Figure S1. Anatomy and organization of the human spinal cord. (A) Dorsal view illustrating the eight cervical, 12 thoracic, five lumbar, five sacral, and one coccygeal region with key landmarks: Cervical and lumbar enlargements, pyramidal decussation and filum terminale. (B) Spinal segmentation diagram highlighting spinal cord regions, spinal nerves, the conus medullaris (orange), and cauda equina (purple). (C) Cross-section illustrating the central canal, dorsal root ganglion, roots, rami, pia mater, arachnoid mater, dura mater, and dentate ligament anchoring the cord. The figure was adapted from the studies by Byrne [Byrne JHe: Neuroscience Online: An Electronic Textbook for the Neurosciences. Department of Neurobiology and Anatomy, McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth), 1997] and Tan *et al* [Tan S, Faull RLM and Curtis MA: The tracts, cytoarchitecture, and neurochemistry of the spinal cord. Anat Rec (Hoboken) 306: 777-819, 2023] after obtaining relevant permission.

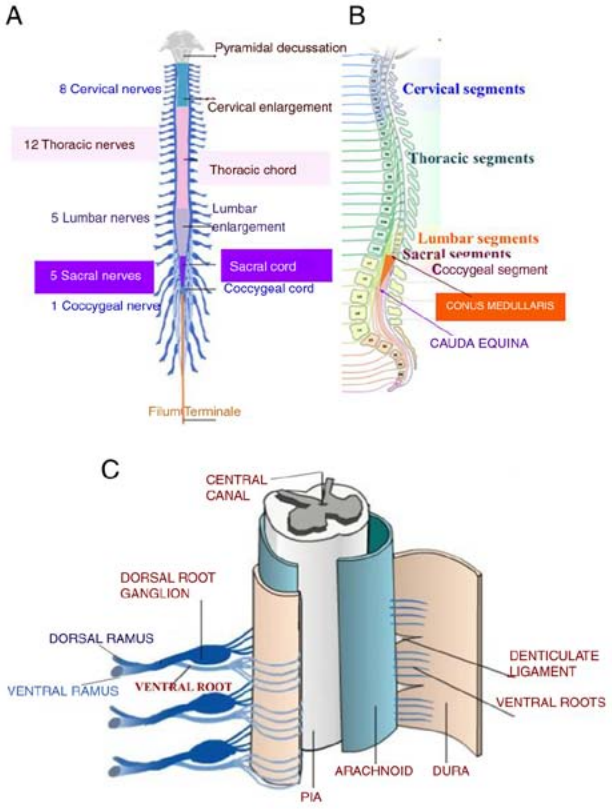

Figure S2. Schematic representation of Rexed laminae and major nuclei within the spinal cord gray matter. Color-coded regions represent functional subdivisions, as follows: Purple, sensory processing (dorsal horn, laminae I-VI); green, visceral/autonomic function (intermediolateral cell column); red, motor function (ventral horn, laminae VIII-IX); gray, commissural neurons and glia around the central canal (lamina X). The information presented in this figure and the figure itself was adapted from the study by Byrne [Byrne JHe: Neuroscience Online: An Electronic Textbook for the Neurosciences. Department of Neurobiology and Anatomy, McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth), 1997] after obtaining relevant permission.

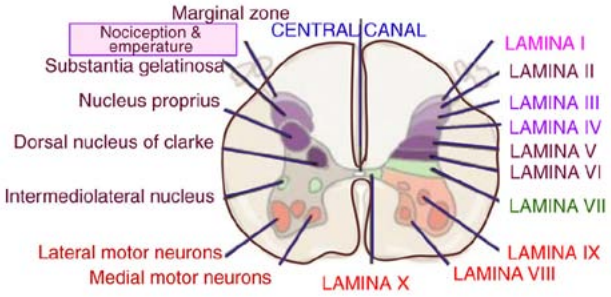

Figure S3. Nociceptive pathways in the spinal cord. Schematic representation of nociceptive signaling from peripheral sensory neurons to the cerebral cortex. First-order neurons, with cell bodies located in the DRGs, relay afferent signals through the dorsal roots into the spinal cord, where they synapse with the second-order interneurons and projection neurons in the dorsal horn. These neurons decussate and ascend via the anterolateral system, including the lateral and anterior spinothalamic tracts and the SRT, to the brainstem nuclei (LPB, CVLM, PAG) and the thalamic nuclei (VPL, VPM). In the thalamus, third-order neurons project to the postcentral gyrus of the parietal lobe, where nociceptive information is perceived. Descending modulation occurs via corticospinal and extrapyramidal tracts, originating in the cortex and brainstem, which regulate nociceptive input at the spinal level. SRT, spinoreticular tract; LPB, lateral parabrachial nucleus; CVLM, caudal ventrolateral medulla; PAG, periaqueductal gray; VPL, ventral posterolateral; VPM, ventral posteromedial; DRG, dorsal root ganglion.

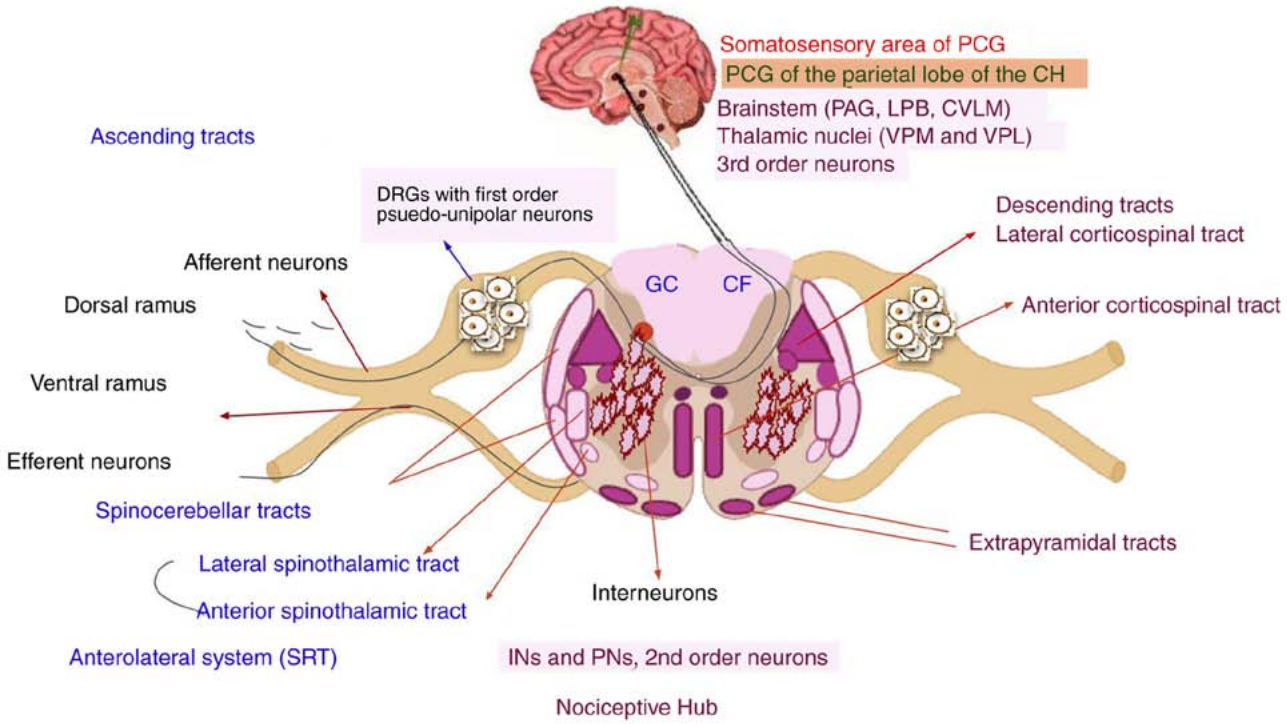

Figure S4. Epigenetic regulation of sodium channel isoforms in DRG nociceptors. Epigenetic activation of *Scn8a* ($Na_v1.6$) by the increased acetylation of histone H4 at the *Scn8a* gene promoter, which recruits phosphorylated STAT3 and its coactivator p300 in DRGs induced by proinflammatory cytokine TNF-α (Ding HH, Zhang SB, Lv YY, Ma C, Liu M, Zhang KB, Ruan XC, Wei JY, Xin WJ and Wu SL: TNF-α/STAT3 pathway epigenetically upregulates Nav1.6 expression in DRG and contributes to neuropathic pain induced by L5-VRT. J Neuroinflammation 16: 29, 2019). Epigenetic repression of *Scn10a* ($Na_v1.8$) and MOP by REST/NRSF in DRG neurons during neuropathic pain. The NRSF repression complex contains HDAC1, SAP30, SAP18 and other proteins (Su XJ, Shen BD, Wang K, Song QX, Yang X, Wu DS, Shen HX and Zhu C: Roles of the neuron-restrictive silencer factor in the pathophysiological process of the central nervous system. Front Cell Dev Biol 10: 834620, 2022). Various miRNAs (miR-30b, miR-96, miR-182, miR-183 and miR-384-5p) downregulate sodium channel expression: miR-30b suppresses *Scn3a*, *Scn8a*, and *Scn9a*; miR-96 downregulates *Scn3a* ($Na_v1.3$); miR-384-5p targets $Na_v1.3$; miR-182 reduces *Scn9a* ($Na_v1.7$); and miR-183 inhibits *Scn3a*, *Scn9a*, and *Scn10a*. The REST/NRSF complex of this figure was adapted from Su et al., 2022 (Su XJ, Shen BD, Wang K, Song QX, Yang X, Wu DS, Shen HX and Zhu C: Roles of the neuron-restrictive silencer factor in the pathophysiological process of the central nervous system. Front Cell Dev Biol 10: 834620, 2022). This diagram was created using BioRender. DRG, dorsal root ganglion; MOP, μ-opioid receptor; NRSF/REST, neuron-restrictive silencer factor or repressor element-1 (RE1)-silencing transcription factor; miRNA/miR, microRNA.

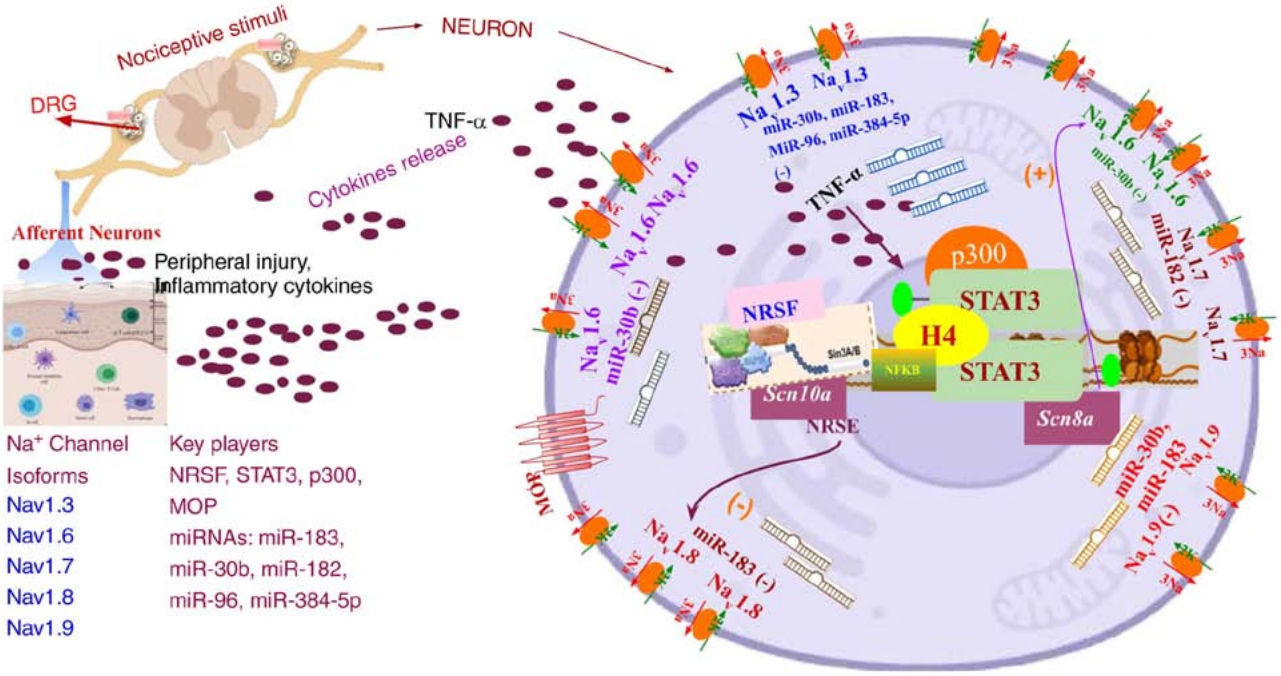

Figure S5. Epigenetic modifications of K channels. Schematic representation of a DRG neuron highlighting key potassium channel isoforms: Voltage-gated (K_v), calcium-activated (K_{Ca}), inward rectifier (K_{ir}) and tandem or two-pore domain (K_{2P}). Inside the nucleus of DRGs and DHN, OXL treatment represses K_v and K_{2P} via NRSF. The N-terminal domain of NRSF binds HDACs and represses target genes while the C-terminal domain binds to CoRESTs and further interacts with HDAC1, HDAC2 and MeCP2 to promote and maintain methylated CPG-dependent gene silencing (Su XJ, Shen BD, Wang K, Song QX, Yang X, Wu DS, Shen HX and Zhu C: Roles of the neuron-restrictive silencer factor in the pathophysiological process of the central nervous system. Front Cell Dev Biol 10: 834620, 2022). miRNAs such as miR-183-5p, miR-137 and the miR-17-92 cluster downregulate K^+ channel expression, ultimately impact nociceptive pathways. The REST/NRSF complex of this figure was adapted from the study by Su *et al* (Su XJ, Shen BD, Wang K, Song QX, Yang X, Wu DS, Shen HX and Zhu C: Roles of the neuron-restrictive silencer factor in the pathophysiological process of the central nervous system. Front Cell Dev Biol 10: 834620, 2022). This diagram was created using BioRender. DRG, dorsal root ganglion; NRSF/REST, neuron-restrictive silencer factor or repressor element-1 (RE1)-silencing transcription factor; miRNA/miR, microRNA; CoRESTs, REST corepressor proteins; DHN, dorsal horn neuron; OXL, oxaliplatin; HDAC, histone deacetylase; MeCP2, methyl-CpG binding protein 2.

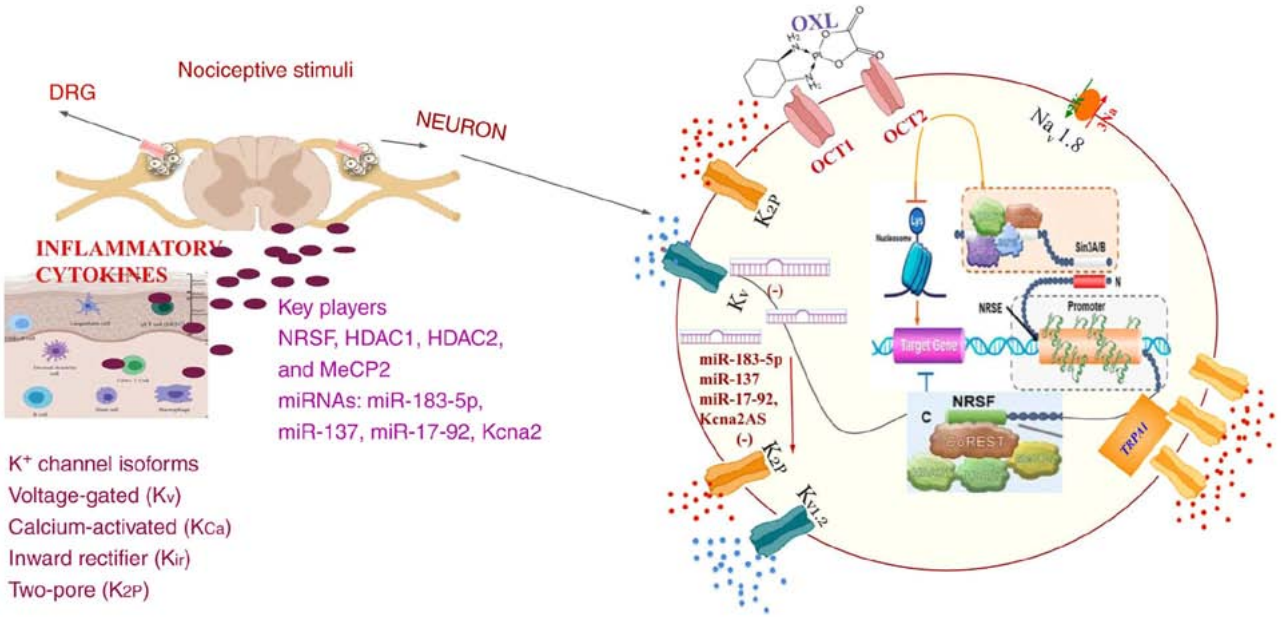

Figure S6. Epigenetic regulation of VGCCs in DRG neurons. Highlighting six classes of Ca^{2+} channels: L ($Ca_v1.1$- $Ca_v1.4$), N ($Ca_v2.1$), P/Q ($Ca_v2.2$), R ($Ca_v2.3$), and T ($Ca_v3.1$-$Ca_v3.3$). Calcium ions (Ca^{2+}) activating the MAPK/JNK pathway, leading to phosphorylation of histone H3 under peripheral inflammation is shown. In chronic nerve injury model, hypomethylation of the *CACNA1C* promoter increases $Ca_v1.2$ expression and enhances Ca^{2+} influx in sensory neurons. HDAC inhibitors suppress the expression of N-type VGCCs ($Ca_v2.1$) and reduce nociceptive hypersensitivity in rodent models. Ca^{2+} influx through L-type VGCCs promotes enhancer RNA (*eRNA*) synthesis via increased H3K4me1 levels and CBP recruitment. Ca^{2+} also activates CaMKII, which phosphorylates MeCP2, causing its release from the BDNF promoter and inducing BDNF transcription. This is associated with reduced H3K9 methylation, increased acetylation at the same site, and lower CpG methylation frequency. miRNAs such as miR-124 and miR-219 via MeCP2/CAMKs; miR-103 and miR-32-5p, downregulate *$Ca_v1.2$*, *$Ca_v3.2$* expression respectively, thereby attenuating nociceptive signaling. This figure was created using BioRender. VGCCs, voltage-gated calcium channels; DRG, dorsal root ganglion; HDAC, histone deacetylase; CBP, CREB-binding protein; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; BDNF, brain-derived neurotrophic factor; MeCP2, methyl-CpG binding protein 2; miRNA/miR, microRNA; DNMT, DNA methyltransferase; TET, ten-eleven translocation methylcytosine dioxygenase.

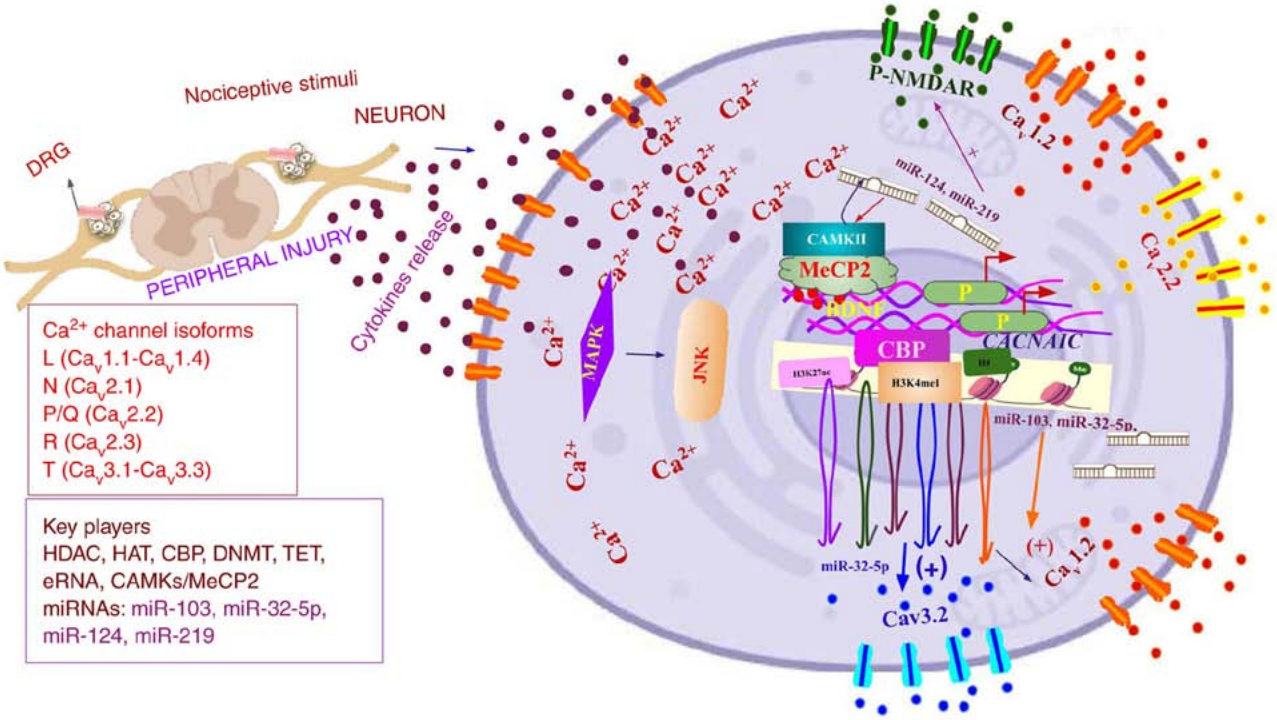

Figure S7. Epigenetic regulation of nociception through peripheral inflammation-induced TRP channel expression in DRG neurons. Peripheral inflammation triggers pro-inflammatory cytokines that induce histone, DNA methylation and miRNA changes, regulating TRP channel expression and nociception. For example, reduced DNA methylation increases TRPA1 promoter activity during states of high pain threshold, while chronic stress downregulates CNR1 and upregulates TRPV1. HAT EP300 and DNMT1 enhance TRPV1 expression and visceral sensitivity in L6-S2 DRGs. HDAC inhibitors lower IL-1β and TNF-α levels, decrease H4 hyperacetylation, and suppress TRP expression via NF-κB. HDACis also exert analgesic effects via mGluR2 in DRG and spinal cord. SET7/9 methyltransferase-mediated H3K4 methylation recruits NF-κB to pro-inflammatory genes. Inhibiting TRPA1 reduces Ca^{2+} influx and CaMKII activity, altering HDAC4 localization and MEF2A DNA binding. miRNAs (e.g., miR-143, miR-21, miR-103, miR-7a, miR-133a, miR-134 and miR-20a/b) target TRP channels, while miR-183 suppresses pro-inflammatory cytokines and ion channels like TRPV1 and $Na_v1.7$, and $Na_v1.8$ in DRG neurons. This figure was created using BioRender. DRG, dorsal root ganglion; TRP channel, transient receptor potential channel; HDAC, histone deacetylase; DNMT, DNA methyltransferase; miRNA/miR, microRNA; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; MEF2A, myocyte enhancer factor 2A.