Epigenetics of pain highways (Review)

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Abstract. According to the International Association for the Study of Pain, 'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Chronic pain may be the result of tissue injury, nerve damage, surgical procedures, chemotherapy and chronic diseases, such as diabetes. In addition to physical causes, emotional and environmental stressors, exacerbated by factors such as climate change, are increasingly recognized as contributors to chronic pain and its associated sensitization patterns. One of the most underexplored areas in pain research is the epigenetic regulation of ion channels that modulate nociceptive pathways. Emerging evidence highlights epigenetic mechanisms, such as histone modifications, DNA methylation, microRNA (miRNA/miR) regulation and the activity of the RE1-silencing transcription factor (REST) complex, as key modulators of ion channel conductance in nociceptors. For example, REST downregulates $Na_v1.8$ sodium channels and K_v and K_{2P} potassium channels and the μ-opioid or MOP receptor (*Oprm1* gene) in dorsal root ganglion (DRG) neurons, contributing to neuropathic pain. Similarly, miRNAs, such as miR-183 directly target *TRPV1* and multiple sodium channel isoforms (*Nav1.3*, *Nav1.7* and *Nav1.8*) in DRG neurons and reduce osteoarthritic pain. Central nervous system-specific miRNAs, such as miR-124 and miR-219 modulate the calmodulin-dependent protein kinase and methyl-CpG binding protein 2 pathways, reducing nociceptive signaling and offering promising avenues for future pain therapies. The present review summarizes the current knowledge of these epigenetic modulators of ion channels and discusses how these findings may complement traditional pharmacological approaches to develop more effective strategies for chronic pain management.

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Abbreviations: DRG, dorsal root ganglion; DHN, dorsal horn neuron; CNS, central nervous system; PNS, peripheral nervous system; WDR neuron, wide dynamic range neuron; GABA, gamma-aminobutyric acid; TRP channels, transient receptor potential channels; STAT3, signal transducer and activator of transcription 3; NRSF/REST, neuron-restrictive silencer factor or repressor element-1 (RE1)-silencing transcription factor; NRSE or RE1, neuron-restrictive silencer element; VGSCs, voltage-gated sodium channels; VDCCs, voltage-dependent calcium channels; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; MeCP2, methyl-CpG binding protein 2; m^6A, N^6-methyladenosine; HOTAIR, HOX transcript antisense intergenic RNA

Key words: nociception, spinal cord, neuropathic pain, dorsal root ganglia, dorsal horn, brainstem, thalamus, DNA methylation, histone modifications, microRNAs

Contents

1. Introduction

According to the National Health Interview Survey (NHIS, 2023), new cases of chronic pain occur more frequently than new cases of other common conditions, such as diabetes, depression and high blood pressure (1). The incidence of new cases of chronic pain is estimated at 52.4 cases per 1,000 individuals per year, compared to 7.1 for diabetes, 15.9 for depression and 45.3 for hypertension (1). Globally, pain affects billions of individuals each day. A previous meta-analysis of 25 studies estimated that the prevalence of chronic widespread pain across cultural groups in Europe, Asia and the Americas

ranged from 0 to 24% (2). Research has demonstrated that women report pain more frequently than men, that pain prevalence increases with age, and that cases of pain tend to be higher in rural than urban areas (3). A recent global survey involving 52 countries, based on data from the 2002-2004 World Health Survey (WHS), found that the prevalence of moderate to extreme pain among adults aged ≥25 years was 27.5%. This prevalence ranged from a minimum of 9.9% in China to a maximum of 50.3% in Morocco (3). Consequently, chronic pain represents a significant public health burden. Pain can generally be categorized into four main types: Acute pain, nociceptive pain, chronic pain and neuropathic pain (4). The present review focuses primarily on nociceptive, acute and chronic pain, with selected examples of neuropathic pain provided where relevant.

The spinal cord serves as the central highway for transmitting ascending and descending information to various body segments, very similar to a network connecting distinct towns or counties. Each spinal cord segment contains a complex network of afferent and efferent neurons, with dorsal root ganglia providing the primary sensory relay, and these components are interlinked via local interneurons and long-range projection neurons that participate in ascending and descending tracts (Fig. S1). This integrated circuitry enables precise sensory-motor coordination and ensures dynamic communication with higher-order processing centers in the cortex, thalamus, and brainstem, which are responsible for perception, motor control and autonomic regulation (5).

Neuronal activity within this system arises from a dynamic interplay among epigenetic regulation, genetic programming, cellular physiology, and environmental influences. These interactions encompass the electrical and chemical activities of neuronal membranes, including the receptors, ion channels, transporters and signaling molecules. Neuronal gene expression is constantly modulated by intra- and extracellular stimuli, such as stress, learning processes, emotional experiences and exposure to toxins, each of which can trigger epigenetic modifications. These modifications are essential to the plasticity of the nervous system, enabling both structural changes e.g., alterations in dendritic spine density and functional adaptations e.g., long-term potentiation and long-term depression (6). Epigenetic modifications are crucial for these long-term neural adaptations, influencing processes, such as pain perception, learning, memory consolidation and susceptibility to neurological disorders. Environmental factors including stress, nutrition and exposure to toxins, which are skyrocketing due to climate change (7), further contribute to remodeling the epigenetic landscape, promoting maladaptive plasticity and chronic pain sensitization.

Key epigenetic mechanisms, namely DNA methylation, histone modification and non-coding RNAs, function as molecular switches or dimmers, altering gene expression without changing the DNA sequence. In the nervous system, these modifications help encode experiences, such as pain or learning events, into long-lasting changes in neuronal function and connectivity (8,9).

The dorsal horn of the spinal cord is a critical hub for processing nociceptive (pain-related) signals and exemplifies how environmental and molecular influences shape neuronal plasticity. As the first central relay for sensory input from peripheral nociceptors (nociceptive neurons), the dorsal horn integrates signals through a finely tuned balance of excitatory and inhibitory neurotransmission. Following nerve injury or inflammation, this balance is often disrupted, resulting in central sensitization, a hyperexcitable state of dorsal horn neurons (DHNs) that underlies phenomena such as allodynia and hyperalgesia (10). Epigenetic alterations are key contributors to these changes in neurotransmission. Modifications in DNA methylation, histone acetylation and non-coding RNA expression within dorsal horn neurons and glial cells regulate the transcription of genes involved in synaptic signaling, neuroinflammation and plasticity (11,12). For example, the enhanced expression of glutamatergic receptors or pro-inflammatory cytokines, along with impaired inhibitory signaling, can be epigenetically programmed in response to persistent nociceptive input or environmental stressors (13,14). Emerging epigenetic-based therapies, such as histone deacetylase (HDAC) inhibitors, microRNA (miRNA/miR) modulators and DNA methylation blockers, which are discussed in the article, are currently under investigation for their potential to reverse chronic pain states by restoring homeostatic gene expression and reducing pain hypersensitivity (15).

Despite these advances, the specific epigenetic regulation of ion channels in nociceptive neurons remains insufficiently understood. Ion channels, including voltage-gated sodium, potassium, and calcium channels, transient receptor potential channels (TRP channels) and acid-sensing ion channels, are critical for generating and propagating pain signals. However, how epigenetic modifications influence their expression and function in the spinal cord remains largely unexplored. The present review represents a first step toward consolidating current knowledge on the epigenetic modulation of pain highways or channels in the spinal cord and identifying key gaps to guide future research. The present review begins with an overview of spinal cord structure, cellular composition, and nociceptive pathways, followed by a detailed examination of the known epigenetic mechanisms regulating ion channels expression in the context of pain.

2. Spinal cord length is unparalleled with that of the vertebral column after birth

The spinal cord begins at the medulla oblongata in the rostral (upper) region at the level of the foramen magnum and extends down to approximately the lumbar, L1-L2 vertebral level in adults, where it tapers into the conus medullaris (Fig. S1A). Beyond the conus medullaris, the cauda equina (‘horse's tail’) consists of a bundle of spinal nerves that continue to the lower vertebrae, including the coccygeal region (Fig. S1B) (16). During fetal development, the spinal cord is aligned with the vertebral column. However, after birth, its growth slows while the vertebral column continues to elongate, resulting in the spinal cord terminating earlier within the vertebral canal, a process known as the ascent of the spinal cord. By 15 weeks of gestation, the cord reaches the lower border of the sacral S1 vertebra; by 6 months, it reaches the L4 level; and by full term, it typically aligns with the lower border of L3. These levels vary slightly between male and female fetuses. In recent research performed on human fetuses, 16 fetuses exhibited a spinal cord termination at level L2, followed by 8 fetuses at

the L3 level and 6 fetuses at the L4 level. Comparing male vs. female fetuses, out of 11 male fetuses, 8 fetuses had spinal cord termination at the L2 vertebra level, two at the L3 level, and one fetus at the L4 level. In female fetuses, eight had a spinal cord termination at the L2 level, six at the L3 level and five at the L4 level (17).

3. Mapping the spinal cord: Spinal nerves and segments

The spinal cord is covered by three layers of meninges: The dura mater, the arachnoid mater and the pia mater (Fig. S1C). In a transverse section of the spinal cord, the outer layer consists of white matter, while the inner layer is made up of gray matter that surrounds ependymal cells lining the central canal, which is filled with cerebrospinal fluid (18). This central canal is continuous with the fourth ventricle-part of the cerebral ventricular system (19). The ratio of white to gray matter varies along the rostro-caudal axis of the spinal cord. At the lower levels, the ratio between gray matter and white matter is greater than in higher levels, mainly as lower levels contain less ascending and descending nerve fibers. Similarly, at the higher levels, the ratio of white matter to gray matter is higher as ascending tracts gain fibers at each successive level and descending tracts lose fibers (20).

The human spinal cord consists of 31 segments: Eight cervical, 12 thoracic, five lumbar, five sacral and one coccygeal. These 31 segments are defined by the 31 pairs of spinal nerves that connect various body segments to the brain. Each spinal nerve exits through the intervertebral foramen, the opening between two adjacent vertebrae (Fig. S1). In a transverse section, the spinal cord has an H-shaped or butterfly-like appearance, featuring four protrusions, the dorsal and ventral horns, that extend dorso- or ventrolaterally toward the attachment zones of the dorsal and ventral root fascicles of each spinal nerve tracts (16) (Fig. S2).

Spinal nerves are categorized based on their vertebral alignment: Cervical (C1-C8), thoracic (T1-T12), lumbar (L1-L5), sacral (S1-S5) and coccygeal (Co1) (Fig. S1). Each spinal nerve is a mixed nerve composed of both sensory (afferent) and motor (efferent) fibers. These nerves consist of fascicles of nerve fibers that innervate specific regions of skin and muscles. Each such region corresponds to a single segment, and the area of skin supplied by peripheral nerve fibers originating from a single dorsal root ganglion (DRG) is known as a dermatome (20).

Each spinal segment is characterized by dorsal roots that enter the spinal cord and ventral roots that exit it. The dorsal roots contain primary afferent neurons, carrying information from the periphery, the cell bodies of these neurons are located in the DRGs. By contrast, the ventral roots of spinal nerves carry efferent neurons, with their cell bodies found in the spinal gray matter (16,20). Immediately after leaving the intervertebral foramina, spinal nerves divide to produce a thin dorsal ramus (supplies the muscles and skin of the back) and a much larger ventral ramus (supplies the muscles and skin of the front of the body and limbs) (Figs. S1C and S3) (16). The DRG is approximately the size of a tiny peanut. The DRG is an enlargement of the dorsal root that houses somata (cell bodies) of primary sensory neurons; an average of 15,000 neurons are present in the DRG, although these numbers vary with their location; for example, there are 60,000 neurons at C5 and 100,000 at the C7 level (21,22). Afferent fibers, originating from the DRG, carry sensory information (touch, pain, temperature and proprioception) from peripheral receptors into the dorsal horn. Ventral (anterior) horns house the cell bodies of lower motor neurons (alpha motor neurons and gamma motor neurons), which send efferent fibers through the ventral root to innervate skeletal muscles (16) (Fig. S2).

4. Spinal Golgi neurons

Across all levels of the spinal cord, there are four types of neurons in spinal cord: Afferent neurons (sensory), efferent (motor) neurons, interneurons, and those interneurons that relay long-range signals to the central nervous system (CNS) and peripheral nervous system (PNS), also known as projection neurons (23,24). Due to the morphological and functional diversity of spinal neurons in the spinal cord, it is a challenge to classify or categorize these. In general, a number of nerve cells in the CNS and PNS are Golgi type or multipolar, as discovered by Camillo Golgi: Golgi type I and Golgi type II neurons (21).

Based upon their location, Golgi type I cells, also known as projection neurons or root cells due to their axons extending to the brain, ranging from several millimeters to up to a meter in length are primarily located in laminae I, III-VIII and X of the dorsal horn, where they play key roles in integrating and relaying nociceptive, mechanosensory and autonomic signals (Fig. S2). Golgi type I cells are very few in the lamina II at lumbar levels and they are also part of the lateral spinal nucleus, where they contribute to long-range sensory pathways, such as the spinothalamic tract (STT) and spinoreticular tract (SRT) (24-27) (Fig. S2). Many dorsal horn projection neurons, including those in lamina I, have axons that cross the midline and travel rostrally in the contralateral white matter to terminate in various brainstem and thalamic nuclei via the anterolateral tract, forming a collection of ascending pathways that are thought to underlie nociception and thermoreception (23) (Fig. S3). The pain-, temperature- and itch-relevant information that originates throughout the body is conveyed to the spinal cord and from the face and head via the medullary trigeminal nucleus caudalis (24). The projection neurons or root cells that contribute their axons to the ventral roots are of two types: i) Somatic efferent root neurons, which innervate the skeletal musculature; and ii) the visceral efferent root neurons, also known as preganglionic autonomic axons, which send their axons to various autonomic ganglia (20).

Golgi type II neurons, interneurons or column cells have short axons confined to a local area, where they arborize locally, mainly within the gray matter of the spinal cord (23) (Figs. S2 and S3). They include virtually all of the neurons in lamina II, and most of those in laminae I and III of dorsal grey horn (23). Some column cells send their axons up and down the cord to terminate in gray matter close to their origin, or to nearby spinal segments and are known as inter-segmental association column cells. Other column cell axons terminate within the segment in which they originate and are known as intra-segmental association column cells (20,28).

Table I. Rexed laminae overview.

Rexed lamina	Cytoarchitecture	Stimuli/functional role
I	Thin layer at the dorsal horn tip (marginal zone/posterior marginalis nucleus); contains multipolar and fusiform cells.	**Processes painful stimuli**: heat, pinching, cold; projects to contralateral spinothalamic tract.
II	Substantia gelatinosa of Rolando; densely packed interneurons.	**Modulates nociceptive pain**; involved in gating noxious stimuli to higher laminae
III	Dense network of neurons receiving Aβ input; includes dendrites from laminae IV-VI; part of nucleus proprius.	**Processes light touch, proprioception, nociception**, and thermoception.
IV	Thickest lamina; lower cell density, larger cells; part of nucleus proprius.	Processes non-noxious stimuli, especially light mechanical touch, contributes to spinothalamic projections.
V	Broad zone with medial/lateral parts; receives Aβ, Aδ and C fibers; projects to brainstem and thalamus via the contralateral and ipsilateral spinothalamic tract. Moreover, descending corticospinal and rubrospinal fibers synapse upon its cells.	**Conveys nociceptive and visceral pain**, as well as proprioceptive input.
VI	Prominent in cervical/lumbar regions, contains interneurons and spinocerebellar pathways.	Proprioceptive processing; involved in reflex arcs.
VII	Zona intermedia/intermediolateral nucleus; relays between afferents and autonomic outputs.	Relay for visceral motor neuronal output and cerebellar pathways.
VIII	Base of ventral horn; receives descending vestibulospinal and reticulospinal input.	Modulates motor output via gamma motor neurons.
IX	Groups of large α and small γ/β motor neurons; larger in cord enlargements.	Main site of somatic motor neuron output.
X	Surrounds central canal; forms the gray commissure.	Contains interneurons and neuroglia; site of axon decussation.

Rexed laminae involved in nociception are indicated in bold font. The table was adapted and modified from the study by Byrne (20).

5. Rexed laminae

The journey through the gray matter of the spinal cord is perplexing. At every less-than-millimeter distance, there are layers, or laminae of neurons, with varying morphologies, composition, as well as neurons that respond differently to neurotransmitters. The gray matter also contains both interneurons and projection neurons as aforementioned. Rexed (29,30) was the first to categorize the spinal cord of cats on the basis of its cytoarchitecture in different zones. Rexed (29) divided the grey matter of the cat dorsal horn into a series of parallel laminae based on variations in the size, packing density and the functional role of neurons. This classification scheme has since been applied to other species (29). The gray matter of the spinal cord has been divided into ten laminae or layers with different complex functions (Fig. S3), for example, lamina I is only 800 μm in diameter and is full of uniformly packed large poorly ramified neurons (31). Laminae I to IV, in general, are related with exteroceptive sensation and comprise the dorsal horn. Lamina I is also known as the marginal nucleus of spinal cord (or posteromarginal nucleus) and lamina II as the substantia gelatinosa; these play central roles in nociception and thermoregulation, projecting to the diencephalon (23) (Table I and Fig. S3). The lamina II is further divided into outer (IIo) and inner (IIi) parts, with the inner having a somewhat lower density of neurons (23). Interneurons primarily inhabit lamina I to lamina III (32). Laminae V and VI are concerned primarily with proprioceptive sensations (Table I). Lamina VII is equivalent to the intermediate zone and acts as a relay between muscle spindles to midbrain and cerebellum, and laminae VIII-IX comprise the ventral horn and contain mainly motor neurons (20) (Table I). The axons of these neurons innervate mainly skeletal muscle. Lamina X surrounds the central canal and contains neuroglia (Table I and Fig. S3).

6. Primary Golgi afferents in the spinal dorsal horn

Primary afferents exhibit different types of axons: Large myelinated Aβ fibers, which are low threshold mechanoreceptors that respond to touch or hair movement; fine myelinated, large in numbers Aδ fibers and unmyelinated C fibers for nociception and thermoreception (23). The myelinated low-threshold mechanoreceptive Aβ afferents arborise and extend from lamina inner (IIi)-VI, whereas nociceptive

and thermoreceptive Aδ and C afferents innervate lamina I and much of lamina II or substantia gelatinosa (23,33) (Fig. S2).

7. Neurochemical reception centers in the spinal dorsal horn

The primary afferents are known for the expression of various neurotransmitters such as substance P (also known as neuropeptide P or SP-L1), (34,35), glycine, glutamate, gamma-aminobutyric acid (GABA), serotonin and endorphins. Based upon the neurotransmitter expression, interneurons can be divided into two main classes: Excitatory (glutamatergic) and inhibitory (glycinergic and GABAergic) neurons (23). These cell bodies of interneurons can be identified with specific antibodies. Substance P is a major nociceptor marker, while GABA is present in ~25-40% of neurons in laminae I-III (36,37). Other neurochemical markers include somatostatin, neurotensin, substance P and neurokinin B in glutamatergic neurons, and neuropeptide Y and galanin in GABAergic neurons; enkephalin and dynorphin occur in both (38,39).

Based upon substance P expression, nociceptive unmyelinated C fibers are of two types: Peptidergic C fibers, which express substance P and calcitonin gene-related peptide; arborise mainly in lamina I and the outer part of lamina II (IIo) (32). Non-peptidergic C fibers bind the lectin IB4 and express Mas-related G-protein coupled receptor member D (MRGPRD), a sensory neuron-specific G protein-coupled receptor in mice (32,40). In a previous study, the removal of MRGPRD afferents in adult mice resulted in a selective loss of sensitivity to noxious mechanical (but not thermal) stimuli (41). Non-peptidergic C fibers are mainly associated with the skin that innervate mainly epidermis (42), whereas peptidergic fibers innervate various other tissues as well as deeper regions of the skin (35,43).

Additional markers include parvalbumin and neuronal nitric oxide synthase in subsets of GABAergic/glycinergic neurons, while calbindin, calretinin and protein kinase C (PKC) γ are largely restricted to glutamatergic neurons (23,44-46). Together, these molecular signatures form a neurochemical map of the dorsal horn, reflecting the balance of excitation and inhibition that ultimately determines nociceptive sensitivity and pain perception.

8. Definition of pain

According to the International Association for the Study of Pain, 'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Two longstanding theories about pain include the specific theory and the pattern theory (47). The specific theory posits that particular receptors are responsible for transmitting pain signals to designated areas of the central and peripheral nervous systems, similar to how auditory and visual information is processed in the brain. By contrast, the pattern theory suggests that there are non-specific receptors for pain, and that there are no distinct nerve endings dedicated solely to pain sensation. The skin contains a diversity of sensory receptors that include touch, cold, warmth and pain, which was the basis of von Frey's (1894) theory of receptor sensitivity (48). Sherrington (49) (1906) was the first to state that all stimuli capable of injuring tissue be labeled 'noxious' and coined the terms 'nociception' and 'nociceptor', to describe unique activity by selective afferents (49). This established a common understanding of the concept of pain-evoking stimuli (49).

These nociceptive signals are relayed from the dorsal horn of the spinal cord to the higher brain centers was first explained by the 'gate theory' described by Melzack and Wall (47). This theory holds that the nociceptor signals travel by Aδ and C fibers of peripheral nerves through lateral spinothalamic tracts in the spinal cord to a pain center in the thalamus (47). Spinal cord is the gate control system that modulates afferent sensory input from the skin before it evokes nociceptive response (47). The inhibitory interneurons of substantia gelatinosa (lamina II), play a key role in modulating somatosensation, by selectively inhibiting primary afferent inputs before these are transmitted to the brain through ascending pathways. The activation of lamina-II or substantia gelatinosa by touch receptors containing the large-myelinated afferents suppresses T-cell activation and pain signals (25); however, the activation of Aδ and C afferents transmit the pain signal (Fig. S2). Recent research has demonstrated that both inhibitory and excitatory interneurons contribute to pain signals through polysynaptic networks (25). The following section provides a detailed explanation of nociceptive components.

9. Components of nociception

First-, second- and third-order neurons in nociceptive pathways. As aforementioned, the spinal cord, with its butterfly-shaped structure, serves as a highly intricate neural highway. Its gray and white matter layers are anatomically divided into dorsal, ventral and lateral horns which are attached to the dorsal and ventral roots. These structures are essential for transmitting somatosensory information, including nociception. For the majority of somatosensory perceptions, first-order neurons reside in the DRG for the body, or in the trigeminal ganglia for the head and face. How do first order neurons relay action potentials to the dorsal horn, comes from their physical shape. These unique neurons in DRG receive inputs from peripheral sensory receptors and transmit action potentials through their pseudo-unipolar T-shaped axons, which bifurcate into a peripheral process that innervates tissues, and a central process that enters the spinal cord through the dorsal root (21,50,51) (Fig. S3).

The first-order neuron axon stays on the same side (ipsilateral) and its axon synapses with the cell body of the second-order neuron that lies inside the spinal gray matter (dorsal or ventral horns), or brainstem, depending on the specific sensory modality. The second-order axon transmits nerve impulse (after crossing over or decussation) to the third order neuron in the thalamus that terminates in the somatosensory cortex located in the postcentral gyrus of the parietal lobe of the cerebral hemispheres (Fig. S3). The primary spinal afferents that carry coarse touch/pressure, pain and temperature information from limbs and trunk, terminate near their level of entry into the spinal cord. They synapse with second-order neurons, the axons of which decussate within a

few segments and thereafter form the key ascending spinothalamic tract (16).

Dorsal horn as a nociceptive hub. The dorsal horn is the major highway for receiving primary afferents from various somites of the body containing skin and deeper tissues of the body. The dorsal root ganglia are the primary reception and transmission centers of these pain highways. Dorsal horns hold diverse types of afferents for accurate, fast and highly efficient neurotransmission. These are classified based upon structure, for example, Golgi type-I projection neurons and Golgi type-II interneurons as discussed in the previous section. Additionally, these are also classified based upon their response to specific sensory impulses: i) Low-threshold mechanoreceptors activated by innocuous stimuli; ii) threshold neurons that react to noxious stimuli; and iii) wide dynamic range (WDR) neurons, also known as the convergent or multi-receptive neurons that receive monosynaptic or polysynaptic synapses for both noxious and innocuous stimuli (52). The WDR neurons distributed through multiple laminae, exhibit graded responses to both innocuous and noxious stimuli, including mechanical, thermal and pruritic inputs (24,53-56). Their response properties under the influence of opioids such as morphine, particularly in trigeminothalamic tract neurons, exhibit an altered sensitivity to pruritogens and algogens (57). Numerous opioid effects are also mediated through superficial dorsal horn interneuron circuitry (24). In rexed laminae 1-VIII, X, except laminae II, the lateral spinal nucleus, deep and superficial layers of lamina contain the projection nuclei for nociception (1,2). Lamina I neuron projections are part of spinothalamic tracts that send signals to periaqueductal gray matter (PAG), which is located around the cerebral aqueduct within the tegmentum of the midbrain of the brain stem (58,59) (Figs. S2 and S3). A series of studies of rat projection neurons in the L4 segment in rats demonstrated that there were 400 projection neurons in lamina I, which can be retrogradely labelled into the lateral parabrachial nucleus (LPb) or the caudal ventrolateral medulla (CVLM) of the brain stem, with smaller numbers projecting to the other sites (23,60-63) (Fig. S3). Lamina IV-VI also gives rise to spinothalamic tracts which project to the sensory ventral posteromedial and posterolateral (VPM and VPL) thalamic nuclei, as well as to the PAG (58) (Fig. S3). Lamina VII (intermediate zone) gives rise to the spinoreticular tract, next to the STT (58,64). Collectively, interneurons and projection neurons of the dorsal horn contribute to several major ascending pain pathways. These project to the nucleus of the solitary tract, dorsal column nuclei, medial brainstem reticular formation, CVLM, LPb, PAG, thalamus, hypothalamus, and ultimately, to the primary somatosensory cortex of postcentral gyrus (23,24) (Fig. S3).

Ascending and descending nociceptive pathways. The white matter of the spinal cord contains both ascending and descending nerve tracts that coordinate nociceptive reception, conduction and modulation. Ascending tracts are distributed throughout the dorsal, lateral and ventral columns. These include the dorsal column-medial lemniscus pathway, comprising the gracile fasciculus and the cuneate fasciculus, which transmits fine touch, vibration and proprioception; the STTs of lateral columns, which convey pain, temperature, crude touch and pressure sensations; and the intermediary spinocerebellar tracts, which relay unconscious proprioceptive information from muscles and joints to the cerebellum (16) (Fig. S3). The STTs are part of the anterolateral system. Before synapsing in the substantia gelatinosa (lamina II), their fibers travel briefly in Lissauer's tract. After synapsing, the second-order neurons decussate and ascend as part of the spinothalamic tract (65). The Lissauer's tracts synapse with second-order neurons of different Rexed laminae. The lamina IV, V and VI receive direct innervation from first-order afferents, as well as from interneurons in lamina II. The axons of these second-order neurons in laminae IV-VI (which are collectively known as the nucleus proprius) cross the midline and ascend all the way to the brainstem and thalamus in the anterolateral quadrant or the contralateral half of the spinal cord. These fibers, together with axons from second-order lamina I neurons, form the spinothalamic tract, this overall pathway is also referred to as the anterolateral system (66). Indirect nociceptive pathways include the spinoreticular tract, which projects from the anterolateral funiculus to the medial brainstem reticular formation or crosses to the medial thalamus. These pathways are collectively referred to as the SRT system, which sends ipsilateral or bilateral projections to supraspinal targets (24). The STT is the direct nociceptive pathway, while the spinoreticular tract is the indirect pathway (64). Hence, key nociception nerve tracts include spinocervical tract (mainly in cats) (67), dorsal column pain pathway (68,69), STT and SRT, part of the anterolateral system (24,70,71).

Descending tracts are found only in the lateral and the anterior (ventral) columns (16). The principal descending tracts are the lateral corticospinal tract and the rubrospinal tracts located in the lateral column, reticulospinal vestibulospinal and the anterior corticospinal tract (Fig. S3) (20). Descending pathways consist of neurons projecting from the sensory cortex to the hypothalamus and amygdala. The neurons synapse in the PAG in the midbrain. The PAG projects, via the rostral ventral medulla, down the spinal cord. The descending tracts can modulate the transmission of nociceptive information at the level of the dorsal horn (72).

Electrophysiology and functional specialization of nociceptive neurons. Pain-relevant electrophysiological studies in mice, cats and monkeys have provided valuable insight into nociceptive neurons. For example, lamina I projection neurons respond to diverse stimuli: Some neurons react to heat, pinch and noxious cold in monkeys (73), while others in the STT population respond only to pinch and/or heat in cats (74), exhibiting distinct intrinsic properties. Certain STT neurons in cats (74) and monkeys (75) are exclusively activated by innocuous cold, whereas a subpopulation of spinoparabrachial neurons in mice responds solely to noxious cold. Chronic pain models further reveal altered thresholds for innocuous stimuli. For instance, mechanical thresholds decrease in the von Frey filament test on naïve mice; in cases of thermal allodynia, animals with chronic pain react to cold stimuli below the usual nociceptive threshold. These behavioral outcomes mirror human pain sensitization and likely involve synaptic changes in dorsal horn circuits, as well as long-term physiological and epigenetic modulation of interneurons, projection neurons and supraspinal centers. While epigenetic mechanisms, such

as histone acetylation or DNA methylation, are increasingly implicated in nociception, their precise roles remain underexplored. A more in-depth understanding may pave the way for targeted interventions.

10. Roads that lead to the pain highways

Ion channels control the major flow of ions across the plasma membrane of neurons that generate and propagate action potentials. Three sodium ions are moved out of the cell for every two potassium ions moved in; this maintains the resting membrane potential of neurons. Due to this distribution of ions, there is a more negative charge inside the cell, which maintains the closure of voltage-gated ion channels in the plasma membrane during negative resting potential. Depolarization occurs when the charge inside the cell becomes less negative when it receives a sensory stimulus or is triggered by a neurotransmitter that generates an action potential (20). With the opening of the sodium-potassium pump, the voltage-gated sodium (Na^+) and calcium channels that had been closed while the cell was at resting potential are opened in response to an initial change in voltage (76). Neurons function as transducers that convert synaptic inputs into output signals in the form of action potentials, which then propagate information to other neurons. This transduction process, known as synaptic integration, is often highly complex and depends on, among other things, the types and distribution of ion channels that populate the neuronal membrane (77). Cells are full of ion channels, and all of these play a role in nociception, particularly in DHNs, DRGs, and ascending and descending tracts. Hence, experimental data have demonstrated role of many of these channels in nociception, e.g., voltage-gated sodium channels (VGSCs), potassium channels (K^+) and voltage-dependent calcium channels (VDCC), all types L, N, P/Q,R T, TRP channels, acid-sensing ion channels (ASICs) and purinergic P2X families (78). The epigenetics of sodium, potassium, calcium and TRP channels will be discussed in the following section.

11. Epigenetics of ion channels, an unexplored frontier in nociceptive neurons

Epigenetics is defined as 'the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in the DNA sequence' by Fincham (79). Chromatin remodeling, DNA methylation, histone modifications and non-coding RNAs (ncRNAs) play key roles in gene expression without changing DNA sequence (80). Histones go through a variety of post-translational modifications, such as lysine acetylation and lysine deacetylation, lysine methylation and arginine methylation, phosphorylation, propionylation and butyrylation, biotinylation, proline cis-trans isomerization, ubiquitylation, glycosylation, citrullination, SUMOylation, ADP ribosylation, deamination and crotonylation. Histone-modifying enzymes are classified into three categories: i) Writers: Histone acetyltransferases and histone methyltransferases; ii) erasers: HDACs and histone lysine demethylases (KDMs and Jumonji families); and iii readers: Proteins that recognize these histone modifications (bromodomain, chromodomain and Tudor domain) (81). The methylation of histone H3 lysine residues occurs at positions K4, K9, K27, K36 and K79, while histone H4 is methylated at K20. Specific patterns of histone methylation are associated with distinct gene regulatory outcomes. For instance, H3K4, H3K36 and H3K79 methylation are typically linked to transcriptionally active genes, whereas H3K9, H3K27 and H4K20 methylation are associated with transcriptional repression (82).

Beyond histone modifications, DNA methylation also plays a crucial role in gene regulation. While the majority of the genome is methylated, CpG islands, which are typically 1kb in length and often include promoter or RNA polymerase II binding sites, are usually unmethylated in the majority of somatic cells. Unmethylated CpG islands, found in euchromatin, are associated with actively transcribed genes, whereas methylated CpG islands in heterochromatin are linked to transcriptionally repressed genes (80).

Another key epigenetic mechanism is RNA interference (RNAi), a process in which noncoding RNAs regulate gene expression at multiple levels, including mRNA degradation, translation inhibition, RNA splicing, chromatin remodeling and chromosome segregation (83). From zygote implantation to adult tissue homeostasis, ncRNAs influence and regulate key processes, such as cell proliferation, differentiation and stress responses, fat metabolism in fruit flies, neuronal patterning in nematodes, the functions of hematopoietic cells, and differentiation in mammals, root, stem and leaf formation in plants (84,85). ncRNAs are increasingly recognized as critical players in numberous medical conditions, including nociception.

The discovery of ncRNAs dates back to the 1950s, when ribosomal RNA (rRNA) and transfer RNA (tRNA) were described by Palade (86) and Hoagland *et al* (87). The first miRNA, *micF* (93 nt), was discovered in *Escherichia coli* in 1984 (88). Another notable ncRNA, 6S RNA (184 nt), was detected in 1967 (89); however, it was not appreciated until its function to inhibit transcription by binding the sigma 70 subunit of RNA polymerase was elucidated (90). In humans, the lncRNA *H19* was reported in 1990 as one of the earliest imprinted transcripts (91). In the context of nociception, ncRNAs modulate pain processing at multiple levels of the nervous system, including peripheral sensory neurons, interneurons within the dorsal horn, ascending spinothalamic pathways and central somatosensory circuits (92,93).

ncRNAs represent a structurally and functionally diverse class. Long ncRNAs (lncRNAs), typically, >200 nucleotides in length, regulate gene expression through transcriptional, post-transcriptional and epigenetic mechanisms. lncRNAs are categorized into five types: i) Sense; ii) antisense; iii) bidirectional; iv) intronic; and v) intergenic (94). Circular RNAs (circRNAs), a more recently characterized group, form covalently closed loops lacking 5' caps and 3' poly(A) tails. Generated by non-canonical back-splicing or exon skipping of precursor mRNAs, circRNAs are enriched in the cytoplasm and often function as miRNA sponges or protein scaffolds (94). Both lncRNAs and circRNAs are known for competing with the target genes of miRNA binding sites, thereby acting as competing endogenous RNA (ceRNAs) (94).

Beyond structural diversity, ncRNAs are also regulated by chemical modifications. To date, >160 types of RNA modifications have been identified (95). Among these, N^6-methyladenosine (m^6A) is the most prevalent and

extensively studied. m^6A influences almost all aspects of RNA metabolism, including splicing, processing, transport, translation and stability. This modification is enriched near the termination codon and in the 3' untranslated regions (3'UTRs) of mRNAs (96-98). In mammals, m^6A occurs at a frequency of ~0.1-0.4% of adenosines, corresponding to ~3-5 m6A sites per mRNA (99-101). The deposition and removal of m^6A are mediated by a dynamic set of enzymes. The core methyltransferase complex (METTL, 'writers') includes METTL3, METTL14 and Wilms' tumor1-associating protein, while demethylases ('erasers') include fat-mass and obesity-associated protein (FTO) and AlkB Homolog 5, RNA demethylase (ALKBH5) and YTH domain family proteins (m^6A-binding protein YTH domain family) and insulin like growth factor 2 mRNA binding proteins as readers (94). Together with m^6A-binding proteins ('readers'), these regulators play essential roles in neuronal development, memory consolidation, CNS homeostasis and pain processing (102). For example, peripheral nerve injury upregulates *FTO* expression in DRGs, reducing m6A modification on euchromatic histone-lysine N-methyltransferase 2 (*Ehmt2*) mRNA, which codes for G9a histone methyltransferase (103). The downregulation of FTO rescues the loss of m^6A and alleviates nerve injury-induced hypersensitivity, indicating that *FTO* contributes to neuropathic pain in an m_6A-dependent manner (103).

Similarly, in a model of inflammatory pain induced by complete Freund's adjuvant (CFA), the downregulation of *METTL3* and the m^6A reader, *YTHDF2*, stabilized the upregulation of ten-eleven translocation methylcytosine dioxygenase 1 (*TET1*) mRNA in spinal cord neurons, thereby contributing to chronic inflammatory pain (102). METTL3 together with YTHDF2 coordinately regulated spinal neuron activation by mediation of the TET1/signal transducer and activator of transcription 3 (STAT3) axis (102). The overexpression of *METTL3* reversed the increase in the levels of spinal STAT3 and C-FOS (a neuron activation marker) on day 3 following the injection of Lenti-METTL3 in mice with CFA-induced inflammatory pain. The loss of spinal METTL3 was associated with a loss of global m^6A levels in spinal RNAs, highlighting the crosstalk between RNA methylation and other epigenetic mechanisms under conditions of chronic pain (102). TET1 is known for its role in converting 5-methylcytosine in DNA to 5-hydroxymethylcytosine, and it has been found to be upregulated in both inflammatory and neuropathic pain states (104). Elevated levels of TET1 promote the expression of genes, such as STAT3, brain-derived neurotrophic factor (BDNF) and metabotropic glutamate receptor subtype 5 (mGluR5). STAT3, BDNF and mGluR5 drive neuronal sensitization (104-106). The genetic knockdown of spinal TET1 prevents this upregulation and alleviates nociceptive hypersensitivity, underscoring the interplay between RNA modifications and DNA hydroxymethylation in pain pathophysiology.

Based on findings from whole-genome and transcriptome sequencing projects, as well as RNAi-based experiments, three main classes of small regulatory RNAs have been identified: miRNAs, small interfering RNAs (siRNAs) and Piwi-interacting RNAs (piRNAs). The present review focuses exclusively on miRNAs in nociceptive processing, while also highlighting recent advances in the fields of lncRNAs, circRNAs and m^6A modifications. The following section addresses epigenetic mechanisms, including DNA methylation, histone modifications and miRNA regulation and m^6A modifications in the modulation of nociceptive ion channels.

12. Epigenetic mechanisms of voltage-gated sodium channels

Structure and function of VGSCs. This journey begins with the epigenetics of VGSCs. Sodium and potassium channels are the primary channels responsible for maintaining the resting potential of neuronal membranes. Upon stimulation, these channels undergo conformational changes, cycling through resting, activated and inactivated states, that lead to membrane depolarization and action potential generation (107). Sodium channels are of two types, VGSCs that are present in all types of body cells, and the epithelial sodium channels only present in skin and kidney cells (107). However, there are variations, namely alpha-amino-3-hydroxy-5-methyl -4-isoxazolepropionic acid and nicotinic sodium channels that are both ligand-gated (107). In most cases, sodium channels are one of the first opened channels in response to depolarization, which results in the influx of sodium ions, increasing the positive charge inside the cells, which results in an action potential and the release of neurotransmitters. The VGSCs are known to have two gates, an activating gate that is dependent upon voltage and an inactivating gate that is time-dependent. These gates work in tandem to ensure a brief Na^+ influx. The activating gate opens, bringing Na^+, and the inactivating gate closes, stopping the flow of Na^+ ions. After briefly opening, VGSCs inactivate, halting sodium flow despite ongoing stimulation. The channel will remain unable to open again until the cell repolarizes to a threshold voltage that varies depending on the cell type. This prevents a constant, unstoppable flow of Na^+ and depolarization inside the cell. This flow is under a higher signal and physiological balance caused by the interaction of other membrane proteins, cytoskeletal proteins, changes in concentration of ions, extracellular proteins, and neurotransmitters. This mode of VGSCs is critical in maintaining the same threshold of stimulus; however, this can change in case of mechanical, chemical and thermal stimuli.

Sodium-channel proteins in the mammalian brain are composed of a complex of a 260 kDa α-subunit in association with one or more auxiliary β-subunits (β1, β2 and/or β3) of 33-36 kDa (108). Of note, nine types of α-subunits ($Na_v1.1$-$Na_v1.9$) have been functionally characterized, and a tenth related isoform (Na_x) may also function as a Na^+ channel. These types differ in their activation threshold, rate of inactivation and sensitivity to tetrodotoxin (TTX), a neurotoxin (107,109). $Na_v1.1$, $Na_v1.6$, and $Na_v1.7$ are fast-inactivating, TTX-sensitive (TTX-S) channels, whereas $Na_v1.8$ and $Na_v1.9$ are slow-inactivating, TTX-resistant (TTX-R) channels primarily expressed in adult peripheral sensory neurons (110). The TTX-S channel $Na_v1.3$ is predominantly expressed in embryonic sensory neurons, but is upregulated following traumatic or metabolic nerve injury in rodent DRG neurons (111).

Role of VGSCs types in nociceptive neurons. Nociceptive pain is caused by tissue or nerve injury-whether mechanical, thermal or chemical, whereas neuropathic pain results from lesions or disease affecting the PNS or CNS (112). The family

of sodium channels has five isoforms: $Na_v1.3$, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ (Fig. S4). All sodium channels have been found in both nociceptive and neuropathic pain. For example, TTX-R channel $Na_v1.8$ mRNA has been shown to be upregulated in an established model of inflammatory pain, which was induced by carrageenan injection into the hind paw (109). In addition, TTX-S channels $Na_v1.3$ and $Na_v1.7$ exhibit an increased expression with a parallel increase in TTX-S currents (109). *SCN9A* gene ($Na_v1.7$) mutations were detected in the II/S5 segment (L858H) and the loop region between II/S4 and II/S5 (I848T), which caused hyperpolarizing shift in the activation kinetics of the mutated $Na_v1.7$ channels (113) present on afferent and efferent small nerve fibers (70), and caused primary erythromelalgia (114). This rare, autosomal-dominant peripheral neuropathic condition of erythromelalgia resulted in episodic burning pain, edema and erythema (115), which may be treated with intravenous lidocaine (116) and future epigenetics-based therapies. $Na_v1.8$ and $Na_v1.9$ are confined to nociceptive primary afferent neurons (117-119). $Na_v1.8$ channels are preferentially found on small-diameter neurons and, to a lesser extent, in medium- and large-diameter cells; they are localized to the soma and the terminal arbors of sensory neurons (120). $Na_v1.9$ is generally confined to small-diameter neurons (120,121). The current generated by $Na_v1.8$, also known as the sensory-neuron-specific current, has a high threshold for activation (~-36 mV) and steady-state inactivation. Unlike TTX-S channels, $Na_v1.8$ activates and inactivates slowly, but recovers rapidly from its inactivated state. This channel has a specialized function in nociceptive sensory neurotransmission. $Na_v1.8$ null mutants exhibit analgesic behavior following noxious mechanical stimulation (2). The majority of sodium channels or highways are critically involved in the transduction and transmission of nociceptive signals. However, the epigenetics-led signals that contribute to the launching and shutting of these channels have not yet been fully elucidated.

Epigenetic regulation of VGSCs in pain pathways. The epigenetic regulation of sodium channels in nociceptors remains largely unexplored, yet several key studies have provided compelling insights. One of the most fascinating epigenetic modifications is the restrictive silencer factor or repressor element-1 (RE1)-silencing transcription factor (REST) complex, also known as neuron-restrictive silencer factor (NRSF), which plays a pivotal role in transcriptional repression during neuropathic pain (122). REST recruits HDAC through its corepressors, mSin3 and REST co-repressor protein (CoREST), for repressing chromatin regions containing neuron-restrictive silencer element (NRSE1/RE1) in target gene promoters (123); for example, the *Scn10a gene for* $Na_v1.8$ sodium channel and the *Oprm1* gene for μ-opioid or MOP receptor in DRGs (Fig. S4) (124). As previously demonstrated, this repression is particularly evident in models of neuropathic pain caused by peripheral nerve injury, resulting in the downregulation of *$Na_v1.8$* and *MOP* expression, C-fiber hypoesthesia and the loss of peripheral morphine analgesia. These neuropathic pain effects are reversed by the knockdown of NRSF in male C57BL/6J mice, restoring both *$Na_v1.8$* and *MOP* expression and rescuing the analgesic response to morphine (124).

Histone modifications also play a critical role in sodium channel expression. For example, the increased acetylation of histone H4 at the *Scn8a* gene promoter (which encodes $Na_v1.6$) enhances transcription by promoting the recruitment of phosphorylated STAT3 and its co-activator p300 (Fig. S4). This interaction is enhanced by the exposure of DRG neurons to the pro-inflammatory cytokine, TNF-α, thereby linking inflammatory signaling to sodium channel upregulation (125) (Fig. S4).

Beyond chromatin-level regulation, miRNAs significantly contribute to the post-transcriptional control of sodium channel expression during neuropathic pain. Both miR-96 and miR-384-5p decrease the expression of *Scn3A* ($Na_v1.3$) (126,127) and alleviate neuropathic pain (Table II) (126). miR-96 also decreases the *in vitro* expression of *$Na_v1.3$* mRNA in embryonic DRGs (126). miR-182 has been shown to reduce *Scn9A* ($Na_v1.7$) expression (128), while overexpression of miR-30b downregulated *Scn3a*, *Scn8a*, and *Scn9a* in DRG neurons of the spinal cord, significantly alleviating pain induced by spinal nerve ligation (SNL) or oxaliplatin (antineoplastic drug) treatment (Table II) (129-131). Similarly, it has been shown that the overexpression of miR-183 inhibits *Scn3a*, *Scn9a* and *Scn10a* via the TGFα-mediated CCL2/CCR2 signaling axis (Table II) (132). Additionally, miR-7a targets the β2-subunit of voltage-gated sodium channels, and its overexpression in injured DRG neurons normalizes the sustained hyperexcitability of nociceptors (133) (Fig. S4).

Together, these findings underscore the underappreciated complexity of epigenetic regulation in sodium channel biology and highlight its potential as a therapeutic target in the treatment of neuropathic and nociceptive pain.

13. Epigenetics of K channels

Functional overview of potassium channels and their role in nociceptive neurons. Potassium channels are known for osmotic regulation, hormonal secretion and electrical impulses in excitable cells of muscles and neurons (134). Potassium channels are also known for a conserved K channel amino acid signature sequence (135) that forms a structural element known as the selectivity filter. This selectivity filter prevents the passage of Na ions, but allows K ions to conduct across the membrane at rates approaching the diffusion limit. This is the hallmark of K^+ channels: Almost perfect selectivity for K^+ ions over Na^+ ions in the setting of very high K^+ conduction rates (136). Based upon their structure, functional characteristics and pharmacologic sensitivity, K channels are divided into four major families: Voltage-gated (K_V), calcium-activated (K_{Ca}), tandem pore or two-pore domain (K_{2P}) and the inward rectifier channels (K_{ir}) (137) (Fig. S5). Specific subtypes of K channels respond to particular antinociceptive drugs, e.g., the ATP-sensitive (K_{ATP}) members of the K_{ir} family, G-protein-regulated inwardly rectifying K+ channels (K_{ir3}), otherwise known as GIRK channels, $K_V1.1$ and the small-(SK) and large-(BK) conductance calcium activated channels (138). The presence of $K_V1.1$ channels on small -iameter trigeminal neurons projecting to the superficial layers of the cervical DHN (139), on larger diameter spinal DHNs, and also on Aδ and C visceral sensory neurons, indicates that they play a role in nociception and pain processing, warranting further investigation.

Table II. MicroRNAs regulating ion channels involved in nociception.

Type of ion channel	MicroRNAs	Known signaling molecules/pathways	(Refs.)
Sodium channels	1. miR-183	- IL-6, IL-1β, TNF-α and (-) TRPV1,	(126-133)
Nav1.3, Nav1.6		Nav1.3, Nav1.7 and Nav1.8	
Nav1.7, Nav1.8	2. miR-30b	- Nav1.3, Nav1.6, Nav1.7	
Nav1.9	3. miR-182	- Nav1.7	
	4. miR-96,	- Nav1.3	
	5. miR-384-5p (-)	- Nav1.3	
Potassium channels	1. miR-183-5p,	Unknown	(142-145)
K_v, K_{Ca}	2. miR-137	Unknown	
K_{ir}, K_{2P}	3. miR-17-92 cluster[a]	Unknown	
Calcium channels	1. miR-103	Unknown	179-182,184)
L, N, P/Q, R, T	2. miR-32-5p	Unknown	
	3. miR-124	- MeCP2	
	4. miR-219	- *CaMKIIγ* and MeCP2	
TRP channels	1. miR-146a-5p	- NFKB	(182,240-247)
TRPV1, TRPV2,	2. miR-381	- HMGB1	
TRPV3, TRPV4,	3. miR-362-3p	- BAMB1	(132)
TRPA1, TRPM8	4. miR155 or miR221	+ SOCS1 via NF-KB and p38 MAPK	(249-252)
	5. miR-183	- IL-6, IL-1β, TNF-α	
	6. miR-28-5p, miR-128-3p, miR-136, miR-150, miR-200b, and miR-429	- ZEB1, no channels known?	(254,255)
	7. miR-140, miR-144	- S1PR1, RASA1	(253)
	8. miR-23a	- CXCR4 and TXNIP/NLRP3	(256)
	9. miR-216a-5p	- Wnt/β-catenin via KDM3	(247,260,261)
	10. miR let-7b	+ TLR7-TRPA1	(258)
	11. miR-141-5p	+ TRPA1 (OXL)	(145,247,259,262-266)
	12. miR-143, miR-21, miR-103, miR-7a, miR-133a, miR-134, miR-20a/b and Kcna2	Unknown	

The symbols '-' and '+' indicate the downregulation and upregulation of these ion channels or signaling molecules, highlighting their significance in pain modulation. The symbol '?' indicates no known signaling pathway thus far in nociceptive or neuropathic pain. [a]The miR-17-92 cluster includes miR-17, miR-18a, miR-19a/b, miR-20a and miR-92a. miR, microRNA; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; MEF2A, myocyte enhancer factor 2A; TRP channel, transient receptor potential channel.

Epigenetic mechanisms regulating potassium channels. As demonstrated in a previous study, in mice lacking the gene for the Shaker-like voltage-gated potassium channel $K_V1.1$ alpha subunit, homozygous null (-/-) animals exhibited significant hyperalgesia compared to their heterozygous (±) and wild-type (+/+) littermates. Pain sensitivity was measured using paw flick and hot plate assays, both of which confirmed enhanced hyperalgesia and a preserved response to morphine-induced antinociception (140). Neuropathic pain induced by oxaliplatin (OXL) involves the downregulation of several K^+ channel subtypes, including members of the K_{2P} family (TREK and TRAAK). A single OXL administration in mice has been shown to cause the transcriptional repression of K_v and K_{2P} channel genes through the action of NRSF and its co-repressors, HDACs (Fig. S5). The knockdown of NRSF in the DRG significantly mitigatesd OXL-induced downregulation of these channels and prevents mechanical and cold hypersensitivity in mice (141). The N-terminal domain of NRSF binds HDACs and represses target genes, while the C-terminal domain binds to CoRESTs, and further attracts HDAC1, HDAC2 and methyl-CpG binding protein 2 (MeCP2) to promote and maintain methylated CPG-dependent gene silencing (123). Additionally, miR-183-5p has been shown to reduce neuropathic pain in a model of chronic constriction injury (CCI) by suppressing expression of TREK-1, a K_{2p} channel (Table II) (142). In another study using a model of CCI, $K_v1.2$ expression was downregulated in both the DRG and spinal dorsal horn, which was associated with the increased expression of miR-137 (143). The intrathecal injection of Kcna2 siRNA targeting $K_v1.2$ in naïve rats led to significant mechanical and thermal hypersensitivity. Conversely, blocking miR-137 in CCI rats alleviated mechanical allodynia and thermal hyperalgesia, restored

K_v1.2 expression, normalized DRG neuronal excitability and recovered K_v currents (143) (Fig. S5). Similarly, the miR-17-92 cluster, which includes six miRNA members, was found to downregulate K^+ channels and reduce outward potassium currents, particularly type A currents, thereby contributing to mechanical allodynia in neuropathic pain models (144) (Table II) (Fig. S5). Moreover, a conserved lncRNA, named Kcna2 antisense RNA is commonly expressed in mammalian spinal cord DRG neurons. During peripheral injury Kcna2 antisense RNA promoter expression is increased via myeloid zinc finger protein 1 transcription factor and leading to the suppression of Kcna2 (Kv1.2) expression, enhanced neuronal excitability and the persistence of neuropathic pain (145).

In summary, potassium channels are essential regulators of neuronal excitability and play a pivotal role in modulating nociceptive signaling. Their dysfunction is increasingly attributed to epigenetic mechanisms, including transcriptional repression by NRSF/HDAC complexes and post-transcriptional regulation via specific miRNAs such as miR-137, miR-183-5p, the miR-17-92 cluster and lncRNA Kcna2 (Table II). These regulatory processes alter the expression and function of key K^+ channel subtypes, such as K_v1.1, K_v1.2, TREK and TRAAK, leading to hyperexcitability and enhanced pain sensitivity. Understanding these epigenetic modifications provides valuable insights into pain pathophysiology and may provide novel therapeutic strategies targeting the epigenetic landscape to restore normal K^+ channel function and alleviate nociceptive and neuropathic pain.

14. Epigenetics of Ca channels (VDCCs)

Introduction to VDCCs and calcium signaling. Calcium ions (Ca^{2+}) act as universal second messengers involved in a wide array of physiological and pathological processes. Numerous intracellular events, such as synaptic vesicle release, muscle contraction and electrical signaling, rely on the maintenance of a precise calcium gradient, largely regulated by VDCCs (146,147). The calcium concentration gradient, and its epigenetic regulation via VDCCs, represents a potential target for nociception-based and neuropathic pain treatments.

VDCC subtypes and their localization. The VDCCs comprise four or five distinct α1, α2δ, β and γ subunits, which are encoded by multiple genes. The largest of all, the α1-subunit, contains the selective calcium ion pore, a voltage sensor, and the binding site for selective high-threshold VDCC blockers (148). A total ten isoforms of the α1 subunit have been identified, which form the basis for the most recent classification (149). The ten isoforms are grouped into three major families according to their sequence homology. VDCCs have also been grouped into six classes: L (Ca_v1.1, Ca_v1.2, Ca_v1.3, Ca_v1.4), N (Ca_v2.1), P/Q (Ca_v2.2), R (Ca_v2.3) and T (Ca_v3.1, Ca_v3.2, Ca_v3.3) according to their electrophysiologic properties and pharmacologic susceptibility to specific blocking agents (146,148). These VDCC subtypes are differentially distributed in neurons. The P/Q-type VDCCs are located predominantly at presynaptic sites (150), N-type are found both pre- and post-synaptically (151), while L- and T-type channels are mainly located on the proximal dendrites and soma of neurons, which are both post and pre/post synaptic sites (152,153). In the dorsal horn of the rat, as with other neuronal systems, such as cortical and hippocampal pyramidal cells, high-threshold calcium currents can generate both regenerative and plateau potentials, contributing to prolonged neuronal activation (154-156), which can cause both nociceptive and neuropathic pain.

VDCCs in nociceptive processing and pain sensitization. As mentioned above in the context of VGSCs, due to shift of resting membrane potential, the sustained plateau potentials can result in nonlinear responses that enhance nociceptive stimulation by L-type VDCCs (157,158). L-type channels have also been implicated in inflammatory pain signaling, at least in models that use chemical irritation of peripheral nerves and joints as a nociceptive stimulus (148). Blockers of N-type channels have demonstrated analgesic properties against acute mechanical and thermal nociceptive stimulation in several animal studies, P/Q-type channel blockers have been reported to have inhibitory, facilitatory, or even no effects on the responses of spinal neurons to nociceptive stimulation, similarly R-type, T-type channels also contribute to nociceptive signaling, although their roles are less well defined (148).

Mechanisms underlying persistent nociceptive signaling. Nociceptive DHNs are capable of encoding persistent noxious stimuli by generating prolonged after-discharges, which often take the form of regenerative plateau potentials or sustained depolarizations. These non-linear membrane responses enhance the transmission of nociceptive signals to supraspinal centers (158). Of note, two primary mechanisms contribute to this phenomenon: First, the slow inactivation of potassium channels, particularly in neurons exhibiting hyperpolarized resting membrane potentials, reduces outward potassium currents and delays repolarization. Second, regenerative plateau potentials can be initiated near the resting membrane potential, further increasing excitability (157,158).

In DHNs, as well as in cortical and hippocampal pyramidal neurons of rats, these plateau potentials are primarily mediated by high-threshold voltage-gated calcium currents, such as those carried by L-type calcium channels. The sustained influx of calcium prolongs depolarization and can shift the resting membrane potential toward the threshold for action potential generation. This voltage shift facilitates repetitive firing and contributes to the nonlinear and amplified response properties observed in nociceptive processing. Such mechanisms are considered to play a pivotal role in central sensitization and the persistence of chronic pain (148,158). All these mechanisms of calcium gradient are regulated by epigenetics, such as DNA methylation, histone modification and ncRNAs (15,159).

Epigenetic regulation of VDCCs. The epigenetic regulation of VDCCs remains a largely unexplored area in nociceptive neurons, particularly in the DRG. Calcium acts as a central second messenger orchestrating diverse cellular processes, including gene transcription, metabolism and apoptosis, and mediates its effects in part through calcium-dependent enzymes such as histone deacetylases (e.g., HDAC4), Ca^{2+}/calmodulin-dependent protein kinases (e.g., *CaMKII*) and calcineurin (160). These enzymes respond to intracellular calcium fluctuations to alter chromatin structure, DNA methylation patterns and transcription factor activity, thereby

modulating gene expression, which are vital for neuronal plasticity and may underlie chronic pain mechanisms, which are underexplored (161,162). For instance, calcium-activated CaMKII can phosphorylate transcription factors such as CREB, thereby influencing chromatin accessibility and transcriptional expression (163). Conversely, epigenetic modifications, including histone marks and DNA methylation, can regulate the expression of key genes involved in calcium homeostasis and signal transduction, such as VDCCs, pumps and buffering proteins, establishing a reciprocal regulatory loop (163). This bidirectional interplay is increasingly recognized as a crucial mechanism in both physiological processes and disease states, including nociception, cardiac hypertrophy, neurodegenerative disorders and cancer.

Notable examples from stem cell differentiation and cancer studies illustrate the functional relevance of calcium-sensitive epigenetic modifications by signaling pathways. The phosphorylation of histone H3 at Ser10 by JNK, initially activated via MAPK signaling, has been implicated in gene activation during stem cell differentiation (Fig. S6) (164). Similarly, during androgen receptor [nuclear receptor and DNA binding transcription factor (165) activated signaling, the phosphorylation of histone H3 at Thr6 by PKCβ blocks the demethylation of H3K4 by lysine-specific histone demethylase 1A (LSD1), promoting gene activation that contributed to prostate cancer progression (166). LSD1 has also been shown to demethylate lysine 9 of histone 3 (H3K9) during androgen receptor-activated gene expression, underscoring the complex regulation of transcription by histone modifiers (167). Notably, PKCβI specifically localizes to androgen response elements (AREs) in the promoters or enhancers of genes, such as kallikrein 2 (*KLK2)*, FK506-binding protein 5 (*FKBP5)* and transmembrane serine protease 2 (*TMPRSS2)*, highlighting the interconnection between calcium-linked signaling and epigenetic modifications (166).

DNA methylation enzymes are also subject to regulation by phosphorylation. For example, the phosphorylation of DNA methyltransferase 1 (DNMT1) at Ser154 and Ser143 by cyclin-dependent kinases and AKT1 (RAC, Rho family-alpha serine/threonine-protein kinase) enhances its stability and enzymatic activity (168,169), whereas the phosphorylation at Ser146 by casein kinase 1δ/ε (CK1δ/ε) reduces its DNA binding affinity (170). Similarly, the casein kinase 2-mediated phosphorylation of DNMT3a diminishes its ability to methylate repetitive elements and alters its localization to heterochromatin (171), further linking calcium-associated signaling to DNA methylation dynamics.

DNA methylation and histone modifications in pain-related calcium channel regulation. The methylation of CpG islands within the promoter regions of genes encoding calcium channel subunits (e.g., *CACNA1C* for $Ca_v1.2$ or *CACNA1B* for $Ca_v2.2$) can lead to the long-term silencing or upregulation of these genes in DRG neurons and spinal cord tissues under pathological pain conditions. For example, chronic nerve injury has been shown to be associated with hypomethylation of the *CACNA1C* promoter, resulting in an increased expression of Cav1.2 and enhanced calcium influx in sensory neurons (172) (Fig. S6).

TET enzymes are well known for their role in DNA demethylation. Their protein stability is regulated by Ca^{2+}-dependent proteases, specifically Calpain 1 and Calpain 2. These proteases influence TET protein levels, thereby modulating the DNA demethylation process (173). When intracellular Ca^{2+} concentrations are low, Calpain activity is reduced, leading to the increased stability of TET1 and TET2 proteins and elevated levels of 5-hydroxymethylcytosine (5hmC) (174), thus regulating calcium dependent DNA demethylation. Similarly, histone acetylation levels at promoter regions of calcium channel genes have been shown to modulate their expression. HDAC inhibitors have been reported to suppress the expression of N-type channels ($Ca_v2.1$) and reduce nociceptive hypersensitivity in rodent models (159). Furthermore, membrane depolarization-driven Ca^{2+} influx through L-type VGCCs promotes enhancer RNA (*eRNA*) synthesis via increased H3K4me1 levels and CREB-binding protein (CBP) recruitment (175) (Fig. S6). The amount of *eRNA* synthesis is positively associated with the level of mRNA synthesis at nearby genes in mouse cortical neurons. Calcium ions facilitate the phosphorylation of MeCP2 by CaMKII, and trigger its dissociation from the *BDNF* promoter and BDNF transcription, accompanied by reduced H3K9 methylation, increased acetylation at the same site, and lower CpG methylation frequency (176,177). Notably, mutations affecting MeCP2 phosphorylation have been linked to the regulation of dendritic morphogenesis and spine maturation and are also associated with Rett syndrome. Active enhancer DNA sequences exhibit H3K27 acetylation along with H3K4me1 methylation as compared to inactive/poised enhancer elements containing H3K4me1 alone.

In another case, the inhibition of HDACs in primary endothelial cells increased small conductance calcium-activated potassium channel (KCa2.3) transcripts, KCa2.3 subunits and subsequently, functional current was increased. The pan HDACi trichostatin-A exposure in both human umbilical vein endothelial cells and primary cultures of human intestinal microvascular endothelial cells increased KCa2.3 protein expression (178).

ncRNAs. A growing body of evidence underscores the pivotal role of ncRNAs, particularly miRNAs, in regulating calcium channel expression and neuronal excitability in pain pathways. These epigenetic regulators contribute to both the initiation and maintenance of chronic pain states by modulating key components of calcium signaling and VDCCs. For instance, miR-103 has been shown to directly target the *CACNA1C* gene that codes for L-type calcium channel $Ca_v1.2$ (179). The downregulation of miR-103 results in an increased expression of $Ca_v1.2$ and enhanced nociceptive signaling in chronic pain models (Table II) (179) (Fig. S6). Likewise, the expression of miR-32-5p is suppressed by histone methylation, leading to reduced targeting of the *CACNA1H* gene that encodes $Ca_v3.2$, T-type calcium channels in trigeminal ganglion neurons. This reduction in miR-32-5p results in *$Ca_v3.2$* upregulation, contributing to trigeminal neuropathic pain (Table II) (180) (Fig. S6). Another critical miRNA is miR-124, also known as the CNS-specific miRNA (181,182). It is constitutively expressed in the spinal dorsal horn neurons and plays a major role in maintaining normal nociceptive thresholds. In

a previous study using a formalin-induced inflammatory pain model, peripheral noxious stimulation led to the significant downregulation of miR-124 expression (181). The intravenous administration of a miR-124 inhibitor further exacerbated pain behaviors, suggesting a protective role for miR-124 in nociceptive modulation. Mechanistically, this downregulation was associated with the increased expression of pro-nociceptive targets, including MeCP2, a transcriptional regulator modulated by CaMKs and other inflammatory genes (Table II) (181).

Another well-characterized CNS miRNA is miR-219, which also targets *CaMKIIγ*. The deregulation of miR-219 is also linked with mental disorders such as schizophrenia (183). The 3' UTR of *CaMKIIγ* contains conserved miR-219 binding sites. In a previous study using a model of CFA-induced chronic inflammatory pain, miR-219 downregulation in spinal neurons, led to elevated *CaMKIIγ* and MeCP2 levels. This, in turn, promoted tge hypermethylation of the miR-219 promoter, forming a feedback loop that perpetuated nociceptive signaling (184). Notably, miR-219 knockdown alone induced pain-like behaviors and upregulated phosphorylated N-methyl-D-aspartate receptor (a subunit of the NMDA-type glutamate receptor), highlighting its broader impact on glutamatergic synaptic plasticity (Table II) (184).

Summary and future directions. The reciprocal association between calcium signaling and epigenetic mechanisms constitutes a novel and under-investigated axis in nociceptive neurons. Calcium influx modulates key pro-inflammatory pathways, such as IRAK/TRAF6, TLR4/NF-κB, CXCR4, TXNIP/NLRP3 inflammasome, MAPK, TNF-α and TLR5, partly since calcium-dependent proteins, such as the CAMK superfamily, regulate the activation of multiple transcription factors, including CREB, ATF1, NF-κB, MeCP2, myocyte enhancer factor 2 (MEF2) and serum response factor (163). By contrast, the phosphatase Calcineurin regulates the activity of transcription factors such as NFAT and MEF2 by dephosphorylation (163). DNA methyltransferases are phosphorylated in response to calcium oscillations (140,141), and the CpG island methylation of calcium channel gene promoters (e.g., *CACNA1C*) has been observed in DRG neurons during chronic pain (172). TET demethylase activity also fluctuates with calcium influx (173,174). Treatment with HDAC inhibitors can enhance Ca^{2+}-dependent *eRNA* synthesis by increasing H3K4me1 levels and CBP recruitment (173). Moreover, MeCP2 phosphorylation by CAMKII releases MeCP2 from the BDNF promoter, enhancing its transcription. The suppression of N-type calcium channel ($Ca_v2.2$) expression in the presence of HDACi reduces hypersensitivity in rodent pain models. ncRNAs, such as miR-124 and miR-219 function via MeCP2/CAMKs; miR-103 and miR-32-5p downregulate *$Ca_v1.2$* and *$Ca_v3.2$* expression respectively, thereby attenuating nociceptive signaling (179-182,184). Future studies that elucidate the precise molecular players in this bidirectional regulatory system may reveal novel therapeutic targets for chronic and treatment-resistant pain.

15. Epigenetics of TRP channels

Structure and function of TRP channels. TRP channels represent the second largest family of ion channels following the potassium channel family (185,186). While some TRP channels exhibit weak voltage sensitivity, most are not truly voltage-gated as they lack the hallmark voltage-sensing domain of classical voltage-gated ion channels (187), thereby challenging the longstanding view that TRP channel gating is entirely voltage independent. Originally discovered in *Drosophila melanogaster* as calcium transport channels by Minke and Selinger (188), TRP channels are currently recognized as polymodal, non-selective cation channels that facilitate fluxes of calcium (Ca^{2+}), magnesium (Mg^{2+}) and sodium (Na^{+}) (186). Due to these cation fluxes, TRP channels play a crucial role in intra-vesicular and extra-vesicular cycles during endocytosis and exocytosis, and they are also found on lysosomes and mitochondria (189,190). TRP channels facilitate the flow of calcium ions that contribute to muscle contraction, gene transcription, cell proliferation, neurotransmitter release, apoptosis and fertilization (191). While the majority of TRP channels are non-selective for cations, there are exceptions. For instance, TRPV5 and TRPV6 are Ca^{2+}-selective channels and are expressed in epithelial tissues, such as the proximal small intestine, distal nephron and placenta, where they are often referred to as epithelial Ca^{2+} channels (EcaC) (192-195). By contrast, TRPM4 and TRPM5 are only permeable to monovalent cations.

TRP channels also serve as multimodal sensors that detect diverse stimuli, including temperature, mechanical stress, pH, osmolarity, light and chemical ligands, both endogenous and exogenous. Their role in somatosensory perception spans species from yeast to mammals (185,191,196). TRP channels are not only ion channels; they are also involved in important signaling pathways, such as the MAPK (197), TGF-β (198), canonical NF-κB (199-201) and AMP-activated protein kinase (AMPK) pathways (186,202-204). Additionally, their activity is regulated through mechanisms, such as transcription, alternative splicing, glycosylation and phosphorylation, contributing to their functional diversity. Due to their widespread expression across cell types and their ability to function alone or synergistically with other ion channels, TRP channels serve as critical cellular sensors. The dysfunction of TRP channels has been implicated in a broad spectrum of diseases, including gastrointestinal, cardiovascular, respiratory and neurological disorders, as well as various types of cancer and chronic pain syndromes. Given their ability to respond to diverse stimuli, including temperature fluctuations, chemical compounds, osmotic stress, mechanical forces, lipid signals, light, oxidative stress, pH change and pheromones, a comprehensive 'ion channel signaling atlas' could significantly advance the understanding of TRP-mediated cellular responses and their pathological consequences.

Role of TRP channels in nociception. Noxious and neuropathic pain states are characterized by heightened excitability of nociceptors, largely driven by alterations in their ionic conductance properties. These changes involve dysregulation of voltage-gated sodium channels (e.g., NaV1.7, NaV1.8), calcium channels and various ligand-gated and mechanosensitive ion channels, such as members of the TRP family and ASICs. These ion channels facilitate the transduction and propagation of noxious mechanical, thermal and chemical stimuli. Based on their responsiveness, nociceptors can be classified

as unimodal-responding selectively to a single modality, or polymodal, integrating multiple types of noxious stimuli.

As aforementioned, TRPs respond to mechanical, chemical and thermal stimuli, due to an influx of non-selective cations that depolarize neuronal cells and generate action potentials (205). The majority of TRP channels are expressed in primary afferent neurons, including those found in the DRG, trigeminal ganglia and nodose ganglia (205). TRP channels are key components of nociceptive neuronal pathways, with TRPV1 being particularly important. Originally identified as the vanilloid receptor-1, TRPV1 is activated by heat, protons and vanilloid compounds, such as capsaicin and resiniferatoxin (206). It serves as a key integrator of thermal and chemical noxious stimuli. In invertebrates, TRPV1 homologue is involved in processes such as phototransduction, mechanosensation, thermosensation and osmosensation. Several TRP channels, including TRPV1, TRPV2, TRPV3, TRPV4, TRPA1 and TRPM8, are found in DRGs. TRPV1, TRPV2, TRPV3 and TRPM8 function as thermoreceptors, while TRPV4 and TRPA1 function as mechanoreceptors (205). Additionally, TRPV1, TRPV3, TRPM8 and TRPA1 serve as chemoreceptors, responding to specific compounds, such as capsaicin, endocannabinoids, camphor (207) menthol (208,209), mustard oil and cinnamon oil (210,211). The TRPV1-4 subfamily exhibits temperature-dependent ion currents, underscoring their role in thermosensation.

In various chronic pain conditions, the expression of TRPV1 is upregulated. Conversely, knockout animal models lacking a functional TRPV1 gene fail to exhibit typical responses to painful stimuli, highlighting its critical role in nociception (205). TRP channels are also highly expressed in trigeminal neurons and brain regions associated with migraine pathogenesis, and transmit migraine-related pain signals (212). Several studies have highlighted their role in migraine, indicating their potential as therapeutic targets (212). TRP channels are constantly influenced by external and internal physiological conditions (213). Given their crucial role in nociception, the aforementioned hallmark studies urge the investigation of the epigenetics of TRP channels, which could pave the way for the development of new therapies for chronic nociceptive pain.

Epigenetic regulation through histone modifications. Both acute and chronic stress have been shown to lower pain thresholds, increase visceral hypersensitivity and elevate gastrointestinal motility, largely via activation of the hypothalamic-pituitary-adrenal axis (214). Epigenetic research on the brain, spinal cord and related disorders is still in its early stages. However, previous studies have indicated that something perplexing occurs under chronic and acute stress conditions, e.g., chronic stress has been shown to downregulate the anti-nociceptive endocannabinoid receptor 1 (CNR1, also known as CB1) in L6-S2 DRG neurons (215). The TRPV1 channel, which is a pro-nociceptive endovanilloid pain ion channel, is upregulated in DRGs that innervate the pelvic organs, including the colon, based on retrograde labeling and functional studies (216,217). Both CNR1 and TRPV1 are reciprocally regulated. For example, in a previous study, control rats treated with serial injections of corticosterone exhibited a significant increase in serum corticosterone levels, which was associated with visceral hyperalgesia (217). This also included an enhanced anandamide content, an increased TRPV1 expression and decreased CB1 receptor protein levels. Co-treatment with RU-486 prevented these changes. Additionally, the exposure of isolated control L6-S2 DRGs *in vitro* to corticosterone reproduced the alterations in CB1 and TRPV1 receptors observed *in vivo*, with these effects also being prevented by co-treatment with RU-486 or WIN55,212-2 (217).

The alterations in TRPV1 and CB1 are likely driven by epigenetic mechanisms, including chromatin remodeling, histone modifications, DNA methylation and miRNA activity. One of the first studies linking epigenetics with TRP channel expression revealed that chronic stress increased levels of the histone acetyltransferase *EP300* gene expression, which promoted histone acetylation at the *Trpv1* promoter in L6-S2 DRGs and enhanced TRPV1 expression. The knockdown of *DNMT1* and *EP300* reversed these modifications and attenuated visceral hypersensitivity (218) (Fig. S7).

Pain-related signals occur within the central nervous system, a process known as central sensitization and also arise in the periphery due to peripheral inflammation. Peripheral inflammation is a complex immune process that leads to the release of inflammatory cytokines in response to injuries, infections, or chronic conditions, such as cancer, diabetes and stress. These cytokines enhance peripheral inflammation through the further release of pain mediators and neurotrophic factors, such as in the case of nerve growth factor, which releases BDNF from DRG neurons, thus further enhancing the sensitization of nociception and neuropathic pain (219,220) (Fig. S7). Most likely, these cytokines trigger epigenetic changes through a vast network of signaling pathways. For instance, in animal models of arthritis, colitis and hepatitis, treatment with HDAC inhibitors, such as phenylbutyrate and trichostatin A, valproic acid (VPA) and suberyolanilide hydroxamic acid (SAHA or vorinostat), and ITF2357 has been shown to reduce the expression of pro-inflammatory cytokines, such as IL-1β and TNF-α (221-224). These cytokines cause the hyperacetylation of H4 histones at pro-inflammatory promoters, such as the granulocyte-macrophage colony-stimulating factor (GM-CSF), through the action of the transcription factor NF-κB and its subunits p50 and p65 (225,226); this enhanced inflammation is perhaps responsible for the enhanced expression of TRP channels (Fig. S7). HDAC inhibitors also exert analgesic effects in inflammatory pain via mGluR2 receptors in both the DRG and spinal cord (227). The mGluR2 receptor gene is upregulated by increased acetylation of p65/RelA on lysine 310 (227). Another example of histone modifications is the methylation of H3K4 via methyltransferase SET7/9, which recruits NF-κB to pro-inflammatory genes (228). Thus, the cytokine activation stimulates downstream signaling pathways that activate NF-κB through histone modifications that alter nuclear gene expression. NF-κB plays a critical role in the downstream regulation of TRP channels. It can directly bind to the promoter regions of TRP genes, and this notable activation of TRP channels can lead to ionic changes both inside and outside the cell, and their interactions, e.g., ankyrin repeat domain binding to the cytoskeleton, ultimately triggering a cascade of downstream signaling pathways. TRP

channels affect multiple signaling pathways, including the MAPK pathway, the TGF-β signaling pathway, the NF-κB pathway and the AMPK pathway (186), as aforementioned.

The activation of TRPA1 has been observed in M1 macrophages in mice. TRPA1 regulates H3K27me3 modification by the EZH2 subunit of the PRC2 complex by protecting it from degradation via the proteasome pathway to inhibit M1 macrophage activation (229). TRPA1 deficiency leads to EZH2 degradation and chromatin opening, promoting M1 macrophage-associated gene transcription and atherosclerotic plaque formation (230). Hence TRPA1 reduces atherosclerosis plaque formation in third-order branches of the superior aorta of patients and mice (230). However, the precise mechanism and the specific PRC2 subunit(s) involved remain unclear, and high-resolution structural confirmation is lacking. In addition to its interaction with PRC2, TRPA1 also links calcium signaling to epigenetic control. Inhibition of TRPA1 reduces CA^{2+} influx, suppressing CaMKII activity, which in turn alters the nuclear localization of HDAC4 (Fig. S7). This disruption prevents MEF2A from binding to DNA, promoting hypertrophic gene expression and contributing to cardiac dysfunction (231). Overall, pain sensitization under conditions of stress involves complex epigenetic mechanisms regulating TRP channel activity, inflammatory receptor expression and downstream signaling pathways. These pathways provide promising therapeutic targets but require further investigation, particularly in well-controlled *in vitro* systems such as isolated L6-S2 DRGs.

Epigenetic regulation through DNA methylation. There is a well-established link between increased CpG methylation, MeCP2 binding and aberrant gene expression in inflammatory pain conditions. For instance, in intervertebral disc degeneration, chronic pain is associated with increased methylation at the *SPARC* gene promoter in both mice and humans (232). Similarly, methylation of the promoter of the endothelin-1 B receptor (*ET_B*) has been observed in biopsies from painful human oral cancers, but not in non-painful oral dysplasia. The restoration of *ET_B* receptor expression has been found to reduce oral pain (233). Perhaps *SPARC* and *ET_B* expression is linked directly or indirectly to TRP channels.

One of the most compelling examples of the role of DNA methylation in pain regulation involves the TRPA1 gene. Increased TRPA1 promoter activity has been associated with a lack of DNA methylation during states of high pain threshold. In a previous study, the researchers employed methylated DNA immunoprecipitation and deep sequencing on peripheral blood leukocytes from 50 identical twins and 50 unrelated individuals to assess responses to high or low heat pain sensitivity. They identified the TRPA1 promoter as a key site influencing both thermal and mechanical pain sensitivity (234). In the same study analyzing DNA from whole-blood samples of 75 healthy volunteers, a specific CpG site within the TRPA1 promoter was found to be hypermethylated in individuals with a low threshold for pressure-induced pain. Moreover, notable sex-based differences were observed: Females exhibited higher methylation levels at this site and exhibited greater sensitivity to pressure pain compared to males (234).

Epigenetic regulation through miRNAs. Epigenetic regulation by miRNAs plays crucial roles as housekeeping and regulatory elements in key biological processes, such as early development, cell proliferation, fat metabolism, differentiation and apoptosis (235). As they regulate over one-third of human genes, miRNAs are implicated in numerous medical conditions, including cardiovascular, cerebrovascular and neurodegenerative disorders. Increasing evidence suggests their involvement in pain modulation, both nociceptive and neuropathic pain models. In several rodent models of pain, such as spinal nerve ligation, spared nerve injury, CFA-induced inflammatory pain and chemotherapy-induced pain (e.g., histone deacetylase inhibitor JNJ-26481585 model), significant changes in miRNA expression profiles have been reported (236). These miRNAs are secreted by immune and non-immune cells during neuroinflammation caused by peripheral nerve injury and function through known pro-inflammatory signaling pathways, including IRAK/TRAF6, TLR4/NF-κB, CXCR4, TXNIP/NLRP3 inflammasome, MAPK, TNF-α and TLR5 (182,237).

Several specific miRNAs contribute to the activation or inhibition of these signaling cascades. For example, miR-590-3p is involved in inflammation in diabetic neuropathic pain (238), while miR-214-3p is downregulated in spinal astrocytes following spinal nerve ligation (239). MiR-146a-5p inhibits NF-κB activation (240,241), and miR-381 suppresses HMGB1 expression (Table II) (242,243). miR-362-3p downregulates BAMBI, and the inhibition of miR-155 or miR-221 alleviates neuropathic pain by enhancing SOCS1 expression via NF-κB and p38-MAPK inhibition (Table II) (182,244-247). In CFA-induced inflammatory pain, blocking miR-22 reduces mechanical allodynia and thermal hyperalgesia (248). Additionally, miR-183 suppresses the expression of pro-inflammatory cytokines (IL-6, IL-1β and TNF-α) and the expression of ion channels, such as *TRPV1*, *Nav1.3*, *Nav1.7* and *Nav1.8* in DRG neurons to reduce osteoarthritic pain (132) (Figs. S4, S7, and Table II).

Additional miRNAs, including miR-28-5p, miR-128-3p, miR-136, miR-150, miR-200b and miR-429 modulate neuroinflammation and neuropathic pain progression by inhibiting zinc finger E-box-binding homoeobox 1 expression (Table II) (249-252). miR-23a reduces hyperalgesia via CXCR4 and the TXNIP/NLRP3 inflammasome in spinal glial cells (253). Moreover, miR-140 and miR-144 alleviate hyperalgesia and decrease the secretion of inflammatory mediators by targeting sphingosine-1-phosphate receptor 1 and RAS p21 protein activator 1, respectively (254,255). Furthermore, miR-216a-5p inhibits Wnt/β-catenin signaling by targeting KDM3A, reinforcing the regulatory potential of miRNAs in chronic pain (Table II) (256).

Chemotherapy-induced peripheral neuropathy is a frequent and debilitating side-effect associated with the use of agents, such as OXL and bortezomib (BTZ), and it has been linked to miRNA dysregulation via the oxidative stress-TRPA1 signaling axis. OXL, a third-generation platinum-based chemotherapeutic used in metastatic gastrointestinal cancers, has been shown to increase miR-155 levels, thereby activating the oxidative stress-TRPA1 pathway (257). This results in mechanical allodynia and cold hyperalgesia. The intrathecal administration of

miR-155 inhibitors in OXL-treated rats has been shown to restore impaired Nrf2-ARE signaling in the dorsal horn of the spinal cord, reduce the expression of NADPH oxidase subtype 4, and decreased oxidative stress markers, such as 8-iso PGF2α and 8-OHdG (257). Conversely, the OXL-induced downregulation of miR-141-5p leads to an increased expression of TRPA1. The intrathecal injection of miR-141-5p reduces TRPA1 levels and attenuates peripheral pain (258) (Fig. S7, Table II). Similarly, miR-155 has been implicated in BTZ-induced neuropathic pain. Its inhibition leads to the reduced expression of TNFR1, p38-MAPK, JNK and TRPA1, contributing to analgesic effects (247,259).

Extracellular miRNAs also contribute to pain signaling. For instance, miRNA let-7b activates nociceptive neurons through TLR7-TRPA1 coupling, inducing rapid inward currents and action potentials in DRG neurons (Table II) (247). This effect is dependent on the presence of both TLR7 and TRPA1, as well as the 5'-GUU GUG U-3' motif in miRNA let-7b (260,261) (Fig. S7). Several other miRNAs, including miR-143, miR-21, miR-103, miR-7a, miR-133a, miR-134 and miR-20a/b, as well as the Kcna2 antisense long non-coding RNA, have been reported to modulate nociceptor activity in DRG neurons and contribute to pain processing (Table II) (145,262-266).

In addition, hyper-methylated m^6A-modified mRNAs of TRP channels were identified by m^6A epitranscriptomic microarray analysis in middle ear cholesteatoma tissues (267). KEGG pathway analysis revealed that these hypermethylated transcripts were involved in 26 signaling pathways, including inflammatory mediator regulation of TRP channels (267). Of note, there appears to be bidirectional communication between lncRNAs, such as HOX transcript antisense intergenic RNA (HOTAIR) and TRP channels, mediated via METTL3-dependent m^6A modifications (268). For instance, in glioblastoma, the upregulation of melastatin-TRPM7 is associated with an increased expression of lncRNA HOTAIR through calcium influx and subsequent NF-κB activation. The increased expression of lncRNA HOTAIR has been linked to a reduced expression of miR-301-3P and a subsequent decrease in FOSL1 expression, promoting tumorigenesis (269).

Although the dynamic expression of various lncRNAs, including rhabdomyosarcoma 2 associated transcript, TCL1 upstream neural differentiation-associated RNA, BDNF-antisense (AS), metastasis-associated lung adenocarcinoma transcript 1 (Malat1), Gomafu, KCNA2-AS and HOTAIR has been well characterized in CNS development, synaptic plasticity, neurodegenerative diseases and cancer (270), their roles in regulating ion channels involved in nociceptive or neuropathic pain remains largely unexplored. For example, the circular RNA hsa_circ_0023305 was found to significantly enhance TRPM7 expression by functioning as a miR-218-5p sponge, thereby promoting proliferation and metastasis of laryngeal squamous cell carcinoma cells (271). Collectively, these findings underscore the central roles of ncRNAs, including miRNAs, lncRNAs, and circRNAs, in the regulation of TRP channels and their potential involvement in both nociceptive and neuropathic pain states. The continued investigation of miRNA and lncRNA regulatory networks may provide novel therapeutic avenues for the development of targeted, non-opioid analgesics aimed at improving outcomes for patients suffering from chronic pain.

16. Pharmacology of pain highways

Since ion channels control the major flow of ions across the plasma membrane of neurons that generate and propagate action potentials, learning about the epigenetic mechanisms that transform sensory afferent pathways would lead to a large breakthrough for all types of pain. From the aforementioned studies, a growing evidence indicates that aberrant changes in DNA methylation, RNA modification complexes, RNA interference and histone modifications affecting ion channels can reshape pain sensitivity trajectories following physical, peripheral, or visceral injury, central or peripheral nervous system lesions, as well as neuropathic or chemotherapy-induced pain. While current treatments rely on analgesics, anticonvulsants and antidepressants, epigenetic-based interventions hold potential to restore or modify normal gene expression, protein function and analgesic responsiveness.

Dysregulated ion channel expression is a hallmark of nociceptive and neuropathic pain, altering neuronal excitability. Identifying critical ion channel targets is therefore essential for developing improved pain therapeutics. For example, Nav1.7, Nav1.8, and Nav1.9 play critical roles in inflammatory pain and research on human inherited disorders of nociception has revealed that Nav1.7 is essential for physiological pain perception, with point mutations leading to chronic pain syndromes (272). Sensitivity to TTX is useful in classifying sodium channel subtypes and distinguishing their functions across regions, such as the CNS, DRGs and dorsal horn, as well as their specific activation during nociception. Peripheral neuronal research has suggested that Nav1.8 interacts more slowly with carbamazepine in DRG neurons compared to TTX-sensitive channels (273). The μO-conotoxin MrVIb (31-amino acid peptide from the venom of the marine snail, *Conus marmoreus*) selectively blocks Nav1.8 currents and produces substantial analgesia, indicating that Nav1.8-selective antagonists may offer superior therapeutic profiles compared to nonselective VGSC inhibitors (274,275). Additionally, peptide toxins from tarantulas and marine cone snails represent promising sources of novel sodium channel inhibitors (276).

REST, also known as NRSF, is a master transcriptional regulator of neuron-specific genes. It functions not only during neurogenesis and neuronal differentiation, but also in mature neurons, particularly during the critical period of postnatal brain development, where it fine-tunes the expression of genes involved in synaptic plasticity (277). REST provides neuroprotective advantage by repressing oxidative stress and β-amyloid toxicity genes in normal aging (277). From its broad regulatory role (123), REST/NRSF has been found as a potential pain therapeutic target; in several pain models, the direct inhibition of its activity has been shown to alleviate pain symptoms.

Biological data have elucidated the mechanism of NRSF binding to NRSE in target genomic sequences, recruiting a network of other proteins, and how they individually or collectively contribute to chronic or neuropathic pain. Specifically, REST recruits histone deacetylase mSin3 at its N-terminal domain and the major corepressor CoREST at its C-terminal

domain (122) (Figs. S4 and S5). CoREST, in turn, recruits the histone demethylase LSD1, further reinforcing transcriptional repression. In addition, NRSF can indirectly recruit the histone methyltransferase G9a via the chromodomain-containing protein CDYL (chromodomain Y-like), which bridges REST to histone methylation activity (122).

Following nerve injury, NRSF upregulation leads to the transcriptional repression of ion channels and reduced analgesia that underlie chronic or neuropathic pain. For example, the upregulation of NRSF downregulates SCN7A (also known as Nav2.1), which is an atypical VGSC, since it is regulated by a higher concentration of sodium rather than voltage (278) and the potassium voltage-gated channel subfamily D member 3 (Kv4.3) in DRG neurons after injury, thereby lowering the firing threshold and enhancing pain signaling (122). NRSF also suppresses the expression of the μ-opioid receptor (MOR), resulting in a loss of analgesic efficacy, as shown in the injury-induced repression of Nav1.8 and MOR genes in damaged C-fibers (279,280). In parallel, G9a (histone methyltranferase, also known as EHMT2) also contributes to long-term pain sensitization by promoting histone methylation and subsequently downregulation of potassium channel genes (281).

The pharmacological targeting of NRSF and its corepressors has revealed promising strategies for alleviating neuropathic pain. As previously demonstrated, two small-molecule mimetics, mS-11 and C737 (mimics the helical structure of REST), which competitively bind to the N-terminal domain of NRSF and disrupt its interaction with mSin3, attenuate REST-mediated repression of gene expression. For instance, in a mouse model of sciatic nerve injury, the administration of mS-11 restored C-fiber pain thresholds to basal levels (282). Similarly, a small quinolone-like compound, C91, was shown to inhibit the NRSF-mSin3b interaction (283), further supporting the therapeutic potential of targeting this pathway.

HDAC inhibitors prevent the removal of acetyl groups from histone and non-histone proteins, leading to increased histone acetylation and a more relaxed chromatin structure that facilitates gene transcription (284). HDAC inhibitors, such as TSA, (VPA and SAHA, restore the expression of Nav1.8, thereby recovering C-fiber-mediated sensory function and alleviating hypoesthesia (285). Moreover, treatment with HDAC inhibitors, including TSA and VPA, restores morphine analgesia, which is associated with an elevated expression of MOR (14,286). In addition, DNMT3a expression is upregulated in the DRG and spinal cord of rats with neuropathic pain, whereas treatment with the isoform-nonspecific DNMT inhibitor N-phthalyl-L-tryptophan (RG108) enhances MOR expression and attenuates thermal hyperalgesia in chronic constriction injury (CCI) models (287).

miRNAs can also be used to target nociceptive signaling pathways of ion channels. miRNAs, such as miR-96 and miR-384-5p have been known to decrease the expression of *Scn3A* ($Na_v1.3$) (126,127) and alleviate neuropathic pain. Additional miNAs involved in DRG nociceptive signaling include miR-182, miR-30b, miR-18, miR-7a, miR-137, miR-183-5p and the miR-17-92 cluster. The ncRNAs, such as miR-124 and miR-219 (via MeCP2/CAMKs), miR-103 and miR-32-5p downregulate *$Ca_v1.2$*, and *$Ca_v3.2$* expression, respectively, thereby attenuating nociceptive signaling. Collectively, these findings highlight how the epigenetic and post-transcriptional modulation of ion channel function provides a foundation for next-generation pain therapeutics.

17. Conclusion and future directions

The majority of ion channels in the spinal cord play critical roles in nociception. These channels include voltage-gated sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and TRP channels. They are typically classified based on their structural features (such as α- and β-subunits), electrophysiological characteristics (e.g., activation and inactivation kinetics), and pharmacological sensitivity to specific modulators or blockers. However, the epigenetic regulation of these ion channels remains underexplored and warrants more in-depth investigations for the development of more effective pain therapies.

These ion channels function in concert to discriminate between noxious and innocuous stimuli and to modulate nociceptive signals. This complex, multilevel 'orchestra' of ion channel regulation and activity spans from primary nociceptive afferents and DRGs to DHNs, spinal interneurons, and projection neurons of Rexed laminae, transmitting pain signals via the anterolateral system, notably the spinothalamic tract to the supraspinal centers. The final destination for the conscious perception of pain is the somatosensory cortex, specifically the postcentral gyrus of the parietal lobe, where the spatial, temporal and intensity features of pain are interpreted. Disruption at any point in this integrated signaling cascade, whether through ion channel dysfunction, epigenetic dysregulation, or synaptic plasticity, can lead to aberrant pain processing and the development of chronic pain syndromes.

The DRGs and dorsal horn are the major afferent nociceptive centers. Within the spinal cord, different spinal segments that correspond to specific body regions have specialized functions, reflecting their diverse neuronal populations and varying role in nociception (20). The Rexed laminae, defined by distinct cytoarchitecture, process different types of sensory stimuli; laminae I to VI are the principal nociceptive layers, containing interneurons, projection neurons, and wide dynamic range neurons distributed across these laminae (29,30). The spinal cord anatomy changes along its rostrocaudal axis. At lower spinal levels (e.g., lumbar and sacral), the ratio of gray matter to white matter is higher due to fewer ascending and descending fiber tracts. By contrast, at cervical levels, the white matter proportion increases as ascending tracts accumulate fibers from lower segments while descending tracts gradually lose fibers (20). This structural variation suggests that the epigenetic landscape, including chromatin accessibility, DNA methylation and histone modifications, may differ across spinal segments and between spinal nerves emerging at different vertebral levels. Such segment-specific epigenetic regulation could influence the local expression of ion channels, receptors, pain-related genes and their pathways, thereby shaping regional sensitivity to injury, patterns of pain sensitization and the development of chronic pain.

Emerging evidence indicates that histone modifications critically regulate nociceptive ion channels. For example, H4 acetylation of *SCN8A* ($Na_v1.6$) promoter enhances its

transcription by promoting the recruitment of phosphorylated STAT3 and its coactivator p300 and TNF-α cytokine during inflammation uses the same pathway for *SCN8A* expression (Fig. S4) (125). Similarly, in animal models of arthritis, colitis and hepatitis, HDAC inhibitors reduce the expression of pro-inflammatory cytokines such as IL-1β and TNF-α (221-224), which otherwise induce hyperacetylation of H4 at promoters such as GM-CSF via NF-κB and its subunits p50 and p65, which increases TRP channel expression (Fig. S7) (225,226). Conversely, NRSF downregulates the *Scn10a* gene (Nav1.8) and the MOP receptor (*Oprm1*) in DRGs by recruiting HDACs, mSin3, and CoREST in neuropathic pain models (124). NRSF and its corepressors also repress K_v and K_{2P} channel genes in OXL-treated mice, while NRSF knockdown in DRGs, mitigates this repression and alleviates mechanical and cold hypersensitivity (141). Moreover, calcium-dependent enzymes, such as HDAC4, *CaMKII* and calcineurin respond to intracellular Ca^{2+} fluctuations to modulate chromatin structure, DNA methylation and transcription factor activity (161,162). In turn, epigenetic modifications, including histone marks and DNA methylation, regulate the expression of key genes involved in calcium homeostasis and signal transduction, such as VDCCs, pumps and buffering proteins, establishing a reciprocal regulatory loop (163). TRP channels exhibit a similar bidirectional interaction. Both VDCCs and TRPs are targets and activators of signaling pathways, including MAPK, TGF-β, NF-κB and AMPK. Thus, the dual role of calcium and TRP channels, as both modulators and effectors of epigenetic and signaling networks, render them promising therapeutic targets for chronic pain. The more in-depth exploration of this bidirectional interplay could uncover novel nociceptive pathways and guide future interventions.

DNA methylation plays a pivotal role in regulating TRP channel expression in peripheral and visceral pain sensitivity. For instance, the knockdown of *DNMT1* and the histone acetyltransferase *EP300* reverses TRPV1 expression by downregulating the endocannabinoid receptor CNR1 in L6-S2 DRGs, thereby attenuating visceral hypersensitivity (218) (Fig. S7). Similarly, increased TRPA1 promoter activity is associated with reduced DNA methylation during states of high pain threshold (234).

In addition to DNA methylation, miRNAs secreted by immune and non-immune cells during neuroinflammation modulate nociceptive pathways by targeting ion channels and related signaling molecules. These miRNAs function through established pro-inflammatory pathways, including IRAK/TRAF6, TLR4/NF-κB, CXCR4, TXNIP/NLRP3 inflammasome, MAPK, TNF-α, and TLR5 (182,237), thereby influencing the activation, transmission, and sensitization patterns of nociceptive circuits. Specific miRNAs, such as miR-30b downregulate *Scn3a*, *Scn8a*, and *Scn9a* (129-131), while miR-183 suppresses *Scn3a*, *Scn9a*, *Scn10a*, and *TRPV1* expression in DRG neurons (132), alleviating neuropathic pain in models such as SNL or OXL-induced neuropathy. Likewise, miR-103, miR-32-5p, miR-125, and miR-219 have been shown to either upregulate or downregulate the expression of VDCCs (179,180), while miR-146a-5p, miR-381, miR362-3p, miR155, miR-183 regulate TRP channels, highlighting miRNAs as promising nociceptive targets (132,182,244-246).

Future studies are required to employ high-throughput miRNA profiling, digital PCR and quantitative PCR to assess miRNA expression patterns. Additionally, chromatin immunoprecipitation sequencing (ChIP-seq), ChIP-chip, ATAC-seq and bisulfite sequencing will be invaluable for characterizing histone modifications and DNA methylation landscapes in DRG and DHNs across different spinal segments. Together, these integrated approaches will advance our understanding of epigenetic regulation in pain pathways and help identify novel therapeutic targets for the management of chronic pain.

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The author declares that there are no competing interests.

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