**Supplementary Table S1.**

**Assessment of Histone H3 PTMs in the dorsal horn of spinal cord post-burn injury using dual immunolabeling**

Quantification of histone H3 PTM levels in DAPI-labeled cells following burn injury, expressed as a percentage of the DAPI-labeled cells.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Ipsilateral**  (mean ± SEM) | **Contralateral**  (mean ± SEM) | **p-value** |
| **Total Histone H3** | 61.4 % ± 10.5 | 49.8 % ± 9.3 | 0.39 |
| **H3K4me1** | 33.4 % ± 12.7 | 20.2 % ± 6.5 | 0.05 |
| **H3K4me2** | 36.4 % ± 2.3 | 27.8 % ± 2.4 | 0.045 |
| **H3K4me3** | 38.0 % ± 2.9 | 23.0 % ± 5.5 | 0.03 |
| **H3K4me3K9ac** | 35.5 % ± 8.8 | 29.2 % ± 15.9 | 0.279 |
| **p-S10H3** | 6.09 % ± 0.6 | 4.14 % ± 1.9 | 0.044 |

**Supplementary Table S2.**

Quantification of histone H3 PTMs colocalization with Pdyn neurons in DAPI-labeled cells post-burn injury, expressed as a percentage of the DAPI-labeled cells.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Ipsilateral**  (mean ± SEM) | **Contralateral**  (mean ± SEM) | **p-value** |
| **Total Histone H3** | 2.62 % ± 0.4 | 1.64 % ± 0.15 | 0.26 |
| **H3K4me1** | 1.95 % ± 0.9 | 1.07 % ± 0.5 | 0.07 |
| **H3K4me2** | 1.85 % ± 0.8 | 1.65 % ± 0.4 | 0.5 |
| **H3K4me3** | 1.79 % ± 0.14 | 1.14 % ± 0.4 | 0.07 |
| **H3K4me3K9ac** | 2.2 % ± 0.4 | 1.59 % ± 0.9 | 0.19 |
| **p-S10H3** | 1.11 % ± 0 | 0.74 % ± 0.3 | 0.012 |

**Supplementary Table S3.**

Quantification of histone H3 PTMs colocalization with Pdyn Neurons post-burn injury, expressed as a percentage of Pdyn neurons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Ipsilateral**  (mean ± SEM) | **Contralateral**  (mean ± SEM) | **p-value** |
| **Total Histone H3** | 76.9 % ± 23.0 | 88.6 % ± 2.9 | 0.33 |
| **H3K4me1** | 62.7 % ± 7.2 | 37.5 % ± 12.5 | 0.11 |
| **H3K4me2** | 53.84 % ± 15.38 | 44.7 % ± 1.9 | 0.3 |
| **H3K4me3** | 74.7 % ± 19.9 | 63.7 % ± 16.9 | 0.34 |
| **H3K4me3K9ac** | 82.6 % ± 6.2 | 65.7 % ± 5.7 | 0.09 |
| **p-S10H3** | 59.0 % ± 3.4 | 31.8 % ± 4.5 | 0.02 |

**Supplementary Table S4.**

**The list of the top 15 up and down-regulated differently expressed genes (DEGs) in the spinal cord in response to burn injury**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Gene symbol** | **Gene name** | **Alteration in gene expression** | **Molecular function** | **Biological process** | **Fold-change vs control** |
| 1 | **RNASET2** | ribonuclease 6 | ↑ | RNA endonuclease activity | immune system process | 1.91 |
| 2 | **COMP** | Cartilage Oligomeric Matrix Protein | ↑ | cell adhesion molecule | negative regulation of the apoptotic process | 1.63 |
| 3 | **FOSB** | FBJ osteosarcoma oncogene B | ↑ | DNA binding | Negative regulation of transcription | 1.52 |
| 4 | **ACP5** | Tartrate-Resistant Acid Phosphatase 5a | ↑ | acid phosphatase activity | negative regulation of nitric oxide biosynthetic process  negative regulation of macrophage cytokine production | 1.52 |
| 5 | **RASGRP4** | RAS Guanyl Releasing Protein 4 | ↑ | guanyl-nucleotide exchange factor activity | [MAPK signaling pathway](https://www.wikipathways.org/index.php/Pathway:WP382)  transmembrane receptor protein tyrosine kinase signaling pathway | 1.5 |
| 6 | **PRSS53** | Polyserine Protease 3 | ↑ | serine-type peptidase activity | proteolysis | 1.5 |
| 7 | **GLT8D2** | Glycosyltransferase 8 Domain Containing 2 | ↑ | UDP-glycosyltransferase activity | None by GO term | 1.48 |
| 8 | **ERG1** | early growth response 1 | ↑ | Transcriptional regulator | Negative regulation of transcription | 1.39 |
| 9 | **MYH2** | Myosin Heavy Chain 2a | ↑ | microfilament motor activity | muscle contraction | 1.35 |
| 10 | **GNGT2** | G Protein Subunit Gamma Transducin 2 | ↑ | guanine nucleotide-binding protein | G protein-coupled receptor signaling pathway | 1.33 |
| 11 | **BANK1** | B Cell Scaffold Protein With Ankyrin Repeats 1 | ↑ | B-cell receptor-induced calcium mobilization | positive regulation of MAPK cascade  negative regulation of interleukin-6 production | 1.33 |
| 12 | **TRPC6** | Transient Receptor Potential Cation Channel Subfamily C Member 6 | ↑ | receptor-activated non-selective calcium permeant cation channel | [BDNF-TrkB signaling](https://www.wikipathways.org/index.php/Pathway:WP3676) and  positive regulation of cytosolic calcium ion concentration | 1.33 |
| 13 | **GPR150** | G protein-coupled receptor 150 | ↑ | Signaling receptor activity | GPCR downstream signaling | 1.29 |
| 14 | **SOCS2** | suppressor of cytokine signaling 2 | ↑ | Negative regulation of cytokine signal transduction | activation of JAK/STAT transcription pathway | 1.29 |
| 15 | **CPT1B** | carnitine Palmitoyltransferase 1B | ↑ | carnitine O-palmitoyltransferase activity | fatty acid metabolic process | 1.28 |
| 16 | **VGLL3** | Vestigial Like Family Member 3 | ↓ | Protein binding | regulation of transcription by RNA polymerase II | -1.21 |
| 17 | **CCDC27** | Coiled-Coil Domain Containing 27 | ↓ | Protein binding | None by GO term | -1.23 |
| 18 | **FOXQ1** | Forkhead Box Q1 | ↓ | DNA binding | negative regulation of transcription by RNA polymerase II | -1.23 |
| 19 | **RBM15** | RNA Binding Motif Protein 15 | ↓ | RNA-binding protein | regulation of alternative mRNA splicing and positive regulation of transcription | -1.26 |
| 20 | **LMLN** | Leishmanolysin like peptidase | ↓ | zinc-metallopeptidase | proteolysis | -1.30 |
| 21 | **D430019H16Rik** | RIKEN cDNA D430019H16 gene | ↓ | unknown | None by GO term | -1.31 |
| 22 | **SH3D21** | SH3 Domain Containing 21 | ↓ | Protein binding | Cell migration | -1.31 |
| 23 | **UNC5D** | Unc-5 Netrin Receptor D | ↓ | Receptor for the netrin NTN4 | [axon guidance](http://www.reactome.org/PathwayBrowser/#/R-HSA-422475)  cell-cell adhesion via plasma-membrane adhesion molecules | -1.34 |
| 24 | **SPAG8** | Sperm Associated Antigen 8 | ↓ | cytoskeletal protein binding | cell differentiation | -1.36 |
| 25 | **SAMD5** | Sterile Alpha Motif Domain Containing 5 | ↓ | protein binding | None by GO term | -1.41 |
| 26 | **6430571L13Rik** | RIKEN cDNA 6430571L13 gene | ↓ | unknown | None by GO term | -1.42 |
| 27 | **RXFP1** | Relaxin Family Peptide Receptor 1 | ↓ | receptor for relaxins | G protein-coupled receptor signaling pathway | -1.47 |
| 28 | **ADORA3** | Adenosine Receptor A3 | ↓ | G-protein-coupled adenosine receptor | G protein-coupled adenosine receptor signaling pathway | -1.53 |
| 29 | **MMP28** | Matrix Metalloproteinase-28 | ↓ | proteolysis of extracellular matrix | tissue homeostasis and burn wound repair | -1.60 |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

**Supplementary Table S5.**

**The list of the top 15 up and down-regulated DEGs in the spinal cord in response to formalin application**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Gene symbol** | **Gene name** | **Alteration in gene expression** | **Molecular function** | **Biological process** | **Fold-change vs control** |
| 1 | **MT-ATP8** | Mitochondrially Encoded ATP Synthase 8 | ↑ | ATP hydrolysis activity and proton transmembrane transporter activity | ATP biosynthetic process | 4.14 |
| 2 | **MT-CO2** | Cytochrome C Oxidase Subunit 2 | ↑ | Component of the cytochrome c oxidase | ATP synthesis coupled electron transport | 2.43 |
| 3 | **NCAPH** | Non-SMC Condensin I Complex Subunit H | ↑ | Regulatory subunit of the condensin complex | positive regulation of chromosome condensation | 1.86 |
| 4 | **4930539E08Rik** | BCL2 interacting protein 5 | ↑ | Unknown | None by GO term | 1.66 |
| 5 | **TMEM181** | Transmembrane Protein 181 | ↑ | G protein-coupled receptor | None by GO term | 1.61 |
| 6 | **CD93** | CD93 Molecule | ↑ | Receptor for C1q | macrophage activation  cell adhesion | 1.52 |
| 7 | **1190007I07Rik** | ubiquinol-cytochrome c reductase complex assembly factor 6 | ↑ | required for the assembly and stability of the mitochondrial ubiquinol-cytochrome c reductase complex | mitochondrial respiratory chain complex III assembly | 1.35 |
| 8 | **DNAH3** | Dynein Axonemal Heavy Chain 3 | ↑ | ATP hydrolysis activity and microtubule motor activity | microtubule-based movement | 1.31 |
| 9 | **SYNE4** | Spectrin Repeat Containing Nuclear Envelope Family Member 4 | ↑ | actin binding | establishment of epithelial cell apical/basal polarity | 1.25 |
| 10 | **REL** | REL Proto-Oncogene, NF-KB Subunit | ↑ | DNA-binding transcription factor activity | negative regulation of gene expression | 1.25 |
| 11 | **Colca2** | POU class 2 homeobox associating factor 3 | ↑ | Transcriptional coactivator | positive regulation of DNA-templated transcription | 1.25 |
| 12 | **IL1RAPL2** | Interleukin 1 Receptor Accessory Protein Like 2 | ↑ | NAD+ nucleosidase activity | cytokine-mediated signaling pathway  regulation of presynapse assembly | 1.21 |
|  |  |  |  |  |  |  |
| 13 | **Ago4** | argonaute RISC catalytic subunit 4 | ↑ | nucleic acid binding and double-stranded RNA binding | regulation of translation | 1.16 |
| 14 | **FANCD2** | Fanconi anemia, complementation group D2 | ↑ | DNA polymerase binding | DNA repair and DNA damage response | 1.15 |
| 15 | **CCN1** | Cellular Communication Network Factor 1 | ↑ | extracellular matrix binding | wound healing  matrix remodeling | 1.15 |
| 16 | **EIF4E** | eukaryotic translation initiation factor 4E | ↓ | RNA binding and translation initiation factor activity | translational initiation | -1.22 |
| 17 | **IFIT1BL11** | interferon induced protein with tetratricpeptide repeats 1B like 1 | ↓ | Interferon-induced antiviral RNA-binding protein | cellular response to type I interferon | -1.26 |
| 18 | **LRRC3** | Leucine Rich Repeat Containing 3 | ↓ | Protein binding | None by GO term | -1.28 |
| 19 | **H4C11** | H4 Clustered Histone 11 | ↓ | Core component of nucleosome | Transcription regulation, DNA repair, nucleosome remodeling | -1.29 |
| 20 | **GM10320** | SEC61 Translocon Subunit Beta | ↓ | ribosome receptor | post-translational protein targeting to membrane, translocation | -1.31 |
| 21 | **GADL1** | Glutamate Decarboxylase-Like Protein 1 | ↓ | aspartate 1-decarboxylase activity | carboxylic acid metabolic process | -1.35 |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| 22 | **DAPL1** | Death Associated Protein Like 1 | ↓ | death domain binding activity | apoptotic signaling pathway | -1.40 |
| 23 | **OMD** | Osteomodulin | ↓ | Protein binding | Cell adhesion | -1.42 |
| 24 | **ZFP185** | Zinc Finger Protein 185 With LIM Domain | ↓ | Nucleic acid-binding protein | None by GO term | -1.44 |
| 25 | **ADAT2** | Adenosine Deaminase TRNA Specific 2 | ↓ | tRNA-specific adenosine deaminase activity | tRNA processing | -1.51 |
| 26 | **LST1** | Leukocyte Specific Transcript 1 | ↓ | membrane protein | dendrite development  immune system process | -1.51 |
| 27 | **CDCA7** | Cell Division Cycle Associated 7 | ↓ | transcriptional regulator | Validated targets of c-myc transcriptional activation and apoptotic process | -1.53 |
| 28 | **PROSER3** | Proline And Serine Rich 3 | ↓ | Protein binding | None by GO term | -1.58 |
| 29 | **C1QTNF1** | Complement C1q Tumor Necrosis Factor-Related Protein 1 | ↓ | Protein binding activity | positive regulation of MAPK cascade | -1.68 |

**Supplementary Table S6.**

**The list of the commonly up and down-regulated DEGs in the spinal cord in response to the two experimental pain models used (burn injury model and inflammatory pain model)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Gene symbol** | **Gene name** | **Alteration in gene expression** | **Molecular function** | **Biological process** | **Fold-change *vs* control\*** |
| 1 | **HBA-A2** | Hemoglobin Subunit Alpha 2 | ↑ | oxygen carrier activity | [Cellular responses to stress](http://www.reactome.org/PathwayBrowser/#/R-HSA-2262752) | 2.92 / 2.94 |
| 2 | **MT-ATP6** | Mitochondrially Encoded ATP Synthase 6 | ↑ | proton-transporting ATP synthase activity | ATP biosynthetic process | 2.39 / 2.80 |
| 3 | **EGR4** | Early Growth Response 4 | ↑ | transcriptional regulator | positive regulation of transcription by RNA polymerase II | 2.36 / 1.10 |
| 4 | **DEGS2** | Delta 4-Desaturase, Sphingolipid 2 | ↑ | sphingolipid delta-4 desaturase activity  sphingosine hydroxylase activity | lipid biosynthetic process | 1.48 / 1.08 |
| 5 | **CUBN** | Cubilin | ↑ | Endocytic receptor | lipid metabolic process | 1.36 / 1.15 |
| 6 | **PRICKLE3** | Prickle Planar Cell Polarity Protein 3 | ↑ | Protein binding | mitochondrial membrane ATP synthase assembly  component of atypical Wnt-signaling | 1.23 / 1.15 |
| 7 | **SYCP2** | Synaptonemal Complex Protein 2 | ↑ | DNA binding | negative regulation of apoptotic process | 1.20 / 1.21 |
| 8 | **RPS26-PS1** | Ribosomal Protein S26 | ↑ | RNA binding | negative regulation of RNA splicing | 1.16 / 1.65 |
| 9 | **KCNA3** | Voltage-Gated Potassium Channel Protein Kv1.3 | ↑ | potassium voltage-gated channel | potassium ion transmembrane transport | 1.05 / 1.52 |
| 10 | **BTG2** | BTG Anti-Proliferation Factor 2 | ↑ | transcription corepressor activity | negative regulation of transcription by RNA polymerase II | 1.04 / 1.08 |
| 11 | **ADA** | Adenosine Deaminase | ↑ | adenosine deaminase activity | purine metabolism and in adenosine homeostasis | 1.01 / 1.12 |
| 12 | **GCH1** | GTP Cyclohydrolase 1 | ↑ | calcium ion binding and GTP binding | tetrahydrobiopterin biosynthetic process  nitric oxide biosynthetic process | 1.018 / 1.00 |
| 13 | **ALOXE3** | Arachidonate Lipoxygenase 3 | ↑ | hydroperoxide isomerase activity | Fatty acid and [arachidonic acid metabolism](http://www.reactome.org/PathwayBrowser/#/R-HSA-2142753) | 1.01 / 1.15 |
| 14 | **KIF23** | Kinesin Family Member 23 | ↑ | cytoskeletal motor activity | microtubule-based movement | 1.01 / 1.15 |
| 15 | **EXPH5** | Exophilin-5 | ↓ | Rab effector protein | intracellular vesicle trafficking, positive regulation of exocytosis | -1.03 / -1.61 |
| 16 | **HFE2** | Hemojuvelin BMP Co-Receptor | ↓ | protein binding | regulation of transcription by RNA polymerase II | -1.05 / -1.35 |
| 17 | **CK137956** | cDNA sequence CK137956 | ↓ | Unknown | None by GO term | -1.08 / -1.04 |
| 18 | **MUSTN1** | Musculoskeletal, Embryonic Nuclear Protein 1 | ↓ | unknown | positive regulation of gene expression  positive regulation of the proteoglycan biosynthetic process | -1.11 / -1.35 |
| 19 | **CBX2** | chromobox 2 | ↓ | Transcriptional repressor | negative regulation of transcription by RNA polymerase II | -1.18 / -1.26 |
| 20 | **GM5901** | predicted gene 5901 | ↓ | Unknown | None by GO term | -1.28 / -1.35 |
| 21 | **CAR15** | carbonic anhydrase 15 | ↓ | hydration of carbon dioxide | regulation of the apoptotic process | -1.82 / -1.25 |
|  |  |  |  |  |  |  |

**\*** Fold change values in burn injury and formalin treatment, respectively.