than purely correlative [42]. Although miRNAs are often framed as transient regulators, in DN they can act as epigenetic reinforcers by persistently suppressing chromatin regulators and regeneration factors, thereby stabilising long-term transcriptional states. The partial phenotypic rescue with intranasal miRNA modulation supports a model in which ncRNA circuits help maintain the non-regenerative set point of injured diabetic nerves [33,34].

4.3.5. Clinical and therapeutic Implications: Biomarkers, Targets, and Timing

Epigenetic patterns can identify DN risk before clinical onset and may explain why late glycemic improvement fails to fully reverse established nerve damage. In the 28-year prospective Pittsburgh EDC analysis, methylation at PKNOX1, CACNA1B, and CHMP6 was strongly associated with future neuropathy independent of conventional risk factors [40,43]. Preclinical work supports targeting DNMTs, HAT/HDAC balance, SET7, SUV39H1 pathways, and ncRNAs to attenuate persistent pathogenic programs even after glucose normalisation, highlighting a therapeutic window early in disease when epigenetic states are less entrenched and more reversible [44]. As drift progresses, chromatin states may become increasingly resistant to reprogramming, emphasising the value of early intervention and of combining metabolic control with epigenetic or anti-inflammatory strategies [44].

Table 1
Epigenetic alterations associated with diabetic neuropathy. Overview of DNA methylation, histone modification, and non-coding RNA changes reported in diabetic neuropathy or closely related diabetic complications. Hyperglycemia, oxidative stress, and inflammatory signalling are associated with persistent epigenetic alterations that may remain after glycemic normalisation and correlate with sustained inflammatory activation, oxidative stress, and reduced neuronal repair capacity. Genes and loci listed represent examples supported by experimental or prospective human studies. References correspond to citations in the main text.

Epigenetic Mechanism	Affected Genes / Loci	Observed Epigenetic Change	Clinical / Functional Outcome	References
DNA Methylation	Genome-wide	Global DNA hypomethylation	Impaired neuronal repair and survival pathways	[26,27,36–38]
	Nrf2 (NFE2L2), BDNF	Promoter hypermethylation	Reduced gene expression and diminished nerve regenerative capacity	[28–30,36–38]
	PKNOX1, CACNA1B, CHMP6	CpG site hypermethylation	Independent predictors of incident distal symmetric polyneuropathy	[39,40,43]
Histone Modifications	Pro-inflammatory gene loci (NF-kB targets)	Loss of repressive H3K9me3 marks; gain of activating acetylation/H3K4me	Consolidation of maladaptive inflammatory transcriptional programs	[28,31,32,35,41]
	Antioxidant genes (e.g., SOD2)	Gain of repressive H4K20me3 marks	Suppression of antioxidant defence gene expression	[28,32,36,37]
Non-coding RNAs	let-7i	Persistent downregulation	Reduced expression of nerve regeneration-associated genes	[42]
	miR-341	Persistent upregulation	Suppression of nerve regeneration-associated genes	[42]

5. Metabolic memory and epigenetic persistence in diabetic neuropathy

5.1. Evidence of sustained nerve damage after glucose control

Despite optimal glycemic control, individuals with diabetes frequently experience continued progression of peripheral nerve dysfunction. This legacy effect or metabolic memory has been consistently documented in both major clinical trials and experimental models (Table 2) [45,46].

5.1.1. Clinical Evidence: DCCT/EDIC & UKPDS cohorts

The DCCT/EDIC trial showed that early, intensive glycemic control ($HbA_1c \sim 7\%$) in type 1 diabetes significantly reduced the incidence of neuropathy compared with conventional therapy ($HbA_1c \sim 9\%$). Crucially, this neuroprotective effect persisted for decades during the EDIC follow-up, even after glycemic levels converged between the two groups. Similarly, the UKPDS trial in type 2 diabetes demonstrated sustained reductions in microvascular complications, including peripheral neuropathy, years after the intensive control period ended [45].

5.1.2. Experimental models demonstrating persistent nerve damage

Experimental models corroborate clinical findings, demonstrating that transient hyperglycemia induces lasting structural and molecular changes within the neurovascular unit. In vitro, brief high-glucose exposure in DRG neurons, Schwann cells, and perineurial endothelial cells causes sustained upregulation of inflammatory and fibrotic genes, persistent ROS production, and prolonged NF-κB activation, even after a return to normoglycemia [46,47]. Similarly, in streptozotocin-diabetic rat models, severe oxidative/nitrative stress and elevated inflammatory cytokine expression persist in the sciatic nerve for months after insulin-induced glucose normalisation [48]. These enduring pathological states are driven by stable epigenetic modifications that lock neural and vascular cells into pro-inflammatory and degenerative

Table 2
Metabolic memory and epigenetic persistence in diabetic neuropathy. Clinical and experimental evidence demonstrates that transient hyperglycemia induces durable epigenetic reprogramming in peripheral nerve and immune cells, leading to sustained oxidative stress and inflammation despite subsequent glycemic normalisation. Persistent histone modifications (increased H3K9ac and H3K4me1, reduced H3K9me3) and stable DNA methylation changes (including TXNIP hypomethylation) maintain pro-degenerative transcriptional programs, driving chronic neuroinflammation, Schwann cell dysfunction, and progressive axonal damage. These findings identify metabolic memory as a key mechanism limiting the reversibility of neuropathy and support the need for epigenetic- and redox-targeted therapies, in addition to glucose control.

Level of Evidence	Model / Cohort	Key Persistent Changes After Glycemic Normalisation	Dominant Epigenetic Mechanisms	Pathophysiological Consequences for Peripheral Nerves	References
Clinical (T1D)	DCCT/EDIC	Reduced neuropathy incidence persists decades after early intensive control despite later HbA_1c convergence	↑ H3K9ac at inflammatory gene promoters; persistent CpG hypomethylation (e.g., TXNIP)	Sustained macrophage priming, chronic neuroinflammation, progressive axonal dysfunction	[45,50]
Clinical (T2D)	UKPDS	Long-term reduction in microvascular complications, including neuropathy, after an intensive control period	Durable DNA methylation changes at inflammation- and redox-related loci	Continued protection from early damage; incomplete reversal of established neuropathy	[45]
In vitro	DRG neurons, Schwann cells, and endothelial cells	Persistent ROS, NF-κB activation, fibrotic and inflammatory gene expression after transient hyperglycemia	SET7-mediated H3K4me1 enrichment; loss of H3K9me3 repression	Schwann cell dysfunction, impaired axonal support, and microvascular injury	[46,47]
In vivo	STZ-diabetic rodents	Oxidative/nitrative stress and cytokine expression persist months after insulin normalisation	Stable histone PTM reprogramming; impaired SUV39H1 activity	Chronic nerve inflammation, demyelination, reduced nerve conduction velocity	[48]
Immune-nerve crosstalk	Circulating monocytes / nerve macrophages	Hyperresponsive inflammatory phenotype independent of glycemia	Sustained H3K9ac at TNF-α, IL-6 promoters	Ongoing macrophage-mediated neurotoxicity and demyelination	[50]
Genome-wide epigenetics	DCCT/EDIC longitudinal methylome	150–250 CpG sites show persistent differential methylation ~ 17 years later	TXNIP promoter hypomethylation; impaired DNMT activity	Chronic oxidative stress, NLRP3 inflammasome activation in nerves	[50]
Molecular feedback loop	Neurovascular unit	Self-sustaining ROS-DAMP-inflammation cycle	ROS-driven DNA hypomethylation; NF-κB-SET7 chromatin recruitment	Entrenched neurodegeneration despite normoglycemia	[4,51–53]

transcriptional programs.

5.2. Epigenetic Memory: Lasting histone and DNA methylation changes

Persistent epigenetic modifications, particularly histone PTMs and DNA methylation, act as the molecular archive of prior hyperglycemic stress. These marks maintain aberrant gene expression in the peripheral nervous system, driving chronic neuroinflammation and axonal degeneration [49].

5.2.1. Persistent histone acetylation (H3K9ac)

In the DCCT/EDIC trial, monocytes from patients receiving conventional glycemic control showed significantly higher H3K9 acetylation (an activating mark) at promoters of inflammatory genes compared with those under intensive control. These differences persisted well into the follow-up phase [50]. In the context of neuropathy, systemic monocyte priming leads to hyperreactive macrophage infiltration into peripheral nerves, where sustained H3K9ac drives continuous local release of neurotoxic cytokines (e.g., TNF-α, IL-6), exacerbating nerve demyelination independently of current blood glucose levels.

5.2.2. Altered histone Methylation: H3K4me1 and H3K9me3

Histone methyltransferases play a critical role in establishing metabolic memory. Transient hyperglycemia induces SET7-mediated monomethylation of H3K4 (H3K4me1) at the NF-κB p65 promoter. This activating mark persists after normoglycemia is restored, maintaining neural and vascular cells in an inflammatory primed state [50]. Conversely, metabolic memory also involves the loss of repressive marks. Decreased SUV39H1 activity leads to a persistent reduction in H3K9me3. In metabolic memory models, this loss of repression spans multiple cell generations, leading to stable chromatin derepression of inflammatory and fibrotic genes that contribute to nerve ischemia and Schwann cell dysfunction [50].

5.2.3. DNA Methylation: Persistent 5-Methylcytosine signatures

Genome-wide DNA methylation profiling of paired blood samples collected ~ 17 years apart from DCCT/EDIC participants identified 150–250 CpG sites with persistently altered methylation in individuals with early poor glycemic control. A critical finding in neuropathy is stable hypomethylation of the TXNIP (Thioredoxin-interacting protein) promoter. Hypomethylation causes persistent TXNIP overexpression, which inhibits the antioxidant thioredoxin system and chronically activates the NLRP3 inflammasome, cementing a highly oxidative and inflammatory microenvironment in peripheral nerves [50].

5.3. The vicious cycle of ROS, DAMPs, and epigenetic reprogramming

Metabolic memory in diabetic neuropathy is ultimately sustained by a self-amplifying positive feedback loop between mitochondrial ROS, Damage-Associated Molecular Patterns (DAMPs), and chromatin remodelling enzymes. This triad ensures that the neuropathic cascade becomes self-sustaining [4].

Hyperglycemia-induced mitochondrial dysfunction generates initial bursts of superoxide, which alter the availability of epigenetic cofactors (such as NAD + and SAM) and directly oxidise DNA. For example, ROS-induced formation of 8-OHdG interferes with DNA methyltransferase activity, leading to hypomethylation of pro-oxidant genes such as p66Shc and TXNIP [51]. This epigenetic shift ensures continued ROS overproduction. Simultaneously, chronic oxidative stress induces cellular injury, releasing DAMPs (such as advanced glycation end-products, HMGB1, and S100 proteins). These DAMPs bind to RAGE (Receptor for AGEs) on Schwann cells and infiltrating immune cells, persistently activating downstream NF-κB and JAK/STAT pathways [52]. NF-κB not only drives acute inflammation but also actively recruits histone-modifying enzymes (such as SET7) to the promoters of inflammatory genes, thereby embedding activating H3K4me1 marks. By upregulating RAGE and downregulating endogenous antioxidants via these stable epigenetic marks, the nerve microenvironment remains locked in a cycle of DAMP release, ROS generation, and neuroinflammation long after the primary hyperglycemic trigger is removed [53].

5.4. Implications for Treating diabetic neuropathy

Understanding metabolic memory fundamentally shifts the therapeutic paradigm for diabetic neuropathy. While strict glycemic control remains essential to prevent the initiation of nerve damage, it is mechanically insufficient to reverse established neuropathic changes driven by epigenetic memory. Therefore, adjunctive therapies that directly sever the ROS-DAMP-epigenetic feedback loop are critical. Emerging and future strategies must look beyond simple glucose-lowering to include epigenetic modulators (e.g., SET7 inhibitors, HAT inhibitors, or DNMT-targeted therapies), alongside targeted RAGE antagonists and advanced antioxidants, to successfully erase metabolic memory and enable peripheral nerve regeneration [28,54].

6. Therapeutic implications and future Directions

6.1. Epigenetic therapies: DNMT inhibitors, HDAC inhibitors, miRNA modulators

Epigenetic therapies provide a promising means to disrupt the persistent maladaptive gene expression programs underlying diabetic neuropathy, with DNMT inhibitors, histone deacetylase (HDAC) inhibitors, and miRNA-based modulators emerging as the principal therapeutic strategies (Table 3) [55].

6.1.1. DNMT inhibitors

DNMT inhibitors, including the nucleoside analogues 5-azacytidine and decitabine and the non-nucleoside inhibitor RG108, suppress pathological DNA methylation and promote reactivation of genes silenced under diabetic conditions. In neuropathic pain models relevant to diabetes, pharmacological inhibition of DNMTs or genetic ablation of DNMT1 attenuates mechanical allodynia and nociceptor hyperexcitability by restoring expression of pain-inhibitory targets, such as the μ-opioid receptor (MOR) and potassium channels, in dorsal root ganglia neurons. Beyond analgesic effects, DNMT inhibition has been shown to reverse hypermethylation of cytoprotective genes, including Nrf2, thereby enhancing antioxidant defences implicated in diabetic complications. Notably, dietary bioactives such as sulforaphane also exhibit demethylating activity and confer neuroprotective effects in preclinical models of diabetes [56].

6.1.2. HDAC inhibitors

HDAC inhibitors function by preventing the removal of acetyl groups from histone proteins, thereby maintaining a relaxed chromatin conformation that facilitates gene transcription. In the context of diabetic neuropathy, this epigenetic modulation has shown promising therapeutic implications. Experimental studies demonstrate that FK228 (romidepsin), a class I HDAC inhibitor, effectively reverses both thermal and mechanical pain hypersensitivity in type 2 diabetic mice. Treatment with FK228 upregulates nerve regeneration markers, such as growth-associated protein 43 (GAP-43), while concurrently reducing inflammatory mediators and histone citrullination within the DRGs and spinal cord. These findings highlight HDAC inhibition as a means of attenuating neuroinflammation and enhancing axonal repair in diabetic conditions [57]. Similarly, Ricolinostat (ACY-1215), a selective HDAC6 inhibitor, has been shown to improve mitochondrial transport, ameliorate neuropathic structural changes, and facilitate functional recovery in rodent models of diabetic neuropathy [58]. Collectively, these studies underscore the therapeutic potential of HDAC inhibitors as dual-acting agents capable of alleviating pain and promoting neural regeneration

Table 3
Therapeutic strategies and emerging epigenetic biomarkers in diabetic neuropathy. The table summarises experimental and translational approaches targeting epigenetic dysregulation, DAMP signalling, and inflammation in diabetic neuropathy (DN). Included are DNA methyltransferase (DNMT) inhibitors, histone deacetylase (HDAC) inhibitors, microRNA (miRNA) modulators, RAGE/TLR4/NLRP3-targeted agents, multifunctional natural compounds, and cytokine/NF-κB-directed strategies. For each, molecular mechanisms, preclinical or clinical evidence, and translational considerations are provided. The table also highlights emerging biomarkers, including DNA methylation and histone modifications, which differentiate painful versus painless DN, predict progression, or reflect neuroinflammation and nerve regeneration. Collectively, these data illustrate potential disease-modifying targets and biomarkers for precision therapeutic development.

Category	Therapy / Target	Key Mechanisms	Preclinical / Clinical Evidence	Translational Notes	Key References
Epigenetic Therapies	DNMT inhibitors (5-Azacytidine, Decitabine; RG108)	↓ Pathological DNA hypermethylation restores MOR, K^+ channels, and Nrf2	↓ Mechanical allodynia, ↓ nociceptor excitability; DNMT1 KO mimics effects in DN models	Repurposed oncology drugs; sulforaphane shows dietary demethylation + neuroprotection	[55,56]
	HDAC inhibitors (FK228/romidepsin; Ricolinostat/ACY-1215)	↑ Histone acetylation; ↑ GAP-43, mitochondrial transport; ↓ inflammation, citrullination	Reverses thermal/mechanical hypersensitivity; enhances axonal regeneration in T2D rodents	Dual analgesic + regenerative potential; isoform selectivity may limit toxicity	[57,58]
	miRNA modulators (miR-146a, miR-25 mimics; miR-29c antagomirs)	Post-transcriptional regulation of TLR4/NF-κB, NOX4, PKCι	↓ Hyperalgesia/allodynia; preserves IENFD and nerve conduction	Precision targeting; delivery remains experimental	[59,60]
DAMP Pathway Inhibitors	RAGE antagonists (Azeliragon)	Blocks AGE/DAMP-RAGE-NF-κB signalling	Reverses mechanical hypersensitivity (≈ pregabalin) in STZ mice; RAGE KO ↑ regeneration	Glucose-independent; repeated dosing required	[61,62]
	TLR4 modulation (genetic KO; indirect: photobiomodulation, SGLT2i)	↓ TLR4/NF-κB signalling; ↓ macrophage infiltration	Preserves IENFD and sensory function in STZ mice	Avoids the safety issues of direct TLR4 inhibitors	[63–68]
	NLRP3 inflammasome inhibitors (MCC950; TXNIP inhibitors)	↓ IL-1β, caspase-1; blocks TXNIP-NLRP3 assembly	↓ Neuropathic pain, inflammation, and nerve damage in DN models	Targets sterile inflammation; disease-modifying potential	[69–71]
Multifunctional Natural Agents	Curcumin, Resveratrol, Quercetin, EGCG, Sulforaphane	Antioxidant + anti-inflammatory + epigenetic (↓ HAT, ↑ SIRT1; DNMT/miRNA modulation)	↓ Oxidative stress, NF-κB; ↑ Nrf2, nerve conduction in STZ models	Broad pathway coverage; bioavailability limits translation	[45,72–76]
Anti-cytokine / NF-κB Strategies	TNF-α, IL-1β, IL-6 biologics	Neutralisation of downstream inflammatory effectors	Limited preclinical and early clinical signals for pain reduction	Infection risk, high cost; not DN-specific	[9,77]
	BET inhibitors / NF-κB epigenetic blockers	Suppress acetyl-lysine-dependent inflammatory transcription	↓ Cytokines, oxidative stress in metabolic models	Targets metabolic memory; long-term safety unclear	[78,79]
Emerging Epigenetic Biomarkers	DNA methylation signatures (CHMP6, CACNA1B, PKNOX1; GCH1, MYT1L)	Reflect nervous system and MAPK pathway dysregulation	Distinguish painful vs painless DN; predict progression	Blood- or nerve-based risk stratification	[40,82,83]
	Histone acetylation (H3K9ac)	Index of NF-κB-driven neuroinflammation	Correlates with pain severity; reversed by HDAC inhibition	Peripheral and CNS applicability	[84]
	Histone citrullination (CitH3)	NET formation; regeneration-linked chromatin remodelling	Reduced following FK228; ↑ GAP-43	Potential circulating biomarker	[84]
	Histone methylation (H3K9me2, H3K27me3; EZH2/G9a)	K^+ channel silencing; glial activation	Correlates with pain hypersensitivity	Epigenetically targetable	[85]
	STAT3 acetylation	Astrocyte survival and anti-inflammatory signalling	HDAC5 inhibition restores STAT3 acetylation, reduces pain	CNS-specific biomarker of painful DN	[87]

in experimental diabetic neuropathy.

6.1.3. *miRNA modulators*

miRNAs are small noncoding RNAs that regulate gene expression at the post-transcriptional level and have emerged as key epigenetic regulators in the pathogenesis of diabetic neuropathy. Aberrant miRNA expression in diabetic conditions contributes to altered neuronal excitability, neuroinflammation, oxidative stress responses, and impaired axonal regeneration, core mechanisms underlying neuropathic dysfunction [59]. Preclinical studies have identified several dysregulated miRNAs, including miR-146a, miR-25, miR-29c, and miR-199a-3p, that modulate transcriptional networks governing pain signalling, inflammatory cascades, and neuroprotective pathways. Targeted modulation of these miRNAs using antisense oligonucleotides or synthetic mimics has demonstrated significant therapeutic potential in experimental diabetic neuropathy models [60].

Among these, miR-146a, miR-25, and miR-29c play complementary and mechanistically distinct roles in disease progression. miR-146a functions as a critical negative regulator of innate immune signalling by targeting the TLR4/NF-κB pathway; its downregulation in diabetic models leads to sustained activation of pro-inflammatory cytokines, including TNF-α and IL-1β, whereas restoration with miR-146a mimics suppresses inflammatory signalling and alleviates thermal hyperalgesia and mechanical allodynia [60]. In parallel, miR-25 directly targets NADPH oxidase 4 (NOX4), and reduced miR-25 expression results in excessive reactive oxygen species generation in Schwann cells, oxidative DNA damage, and distal axonal apoptosis effects that are markedly attenuated by miR-25 mimic administration, preserving nerve structural integrity. Conversely, elevated miR-29c expression in dorsal root ganglia impairs nerve function by inhibiting protein kinase C iota (PKCι); silencing miR-29c with antagomirs restores motor nerve conduction velocity and improves intraepidermal nerve fibre density in long-term diabetic models. Collectively, these findings underscore miRNA-based modulation as a promising, precision-oriented therapeutic strategy for diabetic neuropathy, although translation to clinical application remains in the experimental stage [60].

6.2. *Targeting DAMP Pathways: RAGE, TLR4, and inflammasome inhibitors*

Strategies aimed at blocking DAMP signalling offer potent therapeutic potential in DN by disrupting chronic inflammatory cycles and oxidative stress (Table 3).

6.2.1. RAGE antagonism

Azeliragon (oral RAGE inhibitor): In streptozotocin (STZ)-induced diabetic mice, administration of azeliragon reversed mechanical hypersensitivity in a manner comparable to pregabalin and without altering blood glucose levels. This antinociceptive effect required repeated dosing to persist, supporting the role of RAGE as a therapeutic target for DN. [61]. RAGE-deficient diabetic mice: Global deletion of RAGE in diabetic mice resulted in significantly improved axonal regeneration and conduction velocity following sciatic nerve injury, confirming RAGE's role in nerve injury and repair mechanisms. [62].

6.2.2. TLR4 inhibitors

TLR4-driven innate immune signalling is a key contributor to neuroinflammation in DN. Although direct TLR4 inhibitors such as TAK-242 (resatorvid), CLI-095, and Eritoran have not been evaluated in STZ-diabetic models, likely due to their sepsis-oriented development, the failure of Eritoran in phase III trials, and concerns regarding immunosuppression in diabetic patients' genetic studies provide strong support for TLR4 involvement [63–65]. TLR4 knockout in STZ-diabetic mice prevents small-fibre sensory deficits, preserves intraepidermal nerve fibre density, and reduces dermal macrophage infiltration, implicating TLR4-mediated inflammation in DN pathogenesis [66]. Given safety concerns surrounding direct inhibition, indirect modulation of TLR4 signalling has emerged as a promising alternative. Photobiomodulation therapy suppresses RAGE/NF-κB activity in peripheral nerves, attenuates DAMP-mediated TLR4/RAGE crosstalk, and improves neuropathic outcomes in diabetic rodents [63]. Similarly, SGLT2 inhibitors exert anti-inflammatory effects that partially converge on TLR4-dependent pathways [67]. Collectively, these strategies offer safer, translational avenues for targeting TLR4 in DN [68].

6.2.3. NLRP3 inflammasome inhibitors

MCC950 is a selective small-molecule inhibitor that targets the NLRP3 inflammasome, a critical mediator of sterile inflammation implicated in diabetic neuropathy. Preclinical studies in diabetic animal models have demonstrated that MCC950 effectively suppresses NLRP3 activation, leading to decreased production of IL-1β and inhibition of caspase-1 activity. These molecular effects translate into significant reductions in inflammatory marker expression, attenuation of neuropathic pain behaviours, and preservation of peripheral nerve structure and function [69,70].

Similarly, TXNIP has emerged as a pivotal upstream regulator of NLRP3 activation. Both genetic silencing and pharmacological inhibition of TXNIP have been shown to impede NLRP3 inflammasome assembly, thereby reducing neuroinflammatory responses and mitigating neuropathic alterations in experimental DN models [71]. Collectively, these findings emphasise the therapeutic promise of targeting the TXNIP-NLRP3 axis to suppress neuroinflammation, alleviate neuropathic pain, and protect neuronal integrity in diabetes-induced nerve injury.

6.3. Antioxidants and anti-inflammatory agents with epigenetic effects

A growing list of natural compounds, including curcumin and resveratrol, exhibits combined antioxidant, anti-inflammatory, and epigenetic-modulating properties that are beneficial in DN [72–74]. Curcumin suppresses high-glucose-induced inflammation in monocytes by inhibiting CBP/p300 HAT activity, decreasing histone acetylation at NF-κB-responsive promoters, and increasing HDAC2 expression [45]. Beyond modulating HATs, curcumin has been shown to reverse aberrant DNA methylation and regulate miRNA expression, reinforcing its role as a multifaceted epigenetic agent. [75]. Resveratrol protects peripheral nerves in STZ-induced diabetic mice by activating Nrf2, inhibiting NF-κB, reducing oxidative stress, and ameliorating neuropathic pain and nerve conduction deficits. Mechanistically, resveratrol enhances SIRT1 activity, resulting in deacetylation of NF-κB–p65 and H3K9, and restores epigenetic balance. [76]. It thus simultaneously targets oxidative stress, inflammation, and epigenetic dysregulation via a single pathway. Other natural antioxidants such as quercetin, epigallocatechin gallate (EGCG), and sulforaphane display similar epigenetic effects, including inhibition of DNMTs and modulation of ncRNAs, suggesting a broader therapeutic potential [76].

6.4. Anti-cytokine and NF-κB-targeted therapeutic strategies

Given that sustained cytokine activation is a key downstream effector of metabolic memory and neuroinflammatory damage in diabetic neuropathy, targeting pro-inflammatory cytokines and their transcriptional regulators is a rational therapeutic approach. Clinically approved biologics targeting tumour necrosis factor-α (TNF-α), interleukin-6 receptor (IL-6R), and interleukin-1β (IL-1β) have demonstrated robust anti-inflammatory efficacy in autoimmune and metabolic inflammatory disorders [9]. Preclinical and very limited clinical evidence suggest that these agents may attenuate peripheral nerve inflammation, reduce nociceptor sensitisation, and improve pain outcomes by interrupting cytokine-mediated crosstalk among macrophages, Schwann cells, and neurons. However, their application in diabetic neuropathy remains restricted by systemic immunosuppression (including increased infection risk), high cost, and the absence of large, neuropathy-specific clinical trials with clearly defined risk–benefit profiles for this predominantly non-life-threatening complication [77].

Beyond direct cytokine neutralisation, epigenetic modulation of inflammatory signalling offers a more upstream and potentially more durable strategy. Bromodomain and extra-terminal (BET) protein inhibitors suppress NF-κB-dependent transcription by disrupting acetyllysine recognition at pro-inflammatory gene promoters [78]. Preclinical studies have shown that BET inhibition reduces TNF-α, IL-6, and IL-1β expression, attenuates oxidative stress, and limits neuroinflammatory amplification in metabolic disease models. Such agents are proposed to counteract the persistent transcriptional activation characteristic of metabolic memory, positioning them as candidates with disease-modifying potential rather than purely symptomatic effects. At the same time, their broad impact on gene expression, uncertainty regarding long-term safety, and risk of off-target epigenomic and immune effects presently constrain clinical translation [79]. Collectively, these pharmacological approaches illustrate complementary strategies for targeting cytokine-driven nerve injury, with biologics acting at the effector cytokine level and epigenetic NF-κB-directed inhibitors addressing upstream transcriptional persistence. Future therapeutic paradigms may benefit from combining stringent glycaemic control with selective cytokine blockade or carefully targeted epigenetic modulation to disrupt the self-sustaining inflammatory circuits implicated in the progression of diabetic neuropathy [80].

6.5. Emerging biomarkers based on epigenetic signatures in diabetic neuropathy

Emerging research highlights that specific epigenetic modifications stable disease-associated changes in DNA methylation and histone marks, can serve as biomarkers for DN. These molecular signatures hold promise for early diagnosis, disease monitoring, and risk stratification [81].

6.5.1. DNA methylation signatures in peripheral nerves and blood

A cohort study evaluated sural nerve biopsies from type 2 diabetic patients over 52 weeks. Patients with progressive neuropathy showed 3,460 differentially methylated CpG sites compared to those with nerve regeneration. Affected genes are enriched in pathways tied to nervous system structure and MAPK signalling, indicating potential for molecular phenotyping of neuropathy progression [82]. A whole genome DNA methylation study across two cohorts (PROPGER and PROPENG) revealed distinct CpG methylation patterns separating painful from

painless diabetic neuropathy. Genes like GCH1, MYT1L, and MED16 emerged as top biomarkers and potential therapeutic targets [83]. In the Pittsburgh Epidemiology of Diabetes Complications cohort (28–year follow-up), three CpG sites (CHMP6, CACNA1B, PKNOX1) were inversely associated with risk of peripheral neuropathy. Methylation quantitative trait loci (meQTLs) near PKNOX1 further supported a causal role of epigenetic regulation [40].

6.5.2. Histone modification biomarkers in CNS injury

Epigenetic histone modifications have emerged as both mechanistic drivers and potential biomarkers of painful diabetic neuropathy. In type 2 diabetic models, increased histone H3 lysine 9 acetylation (H3K9ac) in dorsal root ganglia correlates with upregulation of inflammatory mediators, including HMGB1, IL-1β, and TLR4, and interventions that reduce H3K9ac are associated with attenuation of thermal hyperalgesia, supporting its utility as an index of neuroinflammatory activity [84]. In parallel, elevated levels of citrullinated histone H3 (CitH3) have been linked to neutrophil extracellular trap formation in diabetic neuropathy models, and modulation of CitH3 expression following HDAC inhibition (e.g., FK228) coincides with increased expression of nerve regeneration markers, suggesting translational relevance as a circulating biomarker [84]. Beyond acetylation and citrullination, aberrant histone methylation also contributes to neuropathic pathology: nerve injury induces upregulation of the methyltransferases G9a and EZH2 in sensory neurons, leading to increased H3K9me2 and H3K27me3 occupancy at promoters of potassium channel genes, while elevated EZH2/H3K27me3 signalling in the spinal dorsal horn promotes microglial and astrocytic activation and pro-inflammatory cytokine overproduction [85]. Consistent with these findings, increased expression of histone deacetylases in the dorsal root ganglia and spinal cord alongside heightened TNF-α and IL-1β levels has been observed in diabetic models [84,86]. Notably, elevated HDAC5 activity in spinal astrocytes of diabetic rats with painful neuropathy leads to STAT3 deacetylation, astrocytic dysfunction, and pain hypersensitivity, whereas pharmacological inhibition of HDAC5 restores STAT3 acetylation, rescues astrocyte loss, and alleviates neuropathic pain, highlighting STAT3 acetylation as a potential histone-based biomarker of central nervous system involvement in diabetic neuropathy [87].

7. Current research gaps & future perspectives

7.1. Longitudinal human studies & nerve–specific epigenomics

There's a critical need for longitudinal, tissue–specific epigenomic studies in humans to establish causal links between epigenetic changes and DN. While cross-sectional human sural nerve methylome studies identified differentially methylated CpGs associated with nerve degeneration vs. regeneration [53], the absence of serial sampling limits understanding of temporal dynamics. Future research should pursue repeated nerve biopsies alongside epigenomic profiling to capture epigenetic drift, metabolic memory markers, and correlate these with nerve conduction changes and pain scores [53].

7.2. Multi–Omics integration in diabetic neuropathy

Isolated omics analyses provide valuable snapshots but lack insight into molecular networks. Integration of epigenomics, transcriptomics, and proteomics, as applied to diabetic nephropathy can identify driver mechanisms and robust biomarkers [88]. In DN, similar multi-omics pipelines would enable the discovery of causal regulatory axes, revealing therapeutic targets and early diagnostic signatures [88].

7.3. Sex–specific and tissue–specific epigenetic responses

Emerging evidence indicates sex and tissue specificity in DN pathogenesis. Animal studies suggest differences in lipid metabolism pathways and macrophage infiltration in neuropathy between male/female diabetic mice. However, epigenetic profiling has largely overlooked sex as a biological variable. Future research must incorporate sex-balanced cohorts and single-cell approaches to uncover cell type- and sex-specific epigenetic signatures contributing to DN progression and pain susceptibility [54].

7.4. Personalised therapy guided by epigenetic profiling

Identification of epigenetic biomarkers, such as CpG methylation in CHMP6, CACNA1B, or PKNOX1 predictive of neuropathy risk [89], holds promise for precision medicine. Integrating such markers with pharmacoepigenomic insights (e.g., methylation affecting drug response) enables stratified treatment with DNMT inhibitors, HDAC modulators, or natural epigenetic agents such as resveratrol. Longitudinal biomarker-guided trials could then assess tailored therapy efficacy, optimising prevention, symptom control, and nerve regeneration. Develop the Machine Learning-derived Epigenetic Model (MLEM) to identify prognostic epigenetic gene patterns in DN [90].

CRediT authorship contribution statement

Faaz Bin Razi: Writing – original draft, Resources, Conceptualization, Methodology, Validation, Visualization. **Hamid Ashraf:** Writing – review & editing, Validation, Supervision, Conceptualization. **Sangeeta Singhal:** Writing – review & editing, Visualization, Supervision, Methodology. **Ziaul Qamar:** Writing – review & editing, Resources. **Shagufta Moin:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Harithpriya K, Jayasuriya R, Milan KL, Juttada U, Kumpatla S, Viswanathan V, et al. Epigenetic regulation of Nrf2-Mediated angiogenesis in diabetic foot ulcer progression: Role of histone deacetylases. Arch Biochem Biophys 2024 Oct;1(760):110133.
[2] Thakur V, Sadanandan J, Chattopadhyay M. High-mobility group box 1 protein signaling in painful diabetic neuropathy. Int J Mol Sci 2020 Jan 30;21(3):881.
[3] Kowluru RA. Cross talks between oxidative stress, inflammation and epigenetics in diabetic retinopathy. Cells 2023 Jan 12;12(2):300.
[4] Yang T, Qi F, Guo F, Shao M, Song Y, Ren G, et al. An update on chronic complications of diabetes mellitus: from molecular mechanisms to therapeutic strategies with a focus on metabolic memory. Mol Med 2024 May 26;30(1):71.
[5] He Y, Qu L. Non-coding RNAs in diabetic peripheral neuropathy: their role and mechanisms underlying their effects. Metabolism 2024 May;1(154):155833.
[6] Yang J, Yu Z, Jiang Y, Zhang Z, Tian Y, Cai J, et al. SIRT3 alleviates painful diabetic neuropathy by mediating the FoxO3a-PINK1-Parkin signaling pathway to activate mitophagy. CNS Neurosci Ther 2024 Apr;30(4):e14703.
[7] Sriwastawa K, Kumar A. Mitochondrial dysfunction in diabetic neuropathy: Impaired mitophagy triggers NLRP3 inflammasome. Mitochondrion 2024 Oct;2:101972.
[8] Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. Signal Transduct Target Ther 2023;8(1):333.
[9] Nashtahosseini Z, Eslami M, Paraandavaji E, Haraj A, Dowlat BF, Hosseinzadeh E, et al. Cytokine signaling in diabetic neuropathy: a key player in peripheral nerve damage. Biomedicines 2025;13(3):589.
[10] Sifuentes-Franco S, Pacheco-Moisés FP, Rodríguez-Carrizalez AD, Miranda-Díaz AG. The role of oxidative stress, mitochondrial function, and autophagy in diabetic polyneuropathy. Journal of diabetes research 2017;2017(1):1673081.
[11] Sharan L, Pal A, Babu SS, Kumar A, Banerjee S. Bay 11-7082 mitigates oxidative stress and mitochondrial dysfunction via NLRP3 inhibition in experimental diabetic neuropathy. Life Sci 2024 Dec;15(359):123203.
[12] Khanna S, Kumar S, Sharma P, Daksh R, Nandakumar K, Shenoy RR. Flavonoids regulating NLRP3 inflammasome: a promising approach in alleviating diabetic peripheral neuropathy. Inflammopharmacology 2025 Apr;9:1–32.
[13] Zhang X, Zhao S, Yuan Q, Zhu L, Li F, Wang H, et al. TXNIP, a novel key factor to cause Schwann cell dysfunction in diabetic peripheral neuropathy, under the regulation of PI3K/Akt pathway inhibition-induced DNMT1 and DNMT3a overexpression. Cell Death Dis 2021;12(7):642.

[14] Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrinol 2014;2014(1):674987.
[15] Suryavanshi SV, Kulkarni YA. NF-κβ: a potential target in the management of vascular complications of diabetes. Front Pharmacol 2017 Nov;7(8):798.
[16] Kumar A, Negi G, Sharma SS. Suppression of NF-κB and NF-κB regulated oxidative stress and neuroinflammation by BAY 11-7082 (IκB phosphorylation inhibitor) in experimental diabetic neuropathy. Biochimie 2012 May 1;94(5):1158–65.
[17] Du L, Chen Y, Shi J, Yu X, Zhou J, Wang X, et al. Inhibition of S100A8/A9 ameliorates renal interstitial fibrosis in diabetic nephropathy. Metabolism 2023 Jul;1(144):155376.
[18] Wang D, Wang H, Gao H, Zhang H, Zhang H, Wang Q, et al. P2X7 receptor mediates NLRP3 inflammasome activation in depression and diabetes. Cell Biosci 2020 Mar 5;10(1):28.
[19] Lin H, Xiong W, Fu L, Yi J, Yang J. Damage-associated molecular patterns (DAMPs) in diseases: implications for therapy. Molecular Biomedicine 2025 Aug 29;6(1):60.
[20] Chen R, Zou J, Zhong X, Liu J, Kang R, Tang D. DAMP signaling networks: from receptors to diverse pathophysiological functions. J Adv Res 2025.
[21] Serna-Rodríguez MF, Bernal-Vega S, Camacho-Morales A, Pérez-Maya AA. The role of damage associated molecular pattern molecules (DAMPs) and permeability of the blood-brain barrier in depression and neuroinflammation. J Neuroimmunol 2022;15(371):577951.
[22] Yu H, Ren K, Jin Y, Zhang L, Liu H, Huang Z, et al. Mitochondrial DAMPs: Key mediators in neuroinflammation and neurodegenerative disease pathogenesis. Neuropharmacology 2025 Feb;15(264):110217.
[23] Bestall SM, Hulse RP, Blackley Z, Swift M, Ved N, Paton K, Beazley-Long N, Bates DO, Donaldson LF. Sensory neuronal sensitisation occurs through HMGB-1-RAGE and TRPV1 in high-glucose conditions. Journal of cell science. 2018 Jul 15;131 (14):jcs215939.
[24] Sarhan A, Almzaiel AJ, Alrufaie MM. Potential role of S100A8/A9 and RNA-binding protein in microvascular complications of type2 diabetes mellitus. Anaesthesia, Pain & Intensive Care 2023 Dec 13;27(6):673–80.
[25] Pereira CA, Carlos D, Ferreira NS, Silva JF, Zanotto CZ, Zamboni DS, et al. Mitochondrial DNA promotes NLRP3 inflammasome activation and contributes to endothelial dysfunction and inflammation in type 1 diabetes. Front Physiol 2020 Jan;17(10):1557.
[26] Fan X, Qian Q, Li W, Liu T, Zeng C, Jia P, et al. Epigenetic drift score captures directional methylation variability and links aging to transcriptional, metabolic, and genetic alterations. Genome Res 2025 Oct 1;35(10):2173–88.
[27] Diabetes Care 2016 May 1;39(5):686–93.
[28] Dong H, Sun Y, Nie L, Cui A, Zhao P, Leung WK, et al. Metabolic memory: mechanisms and diseases. Signal Transduct Target Ther 2024 Feb 28;9(1):38.
[29] Pirola L, Balcerczyk A, Okabe J, El-Osta A. Epigenetic phenomena linked to diabetic complications. Nat Rev Endocrinol 2010 Dec;6(12):665–75.
[30] Wang J, Xiao M, Wang J, Wang S, Zhang J, Guo Y, et al. NRF2-related epigenetic modifications in cardiac and vascular complications of diabetes mellitus. Front Endocrinol 2021 Jun;25(12):598005.
[31] Kouzarides T. Chromatin modifications and their function. Cell 2007 Feb 23;128 (4):693–705.
[32] Paneni F, Volpe M, Lüscher TF, Cosentino F. SIRT1, p66Shc, and Set7/9 in vascular hyperglycemic memory: bringing all the strands together. Diabetes 2013 Jun 1;62 (6):1800–7.
[33] Esteller M. Non-coding RNAs in human disease. Nat Rev Genet 2011;12(12): 861–74.
[34] Yan B, Yao J, Liu JY, Li XM, Wang XQ, Li YJ, et al. lncRNA-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA. Circ Res 2015 Mar 27;116(7):1143–56.
[35] Chen Z, Miao F, Paterson AD, Lachin JM, Zhang L, Schones DE, et al. Epigenomic profiling reveals an association between persistence of DNA methylation and metabolic memory in the DCCT/EDIC type 1 diabetes cohort. Proc Natl Acad Sci 2016 May 24;113(21):E3002–11.
[36] Wegner M, Neddermann D, Piorunska-Stolzmann M, Jagodzinski PP. Role of epigenetic mechanisms in the development of chronic complications of diabetes. Diabetes research and clinical practice. 2014 Aug 1;105(2):164-75.
[37] Wu YL, Lin ZJ, Li CC, Lin X, Shan SK, Guo B, et al. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Signal Transduct Target Ther 2023 Mar 2;8(1):98.
[38] Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat Rev Nephrol 2019 Jun;15(6):327–45.
[39] Zhou J, Mychaleckyj JC, Onengut-Gumuscu S, Orchard TJ, Costacou T, Miller RG. DNA methylation and 28 year incidence of two neuropathy phenotypes in type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications cohort study. Diabetologia 2025 Apr;23:1–7.
[40] Zhou J, Mychaleckyj J, Onengut-Gumuscu S, Orchard TJ, Costacou T, Miller RG. 1461-P: DNA Methylation (DNAm) and 28-Year Risk of Diabetic Peripheral Neuropathy (DPN) in Type 1 Diabetes (T1D) The Epidemiology of Diabetes Complications (EDC) Study. Diabetes. 2024 Jun 14;73(Supplement_1):1461-P.
[41] Yang Y, Luan Y, Feng Q, Chen X, Qin B, Ren KD, et al. Epigenetics and beyond: targeting histone methylation to treat type 2 diabetes mellitus. Front Pharmacol 2022 Jan;11(12):807413.
[42] Čugalj Kern B, Trebušak Podkrajšek K, Kovač J, Šket R, Jenko Bizjan B, Tesovnik T, et al. The role of epigenetic modifications in late complications in type 1 diabetes. Genes 2022 Apr 15;13(4):705.
[43] Miller RG, Mychaleckyj JC, Onengut-Gumuscu S, Feingold E, Orchard TJ, Costacou T. DNA methylation and 28-year cardiovascular disease risk in type 1 diabetes: the Epidemiology of Diabetes Complications (EDC) cohort study. Clin Epigenetics 2023 Aug 2;15(1):122.
[44] Jankovic M, Novakovic I, Nikolic D, Mitrovic Maksic J, Brankovic S, Petronic I, et al. Genetic and epigenomic modifiers of diabetic neuropathy. Int J Mol Sci 2021 May 5;22(9):4887.
[45] Pop-Busui R, Herman WH, Feldman EL, Low PA, Martin CL, Cleary PA, et al. DCCT/EDIC Research Group. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Curr Diab Rep 2010 Aug;10(4):276–82.
[46] Kowluru RA, Chan PS. Metabolic memory in diabetes-from in vitro oddity to in vivo problem: Role of Apoptosis. Brain Res Bull 2010 Feb 15;81(2–3):297–302.
[47] Alhazzaa RA, Heinbockel T, Csoka AB. Diabetes and epigenetics. Epigenetics to Optogenetics-a New Paradigm in the Study of Biology. 2022 May 5.
[48] Loscalzo J, Handy DE. Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series). Pulmonary circulation 2014 Jun;4(2):169–74.
[49] Ding Q, Gao Z, Chen K, Zhang Q, Hu S, Zhao L. Inflammation-related epigenetic modification: the bridge between immune and metabolism in type 2 diabetes. Front Immunol 2022 May;6(13):883410.
[50] Reddy MA, Natarajan R. Epigenetic mechanisms in diabetic vascular complications. Cardiovascular research 2011 Jun 1;90(3):421–9.
[51] Lu Z, Liu N, Wang F. Epigenetic regulations in diabetic nephropathy. Journal of diabetes research 2017;2017(1):7805058.
[52] Bestall SM, Hulse RP, Blackley Z, Swift M, Ved N, Paton K, Beazley-Long N, Bates DO, Donaldson LF. Sensory neuronal sensitisation occurs through HMGB-1-RAGE and TRPV1 in high-glucose conditions. Journal of cell science. 2018 Jul 15;131 (14):jcs215939.
[53] Damiano G, Rinaldi R, Raucci A, Molinari C, Sforza A, Pirola S, et al. Epigenetic mechanisms in cardiovascular complications of diabetes: towards future therapies. Mol Med 2024 Sep 27;30(1):161.
[54] Yang Y, Zhao B, Wang Y, Lan H, Liu X, Hu Y, et al. Diabetic neuropathy: cutting-edge research and future directions. Signal Transduct Target Ther 2025 Apr 25;10 (1):132.
[55] Odimegwu CL, Uwaezuoke SN, Chikani UN, Mbanefo NR, Adiele KD, Nwolisa CE, et al. Targeting the epigenetic marks in type 2 diabetes mellitus: will epigenetic therapy be a valuable adjunct to pharmacotherapy? Diabetes, Metabolic Syndrome and Obesity 2024 Dec;31:3557–76.
[56] Xiong HY, Wyns A, Campenhout JV, Hendrix J, De Bruyne E, Godderis L, et al. Epigenetic landscapes of pain: DNA methylation dynamics in chronic pain. Int J Mol Sci 2024 Jul 30;25(15):8324.
[57] Thakur V, Gonzalez MA, Parada M, Martinez RD, Chattopadhyay M. Role of histone deacetylase inhibitor in diabetic painful neuropathy. Mol Neurobiol 2024; 61(4):2283–96.
[58] Li J, Yu M, Fu S, Liu D, Tan Y. Role of selective histone deacetylase 6 inhibitor ACY-1215 in cancer and other human diseases. Front Pharmacol 2022 May;16(13): 907981.
[59] Xourgia E, Papazafiropoulou A, Melidonis A. Circulating microRNAs as biomarkers for diabetic neuropathy: a novel approach. World journal of experimental medicine 2018 Nov 30;8(3):18.
[60] Fan B, Chopp M, Zhang ZG, Liu XS. Emerging roles of microRNAs as biomarkers and therapeutic targets for diabetic neuropathy. Front Neurol 2020 Oct;22(11): 558758.
[61] Ma S, Nakamura Y, Hisaoka-Nakashima K, Morioka N. Blockade of receptor for advanced glycation end-products with azeliragon ameliorates streptozotocin-induced diabetic neuropathy. Neurochem Int 2023 Feb;1(163):105470.
[62] Juranek JK, Geddis MS, Song F, Zhang J, Garcia J, Rosario R, et al. RAGE deficiency improves postinjury sciatic nerve regeneration in type 1 diabetic mice. Diabetes 2013 Mar 1;62(3):931–43.
[63] Panou T, Gouveri E, Popovic DS, Papazoglou D, Papanas N. The role of inflammation in the pathogenesis of diabetic peripheral neuropathy: new lessons from experimental studies and clinical implications. Diabetes Therapy 2025 Mar; 16(3):371–411.
[64] Tidswell MD M. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: The ACCESS randomized trial.
[65] Samarpita S, Kim JY, Rasool MK, Kim KS. Investigation of toll-like receptor (TLR) 4 inhibitor TAK-242 as a new potential anti-rheumatoid arthritis drug. Arthritis Res Ther 2020 Jan 23;22(1):16.
[66] Crowards S, Ryals J, Heslop L, Hauser W, Totta-Griese G, Madden T, et al. TLR4 deletion reduces small fiber sensory abnormalities and nerve degeneration in diabetic male mice. Neuroscience 2025 Oct 28.
[67] Zhan X, Cheng L, Huo N, Yu L, Liu C, Liu T, et al. Sodium-glucose cotransporter-2 inhibitor alleviated atrial remodeling in STZ-induced diabetic rats by targeting TLR4 pathway. Front Cardiovasc Med 2022 Sep;6(9):908037.
[68] Aghamiri SH, Komlakh K, Ghaffari M. Toll-like receptors (TLRs) and their potential therapeutic applications in diabetic neuropathy. Int Immunopharmacol 2022 Jan;1 (102):108398.
[69] Zou Y, Tang X, Yang S, Chen Z, Liu B, Zhou Z, et al. New insights into the function of the NLRP3 inflammasome in sarcopenia: mechanism and therapeutic strategies. Metabolism 2024 Sep;1(158):155972.
[70] Das B, Sarkar C, Rawat VS, Kalita D, Deka S, Agnihotri A. Promise of the NLRP3 inflammasome inhibitors in in vivo disease models. Molecules 2021 Aug 18;26(16): 4996.
[71] Borowiec AM, Właszczuk A, Olakowska E, Lewin-Kowalik J. TXNIP inhibition in the treatment of diabetes. Verapamil as a novel therapeutic modality in diabetic patients. Medicine and pharmacy reports. 2022 Jul 26;95(3):243.

[72] Faaz Bin Razi, Perveen Akhter, Aparaajita Bhatnaagar, Sheema Wazib, Vineet Jain and Iqbal Alam (2025). Effects of Triticum aestivum L. supplementation on lipid profiles and oxidative stress markers in overweight and obese individuals. Ann. Phytomed., 14(1):728-735. https://doi.org/10.54085/ap.2025.14.1.71.
[73] Razi FB, Singhal S, Ashraf H, Moin S. Neuroinflammation and metabolic dysfunction drive nerve conduction deficits in diabetic neuropathy: Clinical and in silico insights. J Neuroimmunol 2025 Dec;26:578849.
[74] Islam MR, Rauf A, Akash S, Trisha SI, Nasim AH, Akter M, et al. Targeted therapies of curcumin focus on its therapeutic benefits in cancers and human health: Molecular signaling pathway-based approaches and future perspectives. Biomed Pharmacother 2024 Jan;1(170):116034.
[75] Begum F, Lakshmanan K. Mechanism of metabolic memory: progression in diabetic nephropathy a descriptive review. Egyptian Journal of Medical Human Genetics 2024 Oct 28;25(1):125.
[76] Chen X, Xie N, Feng L, Huang Y, Wu Y, Zhu H, et al. Oxidative stress in diabetes mellitus and its complications: from pathophysiology to therapeutic strategies. Chin Med J (Engl) 2025 Jan 5;138(1):15–27.
[77] Kocot-Kępska M, Zajączkowska R, Mika J, Wordliczek J, Dobrogowski J, Przeklasa-Muszyńska A. Peripheral mechanisms of neuropathic pain—the role of neuronal and non-neuronal interactions and their implications for topical treatment of neuropathic pain. Pharmaceuticals 2021 Jan 20;14(2):77.
[78] Geanes ES, Greening G, Aggelakopoulou M, Truong LH, Khanal S, LeMaster C, et al. Bromodomain and extra-terminal protein inhibitors modulate natural killer cell function and differentiation. Sci Rep 2026 Jan 3.
[79] Barbalho SM, Leme Boaro B, da Silva Camarinha Oliveira J, Patočka J, Barbalho Lamas C, Tanaka M, Laurindo LF. Molecular Mechanisms Underlying Neuroinflammation Intervention with Medicinal Plants: A Critical and Narrative Review of the Current Literature. Pharmaceuticals. 2025 Jan 20;18(1):133.
[80] Rider P, Carmi Y, Cohen I. Biologics for targeting inflammatory cytokines, clinical uses, and limitations. International journal of cell biology 2016;2016(1):9259646.
[81] An Y, Wang Q, Gao K, Zhang C, Ouyang Y, Li R, et al. Epigenetic Regulation of Aging and its Rejuvenation. MedComm 2025 Sep;6(9):e70369.
[82] Guo K, Elzinga S, Eid S, Figueroa-Romero C, Hinder LM, Pacut C, et al. Genome-wide DNA methylation profiling of human diabetic peripheral neuropathy in subjects with type 2 diabetes mellitus. Epigenetics 2019;14(8):766–79.
[83] Kwiatkowska KM, Garagnani P, Bonafé M, Bacalini MG, Sala C, Castellani G, et al. High-resolution whole-genome DNA methylation revealed unique signatures of painful diabetic neuropathy. Diabetes 2025;74(4):640–50.
[84] 2002: Thakur V, Gonzalez MA, Parada M, Martinez RD, Chattopadhyay M. Role of histone deacetylase inhibitor in diabetic painful neuropathy. Molecular Neurobiology. 2024 Apr;61(4):2283-96.
[85] 2004: Luo D, Li X, Tang S, Song F, Li W, Xie G, Liang J, Zhou J. Epigenetic modifications in neuropathic pain. Molecular Pain. 2021 Nov 26;17: 17448069211056767.
[86] 2005: Wang W, Cui SS, Lu R, Zhang H. Is there any therapeutic value for the use of histone deacetylase inhibitors for chronic pain?. Brain research bulletin. 2016 Jul 1;125:44-52.
[87] Fan T, Yu Y, Chen YL, Gu P, Wong S, Xia ZY, et al. Histone deacetylase 5-induced deficiency of signal transducer and activator of transcription-3 acetylation contributes to spinal astrocytes degeneration in painful diabetic neuropathy. Glia 2023 Apr;71(4):1099–119.
[88] Saliba A, Du Y, Feng T, Garmire L. Multi-Omics Integration in Nephrology: Advances, Challenges, and Future Directions. InSeminars in nephrology 2025 Apr 11 (p. 151584). WB Saunders.
[89] Dewanjee S, Vallamkondu J, Kalra RS, Chakraborty P, Gangopadhyay M, Sahu R, et al. The emerging role of HDACs: pathology and therapeutic targets in diabetes mellitus. Cells 2021;10(6):1340.
[90] Guo X, Feng C, Xing J, Cao Y, Liu T, Yang W, et al. Epigenetic profiling for prognostic stratification and personalized therapy in breast cancer. Front Immunol 2025;14(15):1510829.