Pathological consequences of chronic olfactory inflammation on neurite morphology of olfactory bulb projection neurons

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Research

Keywords: Chronic rhinosinusitis, chronic olfactory inflammation, olfactory system, projection neurons, neurite, lipopolysaccharide

Posted Date: November 22nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1054067/v1

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Title
Pathological consequences of chronic olfactory inflammation on neurite morphology of olfactory bulb projection neurons

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ABSTRACT

Background: Chronic olfactory inflammation (COI) in conditions such as chronic rhinosinusitis significantly impairs the functional and anatomical components of the olfactory system. COI induced by intranasal administration of lipopolysaccharide (LPS) results in atrophy, gliosis, and pro-inflammatory cytokine production in the OB. Although chronic rhinosinusitis patients have smaller olfactory bulbs (OBs), the consequences of olfactory inflammation on OB neurons are largely unknown.

Methods: In this study, we investigated the neurological consequence of COI on OB projection neurons, mitral cells (MCs) and tufted cells (TCs). To induce COI, we performed unilateral intranasal administration of LPS to mice for 4 and 10 weeks. Effects of COI on the OB were examined using RNA-sequencing approaches and immunohistochemical analyses.

Results: We found that repeated LPS administration upregulated immune-related biological pathways in the OB after 4 weeks. We also determined that the length of TC lateral dendrites in the OB significantly decreased after 10 weeks of COI. The axon initial segment of TCs decreased in number and in length after 10 weeks of COI. The lateral dendrites and axon initial segments of MCs, however, were largely unaffected. In addition, dendritic arborization and axon initial segment reconstruction both took place following a 10-week recovery period.

Conclusion: Our findings suggests that olfactory inflammation specifically affects TCs and their integrated circuitry, whereas MCs are potentially protected from this condition. This data demonstrates unique characteristics of the OBs ability to undergo neuroplastic changes in response to stress.
KEY MESSAGES

- Tufted cells undergo neurite dysregulation in response to chronic olfactory inflammation, whereas mitral cells are largely unaffected.
- Tufted cells experience complete recovery from neurite dysregulation following a period of ceased inflammation.

KEY WORDS

Chronic rhinosinusitis; chronic olfactory inflammation; olfactory system; projection neurons; neurite; lipopolysaccharide
INTRODUCTION

Individuals are exposed to chemicals and environmental agents on a daily basis, some of which are capable of entering the body and inducing an immune response. Bacteria, viruses, and allergens such as dust, mold, or pollen are common agents that can enter the nasal cavity and induce inflammation of the olfactory mucosa, mucous membranes lining the olfactory epithelium (OE), and the paranasal sinuses1, 2. This inflammatory state is the foundation to the disease known as rhinosinusitis3. Rhinosinusitis is one of the most common medical conditions in the world4, currently affecting about 12.5% of individuals in the United States alone5. Symptoms of rhinosinusitis can include thick nasal mucus, stuffy nose and congestion, facial pain, headache, cough, fever, and hyposmia/anosmia6-8. Rhinosinusitis can be an acute or chronic disease9, 10, yet when the condition lasts longer than 12 weeks it is considered chronic rhinosinusitis (CRS) and is typically due to a bacterial infection4, 8, 11, 12.

Although immune responses are an essential first line of defense for the body against invading pathogens, chronic inflammation can act as a significant stressor on an organ or system and may result in damage of the affected tissue13-15. Although airflow obstruction within the nasal cavity has been linked to hyposmia, clinical studies have demonstrated that the immune response induced during CRS can severely damage the olfactory mucosa and olfactory epithelium, another major contributor to the loss of smell16-19. Patients with CRS also exhibit a decrease in the volumetric size of their olfactory bulbs (OBs)20, 21. Nonetheless, the extent to which the CRS-induced inflammatory responses affect the central nervous system (CNS) including the OB is currently not well understood.

Preclinical research using rodents has established that intranasal (i.n.) administration of various chemical entities can induce inflammation of the olfactory epithelium in the form of immune cell activation, infiltration, and pro-inflammatory cytokine release resulting in apoptosis of olfactory sensory neurons22-28. Our previous studies have also demonstrated that i.n. administration of lipopolysaccharide (LPS) has severe implications on the CNS including OB gliosis and atrophy23, 29, 30. More specifically, beginning as early as 3 weeks of i.n. LPS administrations, a significant upregulation of microglial and astrocytic activity as well as the presence of pro-inflammatory cytokines can be detected in the superficial OB layers including the olfactory nerve layer (ONL), glomerular layer (GL), and the superficial external plexiform layer (sEPL). Interestingly, after 10 weeks of administrations, OB atrophy takes place primarily in the same three superficial OB layers
in which the layers are significantly thinner than in controls\textsuperscript{29, 30}. In this study, and in conjunction with our previous studies, we administered LPS into the mouse nostril repetitively over the course of 4 and 10 weeks to induce a state of chronic inflammation of the olfactory epithelium (or chronic olfactory inflammation, COI). We report that COI induces a decrease in the activity of projection neurons residing in the EPL (tufted cells, TCs), as well as dendritic retraction and axonal instability of the same neurons. Mitral cells (MCs) residing in the mitral cell layer (MCL), however, appear to be almost entirely unaffected. Finally, we report that the COI-induced TC impairments return to homeostasis following a recovery period. These results provide further evidence that the OB consists of highly plastic components capable of undergoing severe stress.
METHODS

Animals
In this study, we used eight-week-old C57BL/6J (stock #000664) and YFP knockin (stock #006148; C57BL/6J background) mice purchased from The Jackson Laboratory, as well as Pcdh21-CreER knockin (BRC #RBRC02410; C57BL/6J background) mice purchased from Riken BRC. Pcdh21-CreER x YFP mice were created by crossing Pcdh21-CreER-positive mice with YFP homozygotes to create Cre-positive/YFP heterozygotes (+/Het mice; this was the only genotype used for this mouse line in this study). Among the +/Het mice, a yellow fluorescent protein (YFP) is specifically expressed in MC/TCs in the OBs following tamoxifen injections. All mice were deeply anesthetized with isoflurane and intranasally administered 10 μL of LPS from Escherichia coli (Sigma; product #L2880; lot #025M4040V) in physiologic saline (1 mg/ml; Sigma). LPS administrations took place three times per week for 4 or 10 weeks and were carried out unilaterally to the left naris of each mouse, with the right side serving as an internal control. For analyses of recovery, one group of eight-week-old +/Het mice (n=3) underwent unilateral 10-week LPS administrations as discussed previously and were subsequently housed for 10 weeks with no additional treatment.

Three days prior to being sacrificed for immunohistochemical analyses, mice were intraperitoneally injected with tamoxifen (30 mg/kg). The dose for tamoxifen was selected after multiple trials at different doses in order to observe optimal YFP expression in fewer OB projection neurons allowing us to trace individual neuron apical and lateral dendrites (data not shown). For histologic preparation, mice were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) and transcardially perfused with PBS, followed by 4% (wt/vol) paraformaldehyde in PBS. Heads were removed and placed in the same fixative at 4°C overnight. The rostral half of the calvaria (anterior to the bregma) and the nasal bone were then placed in 0.45 mol/L EDTA in PBS at 4°C for 2 days for decalcification, cryoprotected with 30% sucrose (wt/vol) at 4°C overnight, embedded in OCT compound (Sakura Finetek USA, Torrance, Calif), and maintained at -80°C until use. All protocols were approved by and all methods were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Penn State College of Medicine.

RNA sequencing analysis
RNA Extraction: OBs were microdissected from fixed and cryopreserved whole mouse brains. Approximately 5 mg of frozen tissue was incubated with proteinase K (500 μg/ml) in 500 μl of 10
mM NaCl, 500 mM Tris (pH 8.0), 20 mM EDTA, and 1% SDS at 55 °C for 3 hours until the tissue was completely dissolved. The acid phenol-chloroform method was applied for RNA extraction using the Direct-zol™ RNA Micro prep Kit (Zymo Research). RNA quality and quantity were determined by RNA Pico BioAnalyzer (Agilent technologies).

**RNA-sequencing and Analysis:** The cDNA libraries were prepared using the QuantSeq 3’mRNA-Seq Library Prep Kit FWD for Illumina (Lexogen) as per the manufacturer’s instructions. Briefly, total RNA was reverse transcribed using oligo (dT) primers. The second cDNA strand was synthesized by random priming, in which DNA polymerase is efficiently stopped when reaching the next hybridized random primer allowing only the fragment closest to the 3’ end being captured for later indexed adapter ligation and PCR amplification. The processed libraries were assessed for their size distribution and concentration using the BioAnalyzer High Sensitivity DNA Kit (Agilent Technologies). The libraries were pooled and diluted to 3 nM using 10 mM Tris-HCl, pH 8.5, and then denatured using the Illumina protocol. The denatured libraries were loaded onto an S1 flow cell on an Illumina NovaSeq 6000 (Illumina) and run for 53-101 cycles according to the manufacturer’s instructions. After the quality and polyA trimming by BBduk and alignment by HISAT2 (version 2.1.0), read counts were calculated using HTSeq by supplementing Ensembl gene annotation (GRCm38.78). DESeq2 R package was used to determine differentially expressed genes by taking into account a paired design where each mouse individual was compared between ipsilateral and contralateral. Significance was defined to be those with adjusted p-value < 0.1 calculated by the Benjamini-Hochberg method to control the false discovery rate (FDR). The ggplot2 R package was used for generating a heatmap. The list of differentially expressed genes was analyzed with Ingenuity Pathway Analysis (IPA). Fastq files and raw read counts generated during this study are available at GEO (GSE185945).

**Immunostaining**

Olfactory tissues were coronally cut on a cryostat into 20µm slices, mounted on slide glasses, dried and stored at −80°C until use. The sections were rehydrated with TBST (10 mmol/L Tris-HCl [pH 7.4] and 100 mmol/L NaCl with 0.3% Triton-X100 [vol/vol]), blocked with blocking buffer (5% normal donkey serum [vol/vol] in TBST) at room temperature for one hour, and incubated with primary antibodies diluted in blocking buffer overnight at 4°C. The antibodies and dilutions used in the present study are as follows: mouse anti-Ankyrin G IgG2a (NeuroMab, catalog #75-146, 1:500), chicken anti-green fluorescent protein (GFP; Abcam, catalog #ab13970, 1:1000), which also recognizes YFP, mouse anti-Calretinin (NeuroMarkers, catalog #MA5-14540, 1:400), Alexa Fluoro 488 mouse anti-Tbx21 (Biolegend, catalog #644830, 1:300), rabbit anti-Phospho-
S6 Ribosomal Protein (PS6; Cell Signaling Technology, catalog #4854S, 1:1000), rabbit anti-
Parvalbumin (Millipore Sigma, catalog #MAB1572, 1:300), and rabbit anti-Somatostatin
(ImmunoStar, catalog #20067, 1:300). For double immunostaining with fluorescence, Alexa
Fluoro 488-conjugated or 555-conjugated donkey antispecies IgGs (Thermo Fisher Scientific)
were used as secondary antibodies (1:300) and incubated on tissue sections at room temperature
for one hour. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI). The sections
were coverslipped with fluorescence mounting medium (Dako Agilent) and imaged using the
Zeiss Axio Imager M2 fluorescent microscope with an automated motorized XY stage. All images
were acquired using the same excitation light intensity, exposure time, and numerical aperture of
the objective lens.

Image analyses and morphometry
Five OB sections were stained from each mouse brain with calretinin and DAPI and divided into
each OB sublayer (including the superficial and deep EPL) to measure their area. Cells that were
positive for DAPI, Tbx21, and YFP in the MCL and EPL were defined as MCs and TCs,
respectively, and were subsequently counted to determine the numbers in their respective layers.
The area of the superficial and deep (s/d)EPL were measured separately by using Photoshop
software. The lengths of YFP-positive (YFP+) dendrites were measured in the sEPL and dEPL
separately by manual tracing in the FIJI/ImageJ software using the ROI Manager tool with the
freehand line tracer. The primary method of normalizing the dendrite data was to divide the total
length of dendrites per OB (in μm) by the number of YFP+ somata in that OB (final units in
μm/cell). Similarly, we also normalized this data with respect to dendrite density by converting the
sEPL and dEPL areas to square millimeters (mm²) and divided the total length of dendrites (in
μm) in each layer of each OB section by the respective area in mm² (resulting units of μm/mm²).
Axon initial segments (AISes) were measured in a region defined by a rectangle with an area of
650x450 μm² in both the medial and lateral portion of the OB. AISes were defined by positive
Ankyrin G staining and all AISes in the region were counted and measured in length (μm), and
were analyzed via manual tracing in the FIJI/ImageJ software using the ROI Manager tool with
the freehand line tracer.

Experimental design and statistical analysis
Comparisons of the relative OB sizes and AIS length/count among contralateral and ipsilateral
OBs were statistically analyzed by one-way analysis of variance followed by Tukey’s HSD post-
hoc tests for multiple comparisons. Comparisons of dendrite length among contralateral and
ipsilateral OBs were statistically analyzed by paired t-tests due to differences in inherent cre-recombination and subsequent expression of YFP. A p-value ≤ 0.05 indicated a significant difference. Statistical analyses were performed using Prism software (GraphPad Software, Inc.). Values are reported as means ± SEM.
RESULTS

Upregulation of interferon-γ-driven inflammatory pathways following 4-week COI

We first aimed to examine gene expression signatures affected by early stage COI. To induce COI, LPS administrations took place three times per week for 4 weeks and were carried out unilaterally to the left naris of each mouse, with the right side serving as an internal control. The OB ipsilateral to the side of the injected naris is referred to as ipsilateral (ipsi), and the opposite OB (control) as contralateral (contra). Differential gene expression analysis was performed between the ipsilateral and contralateral OB from mice administered LPS (n=3). We identified 47 genes upregulated and 18 downregulated in the ipsilateral OBs compared to contralateral OBs (Fig. 1A). To understand the functional relevance of these clusters, we performed functional annotation analysis for these genes using Ingenuity Pathway Analysis (IPA, Qiagen). The Core Analysis highlighted the most significantly enriched and activated Canonical Pathway as “Neuroinflammation Signaling Pathway” (-log(p-value) = 5.95, z-score = 2.646, Fig. 1B). Molecules directly involved in this pathway include B2M, CCL5, CYBB, HLA-A, HLA-DQA1, HLA-DQB1, HLA-DRB5, and RAC2.

Next, we examined the upstream regulator in the IPA Core Analysis and identified interferon-γ (IFN-γ) as the most significant upstream regulator with the largest z-score (p-value = 5.04E-20, z-score = 4.749, Supplementary Table 1). Although the expression level of IFN-γ itself is not altered, the significant number of related downstream molecules including B2M, Bst2, C1QA, C1QB, C4A/C4B, CCL5, CD74, CTSS, Cxcl9, CYBB, GBP2, GFAP, HLA-A, HLA-DQA1, HLA-DQB1, HLA-DRB5, Ifi47, IFITM3, Igtp, Iigp1, IRF1, IRF8, LGALS3BP, PARP14, PENK, RAC2, TAP1, and TAPBP are upregulated. The Mechanistic Network (Fig. 1C), a method to predict signaling cascades that connect other significantly represented upstream regulators to elicit the observed gene expression changes, demonstrated that IFN-γ may orchestrate with other cytokines such as TNF-α and IL-1β and regulate cascades of intracellular signaling to lead to activations of multiple transcription regulators such as IRF1, NF-kB complex, CREBBP, RELA, IRF8, STAT1, and STAT3. NR3C1, on the other hand, is downregulated and its inhibition is predicted to be mediated by TNF-α.

Finally, we summarize our findings by IPA’s Graphical Summary (Fig. 1D) to provide an overview of the major biological themes in the IPA analysis by selecting the most significant entities identified in the Core Analysis such as Canonical Pathways, Upstream Regulators, and Disease
and Biological Functions, further representing how they relate to each other. The Graphical Summary demonstrates how upregulated/activated (shown in orange) and downregulated/inhibited (shown in blue) genes, pathways, or diseases interact with each other. In addition to the activation of Neuroinflammation Signaling Pathway observed in the Canonical Pathway analysis (Fig. 1B) and IFN-γ which was depicted in the Upstream Regulator analysis (Fig. 1C), we revealed that many pathways associated with immune responses and leukocyte activities are activated, while infectious status is predicted to be inhibited.

**Reduction of tufted cell lateral dendrites following 10-week COI**

The presence of proinflammatory cytokines such as IFN-γ and TNF-α are capable of causing dendritic atrophy, retraction, and loss of synapses in primary neuronal cultures. It is important to note that LPS-induced COI does not cause the death of OB projection neurons (MCs/TCs) at any point up to the 24-week time point. Therefore, we aimed to explore the potential phenomenon of dendritic retraction of MC/TCs following our COI paradigm.

The distribution of projection neuron somata and lateral dendrites is unique based on cell type. TC somata are located in the EPL and extend their lateral dendrites throughout the sEPL, whereas MC somata exist in the MCL and extend their lateral dendrites in the dEPL. In order to observe changes to the somata and dendritic morphology of MCs/TCs in the OB, we used Pcdh21-CreER x YFP (+/Het) transgenic mice unilaterally administered with LPS (i.n.) for 10 weeks. Protocadherin-21 (Pcdh21) is a member of the protocadherin homophilic cell-adhesion protein family uniquely expressed in MCs/TCs in the mouse OB. On the final LPS-administration day, the mice were treated with tamoxifen (i.p., 30 mg/kg) to activate CreER for the YFP expression from the ROSA site and sacrificed 3 days after the injection.

As expected, the overall shape of the ipsilateral OB appears to be atrophied and narrower compared to the contralateral OB (Fig. 2A). Cell bodies and dendrites expressing YFP were observed in the GL, EPL, and MCL of both OBs (Fig. 2B, C). There were no differences in the total number of TCs, YFP+ cells in the EPL, counted from 5 coronal OB sections (contra., 72.00 ± 17.58 vs ipsi., 72.67 ± 21.39). The number of MCs, YFP+ cells in the MCL, was smaller than that of TCs but not significantly different comparing the contralateral to the ipsilateral OBs (contra., 23.67 ± 12.86 vs ipsi., 29.00 ± 16.92). This data suggests that the +/-Het transgenic model preferentially labels TCs over MCs in the OB, and LPS treatment does not influence the expression of YFP in OB projection neurons.
Next, we analyzed the YFP+ dendrites in the EPL. In the contralateral OB, the total length of YFP+ dendrites counted from 5 coronal sections was significantly greater in the sEPL than in the dEPL (Fig. 2B; 15217 ± 1332 μm vs 7421 ± 1905 μm, respectively; p=0.0014). However, the length of YFP+ dendrites in the ipsilateral OB was not statistically different between sEPL and dEPL (Fig. 2C; 10095 ± 1470 μm vs 7327 ± 1588 μm, respectively; p=0.2210). The total length of YFP+ dendrites in the sEPL was significantly reduced in the ipsilateral OB compared to that of contralateral OBs (p=0.0178). However, the densities of YFP+ dendrites were not significantly different in the sEPL (p=0.7458) nor in the dEPL (p=0.9751) between contralateral and ipsilateral OBs, which is consistent with the area reduction of the sEPL but not dEPL in the ipsilateral OB.

In order to normalize the effects of COI on the dendrites of MCs and TCs, we calculated ratios of YFP+ dendrites (length in μm) to YFP+ cell bodies measured in each OB (μm/cell). This allows us to normalize for variability in our data that may exist due to animal differences in CreER expression. Upon analysis, we observed a significant reduction of dendrites in the sEPL (Fig. 2D; contra., 223.1 ± 74.70 μm/cell vs ipsi., 152.4 ± 69.77 μm/cell; p=0.0073). However, we did not observe any changes to dendrite density in the dEPL (Fig. 2E; contra., 382.5 ± 190.6 μm/cell vs ipsi., 345.2 ± 244.4 μm/cell; p=0.3594). These results suggest that the overall length of TC, but not MC, dendrites has been reduced.

Alterations in the axon initial segment of tufted cells following 10-week COI

Our findings of decreased TC dendrites have led us to believe that there may be further physiological impairments to TCs following COI. The AIS is the site of a neuron that separates its somatodendritic and axonal compartments, and is primarily responsible for maintaining the neuron’s polarity and initiating action potentials. One of the most essential components of the AIS is the cytoskeletal-associated protein, Ankyrin-G (AnkG). Previous studies have shown that shorter or fewer AISes measured by AnkG are indicative of impairments to the neurons physiology, such as a decrease in excitability. We first co-stained OB sections with AnkG and Tbx21, an OB projection neuron-specific marker, and confirmed that the vast majority of AnkG+ AISes present in the EPL and MCL are derived from TCs and MCs, respectively (Supplementary Fig. 1).
We, then, measured the length of each individual AIS, as well as the number in each OB. Since our previous studies primarily investigated the response of LPS-treatment on the medial and lateral OBs, we chose to focus on these regions as well. Through this analysis, we observed a significant reduction in the number of AISes in the ipsilateral OB EPL (Fig. 3A, B). Our data demonstrated that fewer AISes were present in the lateral EPL of the ipsilateral OB (Fig. 3B2). The number of AISes in the lateral OB EPL decreased from $165.6 \pm 47.45$ AISes in the contralateral OB to $94.20 \pm 29.24$ in the ipsilateral OB (Fig. 3F histogram; $p=0.0175$). This phenomenon, however, was not found in the medial OB EPL (Fig. 3E histogram; contra., $165.4 \pm 26.47$ vs ipsi., $130.8 \pm 24.81$; $p=0.3829$). For both OBs, there were no differences in the number of MCL AISes counted, regardless of laterality (Fig. 3C, D histograms; medial contra., $119.2 \pm 12.76$; lateral contra., $122.6 \pm 23.09$; medial ipsi., $120.2 \pm 16.25$; lateral ipsi., $120.6 \pm 24.17$).

We further analyzed the length of the AISes that were present in each OB. Since TCs reside solely in the EPL and MCs in the MCL, we have classified the AISes measured in the EPL as belonging primarily to TCs and AISes in the MCL as those of MCs. It was determined that the TC AISes in the lateral OB significantly decreased in their length (Fig. 3F; contra., $12.05 \pm 1.079 \mu m$ vs ipsi., $9.399 \pm 1.100 \mu m$; $p=0.0009$). This phenomenon was not found for the TC AISes in the medial OB (Fig. 3E; contra., $14.84 \pm 0.6815 \mu m$ vs ipsi., $13.58 \pm 0.3369 \mu m$; $p=0.1370$). Although there was no change in the number of MC AISes in the medial OB, it did appear that the AISes present in the medial region of the OB significantly decreased in length (Fig. 3C; contra., $21.88 \pm 4.978 \mu m$ vs ipsi., $19.49 \pm 4.964 \mu m$; $p=0.0006$). However, the length of MC AISes in the lateral OB did not appear to shorten (Fig. 3D; contra., $15.84 \pm 0.7814 \mu m$ vs ipsi., $16.29 \pm 0.8635 \mu m$; $p=0.7684$). Collectively, these results suggest that COI has the most significant effect on TCs morphologically and physiologically in the lateral OB.

**Reduction in tufted cell activity following 10-week COI**

To examine the alterations in cellular activity of the OB projection neurons, we stained OBs with an antibody against phoso-S6 ribosomal protein (pS6), one of neuronal activity markers. A recent study demonstrated that pS6 is an exceptional activity marker for OB projection neurons, and that naris occlusion is capable of significantly reducing the expression of pS6 among projection neurons on the ipsilateral OB. It is also worth noting that the vast majority of pS6-expressing projection neuron somata were double-positive for Tbx21 (Supplementary Fig. 2). Upon immunohistochemical analysis of mice that underwent the 10-week unilateral COI paradigm, we observed robust pS6 staining throughout the entire MCL and EPL of the
contralateral OB (Fig. 4). In contrast, we observed fewer pS6-positive projection neuron somata throughout the EPL in the ipsilateral OB. The MCL, however, did not appear to have any reduction in pS6 signal (Fig. 4B, C). These findings further suggest that functional impairments may be occurring to TCs rather than MCs throughout the ipsilateral OB.

No apparent loss of OB interneurons following 10-week COI

Olfactory information is not only processed by OB projection neurons, but requires substantial communication with a variety of OB interneurons. Based on their location in the OB, interneurons play a major role in fine-tuning of olfactory information before it even reaches the cortex. OB interneurons can also be further differentiated by their immunoreactivity\(^ {37} \). For example, the parvalbumin-positive (PV+) and somatostatin-positive (SST+) interneurons are found in the EPL and are distributed primarily throughout the sEPL and dEPL, respectively\(^ {37, 44-46} \). Here, we investigated whether the effects of COI on TCs would extend to interneurons residing throughout the sEPL and dEPL. Figure 5 shows PV+ and SST+ interneurons in the sEPL and dEPL of the contralateral and ipsilateral OBs following the 10-week COI paradigm. To quantify the effects of COI on these interneurons, we counted the numbers from 5 coronal sections (n=5 mice). Consistent with previous literature, there were more PV+ interneurons in the sEPL than in the dEPL of the contralateral OB (333.0 ± 29.04 vs 256.0 ± 30.55, respectively; \( p=0.0037 \)\( ^{40} \)). However, the number of PV+ interneurons in each EPL sublayer of the ipsilateral OB was not significantly different from that of the contralateral OB (Fig. 5A, B; sEPL: contra., 333.0 ± 29.04 vs ipsi., 298.8 ± 33.91, \( p=0.2874 \); dEPL: contra., 274.0 ± 22.15 vs ipsi., 256.0 ± 30.55, \( p=0.7660 \)). Similarly, as SST+ interneurons are not present in the sEPL\(^ {47} \), we counted only from the dEPL. No differences were observed in the number of SST+ interneurons following 10-week COI (Fig. 5C, D; contra., 167.4 ± 16.83 vs ipsi., 169.4 ± 12.64; \( p=0.3859 \)). Collectively, this data suggests that there is no change in the number of PV+ or SST+ interneurons in the OB following the 10-week COI paradigm.

Remodeling of tufted cell lateral dendrites after recovery period following 10-week COI

Our previous studies demonstrated that a 10-week period of no LPS treatment following the 10-week COI paradigm resulted in a recovery of the OB atrophy and depletion of inflammatory responses\(^ {30} \). Therefore, we sought to investigate if the recovery phenomenon would extend to the OB on a cellular level. For this experiment, we used male +/Het mice (n=3) treated with LPS for 10 weeks followed by a 10-week recover period of no treatment. We first investigated if TC lateral dendrites recover from their reduction caused by COI.
Consistent with our previous studies, the overall shape of the ipsilateral OB appears to undergo a complete recovery. We counted the total number of YFP+ cells in the EPL of the contralateral and ipsilateral OBs and observed more YFP+ TC soma in the ipsilateral OB compared to the contralateral (contra., $64.00 \pm 15.52$ vs ipsi., $79.00 \pm 14.42$; $p=0.0131$). The number of YFP+ MCs, however, was not significantly different (contra., $16.00 \pm 6.083$ vs ipsi., $17.33 \pm 1.528$; $p=0.6667$). To compensate the difference in the numbers of labeled YFP+ cells, the total number of YFP+ dendrites in the sEPL and dEPL were divided by the total number of YFP+ TCs and MCs, respectively. Surprisingly, even after this normalization, we still observed a slightly significant increase of dendrites in the ipsilateral sEPL compared to contralateral (Fig. 6D; contra., $202.1 \pm 41.38 \mu m/cell$ vs ipsi., $222.8 \pm 37.70 \mu m/cell$; $p=0.0357$). We did not observe any changes to dendrite length in the dEPL (Fig. 6E; contra., $294.0 \pm 88.64 \mu m/cell$ vs ipsi., $340.6 \pm 101.2 \mu m/cell$; $p=0.1139$). Thus, our results suggest that the overall length of TC dendrites has not only recovered, but the TCs may have more dendrites in the ipsilateral OB following the 10-week recovery period.

Stabilization of tufted cell activity and axon initial segment integrity after recovery period following 10-week COI

Lastly, we investigated the effect of a recovery period on the integrity of the AIS of MCs and TCs following COI. We performed the same analysis as previously stated, and observed no significant differences between the ipsilateral and contralateral OBs in either the length or number of AISes for both MCs and TCs (Fig. 7). These results indicate that no apparent “over-recovery” phenomenon occurs with respect to TC AIS integrity. Combined with our previous findings, these results suggest that the TC AISes in the lateral OB that are damaged following COI are capable of returning back to appropriate lengths, essentially re-stabilizing, allowing for a restoration in the transfer of OB information. Consistent with this observation, there was no apparent reduction of the pS6 expression in the EPL of the ipsilateral OB in mice who underwent the 10-week COI paradigm followed by a 10-week recovery period of no treatment (Fig. 8). These results suggest that a functional recovery of TCs occurs after a sufficient period without exposure to LPS.
In this study, we found that COI induced by i.n. administration of LPS causes dendritic retraction and axonal instability of TCs, but not MCs, in the mouse OB. The superficial OB layers (GL, ONL, sEPL) are the primary region of OB atrophy and inflammation at 10 weeks of LPS administrations\textsuperscript{29, 30}. Our results suggest that the reduction of dendrites that was observed in the ipsilateral OB is primarily attributed to a reduction in the sEPL. Similarly, the shortening and loss of AISes takes place primarily in the lateral EPL of the ipsilateral OB, a region that has been proven to be most susceptible to COI at this time point.

The signaling cascades downstream of proinflammatory cytokines such as IFN-\(\gamma\) and TNF-\(\alpha\) has been demonstrated to occur in the OB as early as at 4 weeks of i.n. LPS administrations. These cytokines are capable of inducing the retraction of neuronal dendrites and synaptic degradation in primary neuronal cultures\textsuperscript{36}. We anticipate that a similar phenomenon is taking place in our current paradigm in which the presence of proinflammatory cytokines and activated glial cells among the superficial OB layers induce neuronal stress and subsequent structural dysregulation. Our previous study, however, demonstrated that cessation of COI results in a reduction of immune responses in the OB. This suggests that anti-inflammatory mechanisms may take place following the absence of persistent inflammation. Microglia and astrocytes are well established to engage in both pro- and anti-inflammatory activities\textsuperscript{48-50}. Our research thus far has established that signaling cascades activated by cytokines such as TNF-\(\alpha\), IFN-\(\gamma\), IL-1\(\beta\), and IL-10 are significantly upregulated in the OB following COI. Although the former three are pro-inflammatory, IL-10 is an anti-inflammatory cytokine released by astrocytes which may act to maintain (or restore) neuronal homeostasis\textsuperscript{51, 52}. The release of IL-10 and other neuroprotective agents may be a necessary step in evading, or recovering from, potential TC degeneration. Similarly, astrocytes and microglia are capable of mediating and amplifying axonal and dendrite growth through mechanisms including the release of fibroblast growth factor and purinergic signaling, respectively\textsuperscript{53-56}. The present study demonstrating a recovery effect of the observed TC dendritic retraction may be attributed to similar neuroprotective mechanisms via glial cell activity.

Our findings of reduced TC AIS number and length is highly suggestive of functional impairments to TC-integrated neural circuits. AISes are responsible for action potential initiation and maintenance of neuronal polarity\textsuperscript{39, 57}. The actual assembly of the AIS is coordinated primarily by AnkG, a cytoskeletal-associated protein\textsuperscript{40, 58}. It remains unknown whether the mechanisms of AIS...
maintenance and AIS assembly (or reassembly) as controlled by AnkG are related. However, we speculate that the ability of TCs to reconstruct their AISes in the recovery period following COI is possibly also coordinated by AnkG-mediated mechanisms. Nonetheless, dysfunctional AISes induced by diminished AnkG integrity will likely contribute to a decrease in excitability and signal transmission to a neuron’s downstream targets. It is also interesting to note that AnkG is necessary to maintain the structural and functional segregation of a neuron’s axon from its dendrites. These implications suggest a potential biological connection between axon destabilization and dendritic retraction in our COI paradigm.

All of our sensory systems are comprised of first-, second-, and third-order neurons which uniquely relay sensory information to the CNS at each level. Therefore, it is plausible to assert that damage to the neural components at any of these levels will impair sensory processing in the CNS. Multiple clinical studies reported cortical atrophy and altered brain activity in response to spinal cord injury. Similarly, clinical studies investigating the role of diabetic retinopathy on CNS have found remapping and impairments of the primary visual cortex following disease onset. This phenomenon, however, has yet to be thoroughly investigated with respect to the olfactory system. COI causes ablation to the first-order neurons of the olfactory system, olfactory sensory neurons, which can occur after only one day of i.n. LPS administration, and this phenotype will persist for the duration of COI. Our current findings which model CRS suggest that olfactory information processing and transmission at the level of the second-order neurons (specifically, TCs) may be disrupted due to structural and functional pathophysiology. While the olfactory second-order neurons (MCs/TCs) share a multitude of features, they differ in two distinct ways, anatomically; (1) somata location within the OB, and (2) neurite projection patterns. MCs project their axons to most structures within the olfactory cortex (OC), whereas TC axons are more localized to targets including the anterior olfactory nucleus, olfactory tubercle, and anterior piriform cortex. When drawing comparisons to other sensory systems, this information leads us to speculate that the differences in axonal projection patterns of MCs and TCs may also be a component of the olfactory system impacted by the pathophysiological nature of COI. More specifically, the third-order neurons of the olfactory system residing in the TC-targeted OC regions may also be impacted by COI in the form of cortical atrophy or even immune responses. Further studies are needed to address whether these OC regions are also susceptible to the neuropathological effects of COI.
CONCLUSIONS

In conclusion, the findings presented in this report demonstrate that TCs undergo significant neurite dysregulation following COI primarily in the forms of lateral dendrite retraction and AIS shortening, whereas MCs, as well as PV+ and SST+ interneurons, are largely unaffected. Our study also suggests that the mechanisms underlying neurite dysregulation are induced through common pathways involving the pro-inflammatory cytokine, IFN-γ. Furthermore, the pathological responses of TCs to COI was shown to recover following a period without olfactory inflammation. In summary, this study provides a strong foundation for investigating the cellular and molecular mechanisms responsible for regulating the reversible changes occurring in TC-integrated OB neural circuits. Overall, we have revealed some of the major consequences of inflammation on the homeostatic functioning of olfactory bulb projection neurons, as well as unveiled a novel pathway of neuroinflammation from the periphery to the CNS. Developing a deeper understanding of the biological mechanisms underlying CRS and the consequences of inflammation-induced hyposmia is a vital next step to the overarching goal of enhancing human health.

ABBREVIATIONS

AIS: axon initial segment; AnkG: Ankyrin G; CNS: central nervous system; COI: chronic olfactory inflammation; CRS: chronic rhinosinusitis; dEPL: deep external plexiform layer; EPL: external plexiform layer; GL: glomerular layer; i.n.: intranasal; IFN-γ: interferon-γ; LPS: lipopolysaccharide; MC: mitral cell; MCL: mitral cell layer; OB: olfactory bulb; OC: olfactory cortex; OE: olfactory epithelium; ONL: olfactory nerve layer; Pcdh21: protocadherin-21; pS6: phoso-S6 ribosomal protein; PV: parvalbumin; sEPL: superficial external plexiform layer; SST: somatostatin; TC: tufted cell; YFP: yellow fluorescent protein.
DECLARATIONS

Ethics approval and consent to participate
All protocols were approved by and all methods were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee of Penn State College of Medicine.

Consent for publication
Not applicable.

Availability of data and material
The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests
The authors declare no competing interests.

Funding Source
The present study was supported by NIH grant R01DC016307 (F.I).

Authors contributions
B.J.L. and F.I. designed research; B.J.L., Y.I., and A.I. performed research; B.J.L., Y.K., and F.I. analyzed data; B.J.L., Y.K., and F.I. wrote the paper.

Acknowledgement
This work was supported by NIH grant R01DC016307 (F.I.). We thank Dr. Andras Hajnal for critical reading of this manuscript.
FIGURE LEGENDS

Figure 1: Differentially expressed genes in the OB following 4-week COI.
(A) Heatmap of differentially expressed genes. (B) Most significant Canonical Pathways of differentially expressed genes. (C) Mechanistic Network of the most significantly activated Upstream Regulator, IFN-γ. (D) Graphical summary of differentially expressed genes illustrated with their subcellular localizations. Each entity has passed a fisher’s exact test p-value cut-off of 0.05 and absolute z-score cut-off of 2 or greater. In panels (B-D), orange represents upregulated genes or activated pathways, where blue represents downregulated genes or inhibited pathways. Details for shapes of nodes and colors or patterns of lines can be found in the IPA’s website (https://qiagen.secure.force.com/KnowledgeBase/articles/Basic_Technical_Q_A/Legend).

Figure 2. Reduction of tufted cell lateral dendrites following 10-week COI.
(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. The Pcdh21-CreER x YFP transgenic mouse model (+/Het) preferentially labels TCs and their lateral dendrites compared to MCs. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites decreased significantly in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: **p < 0.01 compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 3. Reduction and shortening of tufted cell axon initial segments following 10-week COI.
(A, B) Coronal sections of the OBs stained for Ankyrin G and DAPI. Axon initial segments of TCs and MCs exist in the EPL and MCL, respectively. (A) Enlarged views of the medial (A1) and lateral (A2) contralateral OB. (B) Enlarged views of the medial (B1) and lateral (B2) contralateral OB. (C-F) Histograms show the frequency of axon initial segments at various lengths from five coronal OB sections for each mouse (n=5). Graphs show differences in the average length of AIS length comparing the contralateral to ipsilateral OB. Data are shown as mean ± SEM. There were no differences in the number of MC AISes counted in either the medial (C; histogram) or lateral OBs (D; histogram). MC AISes in the medial OB appeared to have shortened in length (C; graph),
whereas those in the lateral OB did not change in length (D; graph). There were no differences in the number of TC AISes counted in medial OB (E; histogram). The TC AISes in the lateral OB were the only AISes to significantly decrease in number (F; histogram). TC AISes in the medial OB did not change in length (E; graph), whereas those in the lateral OB significantly decreased (F; graph). Data in C-F were analyzed by one-way analysis of variance followed by Tukey’s HSD post-hoc tests for multiple comparisons: *p < 0.05, ***p < 0.001 compared to contralateral OB (control). Scale bars, 100 μm.

Figure 4. Reduced cellular activity of the OB following 10-week COI.
(A) Coronal sections of the OB stained with pS6 and DAPI. TCs express less pS6 in the ipsilateral OB compared to the contralateral OB following 10-week COI, whereas MCs are unaffected. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μm (A), and 100 μm (B, C).

Figure 5. No changes in the number of OB interneurons following 10-week COI.
(A, B) Coronal sections of the OBs stained for PV and DAPI. More PV+ interneurons exist in the sEPL than in the dEPL of the untreated OB. However, the number of PV+ interneurons in each EPL sublayer of the ipsilateral OB was not significantly different from that of the contralateral OB. (C, D) Coronal sections of the OBs stained for SST and DAPI. There were no differences in the number of SST+ interneurons in the dEPL between the contralateral and ipsilateral OBs. Data in C-F were analyzed by one-way analysis of variance followed by Tukey’s HSD post-hoc tests for multiple comparisons. Scale bars, 100 μm.

Figure 6. 10-week recovery period restores tufted cell lateral dendrites following 10-week COI.
(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites were greater in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: *p < 0.05 compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).
Figure 7. 10-week recovery period restores tufted cell axon initial segments following 10-week COI.

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Figure 8. 10-week recovery period restores cellular activity of the OB following 10-week COI.

(A) Coronal sections of the OB stained with pS6 and DAPI. The expression of pS6 among TCs has recovered in the ipsilateral OB after the 10-week recovery period following 10-week COI. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μm (A), and 100 μm (B, C).

Supplementary Figure 1.
Labelling of the AIS using AnkG preferentially occurs in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.

Supplementary Figure 2.
Using pS6 as a marker for OB projection neuron cellular activity was demonstrated to occur in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.
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(A) Heatmap of differentially expressed genes. (B) Most significant Canonical Pathways of differentially expressed genes. (C) Mechanistic Network of the most significantly activated Upstream Regulator, IFN-γ. (D) Graphical summary of differentially expressed genes illustrated with their subcellular localizations. Each entity has passed a fisher's exact test p-value cut-off of 0.05 and absolute z-score cut-off of 2 or greater. In panels (B-D), orange represents upregulated genes or activated pathways, where blue represents downregulated genes or inhibited pathways. Details for shapes of nodes and colors or patterns of lines can be found in the IPA's website (https://qiagen.secure.force.com/KnowledgeBase/articles/Basic_Technical_Q_A/Legend).
Figure 2. Reduction of tufted cell lateral dendrites following 10-week COI.

(A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. The Pcdh21-CreER x YFP transgenic mouse model (+/+Het) preferentially labels TCs and their lateral dendrites compared to MCs. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites decreased significantly in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: *p < 0.01 compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).
Figure 3. Reduction and shortening of tufted cell axon initial segments following 10-week COI.

(A, B) Coronal sections of the OBs stained for Ankyrin G and DAPI. Axon initial segments of TCs and MCs exist in the EPL and MCL, respectively. (A) Enlarged views of the medial (A1) and lateral (A2) contralateral OB. (B) Enlarged views of the medial (B1) and lateral (B2) contralateral OB. (C-F) Histograms show the frequency of axon initial segments at various lengths from five coronal OB sections for each mouse (n=5). Graphs show differences in the average length of AIS length comparing the contralateral to ipsilateral OB. Data are shown as mean ± SEM. There were no differences in the number of MC AISes counted in either the medial (C; histogram) or lateral OBs (D; histogram). MC AISes in the medial OB appeared to have shortened in length (C; graph), whereas those in the lateral OB did not change in length (D; graph). There were no differences in the number of TC AISes counted in medial OB (E; histogram). The TC AISes in the lateral OB were the only AISes to significantly decrease in number (F; histogram). TC AISes in the medial OB did not change in length (E; graph), whereas those in the lateral OB significantly decreased (F; graph). Data in C-F were analyzed by one-way analysis of variance followed by Tukey’s HSD post-hoc tests for multiple comparisons: *p < 0.05, ***p < 0.001 compared to contralateral OB (control). Scale bars, 100 μm.
Figure 4. Reduced cellular activity of the OB following 10-week COI.
(A) Coronal sections of the OB stained with pS6 and DAPI. TCs express less pS6 in the ipsilateral OB compared to the contralateral OB following 10-week COI, whereas MCs are unaffected. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μm (A), and 100 μm (B, C).
Figure 5. No changes in the number of OB interneurons following 10-week COI.

(A, B) Coronal sections of the OBs stained for PV and DAPI. More PV+ interneurons exist in the sEPL than in the dEPL of the untreated OB. However, the number of PV+ interneurons in each EPL sublayer of the ipsilateral OB was not significantly different from that of the contralateral OB. (C, D) Coronal sections of the OBs stained for SST and DAPI. There were no differences in the number of SST+ interneurons in the dEPL between the contralateral and ipsilateral OBs. Data in C-F were analyzed by one-way analysis of variance followed by Tukey’s HSD post-hoc tests for multiple comparisons. Scale bars, 100 μm.
Figure 6. 10-week recovery period restores tufted cell lateral dendrites following 10-week COI. (A) Coronal section of the OBs stained for YFP, calretinin, and DAPI. Calretinin is used to delineate between the superficial and deep EPL, where the lateral dendrites of TCs and MCs exist, respectively. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. (D, E) Graphs show the densities of lateral dendrites for TCs (D) and MCs (E) in μm of dendrites per cell. Dendrite densities of TC lateral dendrites were greater in the ipsilateral OB compared to contralateral. There were no changes in the densities of MC lateral dendrites. Individual data are plotted, and the means are shown as bars. Data in D and E were analyzed with a paired t-test: *p < 0.05 compared to contralateral OB (control). Scale bars, 500 μm (A), and 100 μm (B, C).
Figure 7. 10-week recovery period restores tufted cell axon initial segments following 10-week COI.

(A, B) Coronal sections of the OBs stained for Ankyrin G and DAPI. Axon initial segments of TCs and MCs exist in the EPL and MCL, respectively. (A) Enlarged views of the medial (A1) and lateral (A2) contralateral OB. (B) Enlarged views of the medial (B1) and lateral (B2) contralateral OB. (C-F) Histograms show the frequency of axon initial segments at various lengths from five coronal OB sections for each mouse (n=5). Graphs show differences in the average length of AIS length comparing the contralateral to ipsilateral OB. Data are shown as mean ± SEM. There were no differences in the number of MC AISs counted in either the medial (C; histogram) or lateral (D; histogram) OBs. No differences were observed in the lengths of MC AISs in either the medial (C; graph) nor lateral (D; graph) OBs. There were also no differences in the number of TC AISs counted in medial (E; histogram) or lateral (F; histogram) OBs. TC AISs in the medial OB did not change in length (E; graph), nor did those in the lateral OB (F; graph). Data in C-F were analyzed by one-way analysis of variance followed by Tukey's HSD post-hoc tests for multiple comparisons. Scale bars, 100 µm.
Figure 8. 10-week recovery period restores cellular activity of the OB following 10-week COI.

(A) Coronal sections of the OB stained with pS6 and DAPI. The expression of pS6 among TCs has recovered in the ipsilateral OB after the 10-week recovery period following 10-week COI. (B) Enlarged view of the medial (B1) and lateral (B2) contralateral OB. (C) Enlarged view of the medial (C1) and lateral (C2) ipsilateral OB. Scale bars, 500 μm (A), and 100 μm (B, C).
Supplementary Figure 1.
Labelling of the AIS using AnkG preferentially occurs in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.
Supplementary Figure 2.
Using pS6 as a marker for OB projection neuron cellular activity was demonstrated to occur in conjunction with somata expressing Tbx21 both in the MCL and EPL in untreated mice.
| Upstream Regulator | Expr Fold Change | Molecule Type | Predicted Activation State | Activation z-score | Flags | p-value of overlap | Target Molecules in Dataset | Mechanistic Network |
|-------------------|-----------------|--------------|---------------------------|--------------------|-------|-------------------|---------------------------|---------------------|
| KDM1A             | 0.088           | enzyme       |                           |                    |       |                  |                           |                     |
| IFNG              |                 | cytokine     | Activated                 | 4.749              |       |                  |                           |                     |
| STAT1             | 1.108           | transcription regulator | Activated               | 2.826              | bias  | 9.4E-20           |                           |                     |
| Ifnar             |                 | group        | Activated                 | 3.576              |       | 3.16E-19          |                           |                     |
| MAPT              |                 | other        |                           |                    |       |                  |                           |                     |
| DYSF              | 0.984           | other        |                           |                    |       |                  |                           |                     |
| SIRT1             | 0.155           | transcription regulator | Inhibited             | -3.45              |       | 2.18E-19          |                           |                     |
| ZBTB10            | 0.096           | other        | Activated                 | 3.17              | bias  | 4.19E-13          |                           |                     |
| Interferon alpha  |                 | group        | Activated                 | 3.573              |       | 8.51E-13          |                           |                     |
| STAT3             | 0.016           | transcription regulator |                     | 0.931              |       | 1.15E-12          |                           |                     |
| IL4               |                | cytokine     |                           |                    |       |                  |                           |                     |
| IRF1              |                 | transcription regulator | Activated             | 2.223              |       | 9.62E-12          |                           |                     |
| SNCA              | 0.514           | enzyme       | Activated                 | 3.138              |       | 3.06E-12          |                           |                     |
| QKI               | 0.205           | other        |                           | 1.941              |       | 4.35E-12          |                           |                     |
| IL27              | 0.759           | cytokine     | Activated                 | 2.609              |       | 6.25E-12          |                           |                     |
| ELAVL1            |                 | other        | Activated                 | 2.985              |       | 7.53E-12          |                           |                     |
| PKC3G             | 2.644           | kinase       | Inhibited                 | -2.813             |       | 1.03E-11          |                           |                     |
| JAK1/2            |                 | group        | Activated                 | 2.528              |       | 1.54E-11          |                           |                     |
| STAT6             | 1.324           | transcription regulator | Inhibited             | -2.487             |       | 1.68E-11          |                           |                     |
| TRIM24            | 0.301           | transcription regulator | Inhibited             | -2.343             | bias  | 1.85E-11          |                           |                     |
| lipopolysaccharide|                 | chemical drug | Activated             | 4.2                |       | 3.94E-11          |                           |                     |
| IRF9              | 0.077           | transcription regulator |                     | -0.277             |       | 7.35E-11          |                           |                     |
| SLC3A3            |                 | ion channel  |                           |                    |       |                  |                           |                     |
| nosine            |                 | chemical - endogenous mammalian |                     | 2.646              |       | 8.48E-11          |                           |                     |
| IRF3              | 0.052           | transcription regulator |                     | 3.1                |       | 1.96E-10          |                           |                     |
| IL6               |                 | cytokine     | Activated                 | 2.93               |       | 2.12E-10          |                           |                     |
| poly rI:rC-RNA    |                 | biologic drug | Activated             | 3.648              |       | 2.86E-10          |                           |                     |
| CiliTA            | 1.944           | transmembrane receptor | Activated            | 2.149              |       | 5.38E-10          |                           |                     |
| IL1B              | 0.77            | cytokine     | Activated                 | 2.654              |       | 1.5E-09           |                           |                     |
| Immunoglobulin    |                 | complex      |                           | 0.858              |       | 3.02E-09          |                           |                     |
| NRAS              | 0.378           | enzyme       | Inhibited                 | -2.03              |       | 4.29E-09          |                           |                     |
| INFg               | 0.301           | transcription regulator |                     | 0.933              |       | 6.13E-09          |                           |                     |
| Tigm1             | 1.289           | other        | Inhibited                 | -2.588             |       | 7.97E-09          |                           |                     |
| Compound             | Chemical Drug/Regulator Type | Regulation Type | Beta-score | p-value   |
|----------------------|-----------------------------|----------------|-----------|-----------|
| EB3                  | cytokine                    | Activated      | 2.425     | 1.05E-08  |
| B2M                  | transmembrane receptor      | Activated      | 2.104     | 0.0000015 |
| IFNα2                | cytokine                    | Activated      | 2.777     | 2.16E-08  |
| APP                  | enzyme                      | Activated      | 3.073     | 2.34E-08  |
| PGR                  | enzyme                      | Inhibited      | -2.621    | 8.98E-08  |
| TNF                  | cytokine                    | Activated      | 3.761     | 3.00E-08  |
| IL10                 | cytokine                    | Activated      | 4.085     | 8.69E-08  |
| TLR2                 | cytokine                    | Activated      | 1.911     | 1.00E-08  |
| IL10                 | growth factor               | Activated      | 1.903     | 0.0000016 |
| Rosiglitazone        | chemical drug               | Activated      | 0.937     | 0.0000065 |
| Beta-estradiol        | chemical drug               | Inhibited      | -2.236    | 1.99E-08  |
| DNA polymerase II    | complex                     | Activated      | 3.073     | 2.34E-08  |
| Ezh2                 | methyltransferase           | Activated      | 2.269     | 3.86E-08  |
| Myc                  | cytokine                    | Activated      | 2.425     | 1.05E-08  |
| ELF5                 | growth factor               | Activated      | 2.625     | 1.05E-08  |
| IL2                  | cytokine                    | Activated      | 2.104     | 0.0000015 |
| ZC3H11C              | transcription regulator      | Activated      | 2.425     | 1.05E-08  |
| ERK1/2               | enzyme                      | Inhibited      | -1.222    | 0.000016  |
| CX3CL1               | cytokine                    | Activated      | 2.269     | 3.86E-08  |
| IL10RA               | transmembrane receptor      | Activated      | 2.135     | 3.00E-08  |
| AGN194204            | cytokine                    | Activated      | 2.625     | 1.05E-08  |
| JUN                  | transcription regulator      | Activated      | 2.269     | 3.86E-08  |
| IFNα/β               | group                       | Activated      | 2.425     | 1.05E-08  |
| CpG ODN 1826         | chemical reagent            | Activated      | 2.142     | 0.0000029 |
| IL2R                 | cytokine                    | Activated      | 2.269     | 3.86E-08  |
| Jak2                 | enzyme                      | Activated      | 2.269     | 3.86E-08  |
| SSB                  | enzyme                      | Inhibited      | -2.236    | 1.99E-08  |
| 17α-ethinylestradiol | chemical drug               | Inhibited      | -0.896    | 0.0000398 |
| Chemical/Drug | Type | Effect | Log2 Fold Change | p-value |
|---------------|------|--------|-----------------|---------|
| Cyclophosphamide | Chemical Drug | -1.432 | 0.00000409 | B2M,C4A/C4B,CCL5,CD74,RAC2 |
| Kainic Acid | Chemical Toxicant | -1.432 | 0.00000409 | APOL1,DCL2,ERBB4,GFAP,NPTX2,PEK6 |
| BAGALNT1 | Enzyme | 0.563 | 0.00000515 | C1QA,C1QB,C4A/C4B |
| ACKR2 | G-protein coupled receptor | 1.000 | 0.0000046 | CCL5,Cxcl9,Ifi47,Ifg1 |
| BMP10 | Growth Factor | -1.342 | 0.00000536 | C1QA,C1QB,C4A/C4B,CCL5,CD74,HLA-A,NPPA,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| E. coli B5 lipopolysaccharide | Chemical - Endogenous Non-mammalian | Activated | 2.586 | 0.00000635 | B2M,CCL5,CYBB,GBP2,HLY-A,Ifg1,Irgf1 |
| CSF1 | Cytokine | 1.000 | 0.00000651 | CCL5,Cxcl9,Ifi47,Ifg1,Ifg1,IRF1 |
| BMP10 | Growth Factor | 1.000 | 0.00000651 | C1QA,C1QB,HLY-A,IRF8,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| TGF2 | G-protein coupled receptor | Activated | 2.000 | 0.00000651 | B2M,CCL5,CYBB,GBP2,HLY-A,IRF8,PTN,SERPINA3 |
| FGF2 | Cytokine | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| E. coli B5 lipopolysaccharide | Chemical - Endogenous Non-mammalian | Activated | 2.586 | 0.00000635 | B2M,CCL5,CYBB,GBP2,HLY-A,Ifg1,Irgf1 |
| CSF1 | Cytokine | 1.000 | 0.00000651 | CCL5,Cxcl9,Ifi47,Ifg1,IRF1 |
| BMP10 | Growth Factor | 1.000 | 0.00000651 | C1QA,C1QB,HLY-A,IRF8,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| BMP10 | Growth Factor | -1.342 | 0.00000536 | C1QA,C1QB,C4A/C4B,CCL5,Cxcl9,IFi47,Ifg1,IRF1 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| IFN type 1 | Group | Activated | 2.586 | 0.00000635 | B2M,CCL5,CYBB,GBP2,HLY-A,IRF8,PTN,SERPINA3 |
| CSF1 | Cytokine | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| BMP10 | Growth Factor | 1.000 | 0.00000651 | C1QA,C1QB,HLY-A,IRF8,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| TGF2 | G-protein coupled receptor | Activated | 2.000 | 0.00000651 | B2M,CCL5,CYBB,GBP2,HLY-A,IRF8,PTN,SERPINA3 |
| FGF2 | Cytokine | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| E. coli B5 lipopolysaccharide | Chemical - Endogenous Non-mammalian | Activated | 2.586 | 0.00000635 | B2M,CCL5,CYBB,GBP2,HLY-A,Ifg1,Irgf1 |
| CSF1 | Cytokine | 1.000 | 0.00000651 | CCL5,Cxcl9,Ifi47,Ifg1,IRF1 |
| BMP10 | Growth Factor | 1.000 | 0.00000651 | C1QA,C1QB,HLY-A,IRF8,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| BMP10 | Growth Factor | -1.342 | 0.00000536 | C1QA,C1QB,C4A/C4B,CCL5,Cxcl9,IFi47,Ifg1,IRF1 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| PSMB11 | Peptidase | -3.84 | 0.00000762 | CCL5,Cxcl9,HLA-A,IRF1,IRF8,NPPA,OMP,SERPINA3 |
| IL1R1 | Transmembrane Receptor | Activated | 2.586 | 0.00000635 | B2M,CCL5,CYBB,GBP2,HLY-A,IRF8,PTN,SERPINA3 |
| CSF1 | Cytokine | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| BMP10 | Growth Factor | 1.000 | 0.00000651 | C1QA,C1QB,HLY-A,IRF8,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| TGF2 | G-protein coupled receptor | Activated | 2.000 | 0.00000651 | B2M,CCL5,CYBB,GBP2,HLY-A,IRF8,PTN,SERPINA3 |
| FGF2 | Cytokine | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| E. coli B5 lipopolysaccharide | Chemical - Endogenous Non-mammalian | Activated | 2.586 | 0.00000635 | B2M,CCL5,CYBB,GBP2,HLY-A,Ifg1,Irgf1 |
| CSF1 | Cytokine | 1.000 | 0.00000651 | CCL5,Cxcl9,Ifi47,Ifg1,IRF1 |
| BMP10 | Growth Factor | 1.000 | 0.00000651 | C1QA,C1QB,HLY-A,IRF8,PTN,SERPINA3 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| BMP10 | Growth Factor | -1.342 | 0.00000536 | C1QA,C1QB,C4A/C4B,CCL5,Cxcl9,IFi47,Ifg1,IRF1 |
| ZNF106 | Other | -0.029 | 0.00000586 | C4A/C4B,FITM3,LYZ,SERPINA3 |
| Gene/Protein | 2.237 | ligand-dependent nuclear receptor | 1.091 | 0.0000468 | CCL5, HLA-DQB1, IGF1, NP2A, SERPINA3 | 27 (7) |
|-------------|-------|----------------------------------|-------|------------|-----------------------------------|--------|
| KRAS        | -0.316 | enzyme                           | -0.378 | 0.0000504 | B2M, CD74, CYBB, GFAP, ITIM3, IRF1, IGF1, LYZ, PCDH1, SERPINA3, TAP1 | 30 (9) |
| PROC (I)    | 0.84  | other                            | 0.000513 | GBB2, Igp1, IGF5 |                                    |        |
| PLK4        | 1.739 | kinase                           | 0.000513 | Cc9, Igp1, IGF1 |                                    |        |
| THRA        | 0.388 | ligand-dependent nuclear receptor | -1.067 | 0.000531 | IG1F, IRF1, NP2A, Ngn, PENK         |        |
| prostaglandin E2 | chemical - endogenous mammalian | -1.52  | 0.000572 | CCL5, Cxcl9, GFAP, IGF1, Igp1, IRF1, PENK | 34 (18) |
| DUSP1       | -0.176 | phosphatase                       | -0.528 | 0.000602 | CYBB, ITIM3, Igp1, IGF1, IRF1      | 20 (4) |
| MAP3K7      | 0.063  | kinase                           | 0.000605 | CCL5, BGBP2, IRF1, NP2A |                                    | 26 (10) |
| IFNAR1      | 0.654  | transmembrane receptor            | Activated | 2.2 | bias | 0.000602 | B2M, CCL5, Cxcl9, HLA-A, IRF1 | 32 (17) |
| dehydroisoandrosterone | chemical - endogenous mammalian | 1.739 | 0.000667 | B2M, GFAP, IGF1, NP2A |                                    | 17 (6) |
| NCOA2       | 0.137  | transcription regulator           | 1.96  | 0.000679 | CCL5, Cxcl9, HLA-A, IRF1, LYZ      |        |
| fingolimod  | -1.969 | bias                             | 0.000007 | CCL5, Cxcl9, DQA1, DQB1         |        |
| etonox      | -0.378 | chemical drug                     | 0.000704 | B2M, NP2A |                                    |        |
| RPSA        | 0.035  | translation regulator             | -2.449 | 0.000708 | CCL5, IGF1, TAP1                  |        |
| CNTF        | -2.154 | cytokine                          | 0.000734 | GFAP, IRF1, PENK, SERPINA3 |                                    | 19 (5) |
| TLR3        | 0.655  | transmembrane receptor            | 1.941  | 0.000734 | CCL5, Cxcl9, BP2, IGF1, IRF1      | 29 (15) |
| Nuclear factor 1 | group | 0.161  | kinase                           | 0.000945 | IGF1, Igp1, IRF1 |                                    |        |
| IL1B        | 0.472  | kinase                           | 0.001113 | CCL5, Cxcl9, HLA-DQ, BGP2, Igp1, TAP1 | 27 (7) |
| RARB        | -0.468 | ligand-dependent nuclear receptor | Activated | 2.236 | 0.001113 | GBB2, IGF1, Igp1, LYZ          |        |
| ACE2        | 0.522  | peptidase                         | 0.001113 | CCL5, Cxcl9, CYBB |                                    |        |
| Hb2-1       | 0.472  | kinase                           | 0.001114 | C1Q, C1QB, Cxcl9, CYBB |                                    |        |
| 6-hydroxydopamine | chemical toxicant | -2.449  | 0.001114 | CCL5, CYBB, GFAP, PENK |                                    | 28 (7) |
| dextran sulfate | chemical drug | Activated | 2.767  | 0.001227 | B2M, CCL5, BP2, HLA-A, IRF1, SERPINA3, TAP1 | 26 (13) |
| hemin       | chemical - endogenous mammalian | 1.186  | 0.001213 | CCL5, Cxcl9, BP2, HLA-A, IRF1, NP2A | 28 (13) |
| IL18        | 0.151  | kinase                           | 0.001234 | IRF1, NP2A, SERPINA3 |                                    | 22 (7) |
| IFN gamma   | 0.161  | kinase                           | 0.001355 | IGF1, NP2A, SERPINA3 |                                    |        |
| E. coli serotype 0127B8 lipopolysaccharide | chemical - endogenous non-mammalian | 2.219  | 0.001355 | CCL5, Cxcl9, IRF1, IRF5 |                                    | 13 (3) |
| NRC1        | 0.437  | ligand-dependent nuclear receptor | Activated | -1.446 | 0.001356 | B2M, C4A, C4B, CCL5, Cxcl9, BP2, IGF1, IRF1, IRF5, NP2A | 34 (15) |
| IL17A       | 0.849  | cytokine                          | 0.001358 | B2M, CCL5, Cxcl9, BP2, IGF1, IRF1 |                                    | 31 (16) |
| IL13        | 0.521  | cytokine                          | 0.001561 | CCL5, Cxcl9, IGF1, IRF1 |                                    | 32 (12) |
| ethanol     | 0.521  | cytokine                          | 0.001667 | CCL5, Cxcl9, IGF1, IRF1 |                                    | 16 (2) |
| RNAE2H2A    | 1.63   | enzyme                           | 0.00182 | GBB2, IGF1, IRF1 |                                    |        |
| CYP191A     | 0.762  | enzyme                           | 0.00183 | GBB2, GFAP, HLA-A, IGF1 |                                    |        |
| sildenafil  | 1.655  | chemical drug                     | 0.00196 | CYBB, GFAP, SERPINA3 |                                    | 22 (6) |
| S-nitrosoglutathione | chemical toxicant | 1.655  | 0.00196 | CYBB, GFAP, IGF1 |                                    |        |
| GSK0660     | 0.008  | chemical reagent                 | 0.00196 | C1Q, C1QB |                                    |        |
| CLTC        | 0.008  | other                            | 0.00196 | CD74, HLA-A |                                    |        |

**Notes:****NR3C2** and **NR3C1** are ligand-dependent nuclear receptors. The table includes various genes and their roles, with a focus on their relationships to different processes such as regulation, signal transduction, and immune responses. The table also highlights the activation status of certain genes. For example, **IFNAR1** is shown to be activated, and **IL18** is demonstrated as a cytokine that can influence immune responses. The table is comprehensive, listing numerous genes and their interactions, providing a detailed overview of the molecular interactions within the context of the document.
| Gene    | Description               | Value | Group     | Bias     | Z-Score |
|---------|---------------------------|-------|-----------|----------|---------|
| TAPBP   | transporter               | 1.268 | 0.000196  | HLA-A,TAP1|
| dihydrotestosterone | chemical - endogenous mammal | -0.047 | 0.000201 | B2M,C4A/C4B,CD74,CYBB,GFAP,HLA-A,IGF1,LYZ |
| AIRHGAP21 | other                  | 0.552 | 0.000201 | Cc09,IgG1,IGF1 |
| Cc02    | enzyme                    | 0.016 | 0.000201 | CTSS,GFAP,HPPA |
| VIP     | other                     | 0.691 | 0.000211 | CD74,HLA-DRB1,LYZ |
| CEBPB   | transcription regulator    | -0.102 | 0.000214 | C1QA,CCL5,CD74,GFAP,HLA-A,IGF1,IGP1,RAC2 |
| SOX4    | transcription regulator    | 0.138 | 0.000234 | CD74,HLA-DQB1,IGF1,LYZ,TUBB2B |
| IL12(complex) | complex              | -0.047 | 0.000244 | CCL5,CX09,IgG1,IGF1,IGF8 |
| PSMB9   | peptidase                 | 5.28  | 0.000252 | HLA-A,TAP1 |
| RXAP    | transcription regulator    | 0.649 | 0.000252 | B2M,HLA-DQA1 |
| HRA000  | chemical reagent          | 0.332 | 0.000259 | Cc09,IgG1,IGF1 |
| KOT     | transmembrane receptor     | -0.328 | 0.000274 | CCL5,HLA-DRB1 |
| ZFTA-RELA | fusion gene/product       | 0.000274 | IRF1,TAP1,TAPBP |
| ARHGAP21 | other                   | 0.552 | 0.000274 | CCL5,CX09,IgG1 |
| SMAA4   | transcription regulator    | -0.088 | 0.000281 | CD74,CTSS,IGF1,LYZ |
| DMD     | other                     | -0.099 | 0.000303 | C1QB,CTSS,GFAP,IGF1,LYZ |
| B4GALT6 | enzyme                    | -0.263 | 0.000314 | CCL5,GFAP |
| ZFTA-RELA | fusion gene/product       | 0.000314 | IRF1,IgG1 |
| RELA    | transcription regulator    | 0.137 | 0.000314 | C1QB,CTSS,GFAP,IGF1,LYZ |
| SFRS1   | other                     | 0.332 | 0.000325 | CCL5,CX09,IgG1 |
| JUN     | transcription regulator    | -0.377 | 0.000385 | C1QB,Cc02a/Cc02a,Cx09,FABP7,IGF1,HPPA,PEK |
| BAX     | transporter               | 0.341 | 0.000391 | CCL5,CTSS,HLA-A |
| NR1H3   | ligand-dependent nuclear receptor | 0.841 | 0.000395 | Bz2,C1QA,CCL5,LYZ,TAP1 |
| epigallocatechin-gallate | chemical drug | Inhibited | -2.204 | 0.000419 | CCL5,IgG4,IRF1,PTN,TAP1 |
| ILRN    | cytokine                  | -0.208 | 0.000425 | C1QA,HLA-DRB1,IGF1,IRF1 |
| DOC5    | other                     | 0.554 | 0.000436 | CCL5,CX09,GFAP,HPPA |
| CDK9    | kinase                    | 1.441 | 0.000436 | CCL5,HLA-DQA1,HNRPH1 |
| FGFR2A  | transmembrane receptor     | 0.857 | 0.000436 | CCL5,GF2B,IFITM3 |
| RAB2    | group                     | 0.000438 | C6B2,IGG4,IFG1 |
| dexamethasone | chemical - endogenous mammal | -0.714 | 0.000461 | CCL5,CYBB,GFAP,HPF1,NPPA |
| CTCF    | transcription regulator    | 0.179 | 0.000476 | HLA-DQA1,HLA-DQB1,HLA-DRB5,LYZ |
| LDLR    | transporter               | 0.624 | 0.000479 | Bz2,C1QA,CCL5,LYZ,TAP1 |
| Growth hormone | group             | 0.615 | 0.000487 | CCL5,GFAP,IGF1,IRF1,NPPA |
| ADAM10  | peptidase                 | -0.016 | 0.000532 | CD74,FAFP7,OMP,TUBB2B |
| IKBKG   | kinase                    | 1.528 | 0.000532 | CCL5,GF2B,HLA-A,NPPA |
| mibolerone | chemical drug | Inhibited | -2.204 | 0.000546 | C1QA,CCL5,IGF1,IRF1 |
| cortisatin | chemical - other   | 1.943 | 0.000546 | C1QA,CCL5,IGF1,IRF1,PTN |
| NCOR2   | transcription regulator    | 0.274 | 0.000536 | C1QA,CTSS,IGF1 |
| Co2     | cytokine                  | 0.000536 | C1QA,CCL5,LYZ,TAP1 |
| heme    | chemical - endogenous mammal | -0.714 | 0.000536 | CCL5,LYZ,TAP1 |
| CCL3L3  | cytokine                  | 1.626 | 0.000542 | CCL5,CX09 |
| tacrolimus | chemical drug               | 1.943 | 0.000545 | CCL5,CTSS,GFAP,HPPA,PEK |
| Clitzazone | chemical drug             | -1    | 0.000561 | CCL5,CYBB,GFAP,HPPA |
| CSF2    | cytokine                  | 1.218 | 0.000562 | C1QA,CCL5,CD74,Cx09,CYBB,HLA-DQB1,IGF1,LYZ |
| IL11    | cytokine                  | 0.989 | 0.000563 | IGF1,IRF1,PEP3A3 |
| IL1A    | cytokine                  | 0.139 | 0.000555 | C1QA,CCL5,LYZ,TAP1,IRF1,PEP3A3 |
| SOCS1   | other                     | 3.005 | 0.000576 | Cc09,IgG1,IGF1 |
| LY294002 | chemical drug | Inhibited | -1.132 | 0.000587 | CCL5,CCL5,CD74,GFAP,IRF1,IRF1,PTN |
| ACOX1   | enzyme                    | 0.224 | 0.000623 | HLA-DQA1,HLA-DRB5,IGF1,LYZ,TUBB2B |
| TRP1    | ion channel               | 0.224 | 0.000631 | B2M,C1QA,CCL5,CD74,FAFP7,GFAP,PEP3A3,PEK,PEP3A3 |
| trichostatin A | chemical drug   | 1.238 | 0.000631 | B2M,CYBB,HLA-DQB1,IGS95,IFG1,IRF1,IRF3,NPPA,PEK,SEZ1L |
| IFCAM1  | other                     | -0.283 | 0.000664 | CCL5,CX09,IGF1,IRF1 |
| PRDM1   | transcription regulator    | -0.528 | 0.000665 | CD74,HLA-DQA1,IRF1,PEP3A3,TAPBP |
| morphine | chemical drug             | -0.83  | 0.000656 | CYBB,GFAP,HPPA,PEK |

**Note:** Values are given as Z-Score, with significance levels indicated by bolded text.
| Gene | Description | Fold Change | p-Value | Associated Genes |
|------|-------------|-------------|---------|------------------|
| AGT  | -0.795 growth factor | 1.379 | 0.000667 | C4A/C4B,C55,CTS5,CYBB,IGF1,NPPA,NPTX2,PTN,SERPINA3 |
| CA8  | -0.00689 | 0.000689 | 30 (14) | B2M,CC55,CD74 |
| U126 | chemical drug | -0.025 bias | 0.000705 | CCL5,CYBB,GAPF,HLA-DQA1,IRF1,NPPA,RAC2 |
| lovastatin | chemical drug | -0.025 bias | 0.000705 | CCL5,CYBB,GAPF,HLA-DQA1,IRF1,NPPA,RAC2 |
| U0126 | chemical drug | -0.025 bias | 0.000705 | CCL5,CYBB,GAPF,HLA-DQA1,IRF1,NPPA,RAC2 |
| PPARG | -0.121 ligand-dependent nuclear receptor | 0.537 | 0.000734 | C1QA,C1QB,FABP7,MPEG1,NPPA |
| PRKCA | 0.563 | 0.000837 | CCL5,CFAP,HILA-DQA1,HILA-DQB1,NPPA,NTX2,RENK |
| PIAS4 | 0.019 other | 0.000848 | CCL5,CIFAP,HILA-DQA1,HILA-DQB1,NPPA,NTX2,RENK |
| NFKB1 | -0.277 | 0.000921 | HLA-A,IRF1,TAP1 |
| MAPK9 | -0.154 enzyme | 0.00112 | CCL5,CIFAP,HILA-DQA1,HILA-DQB1,NPPA,NTX2,RENK |
| NFYA | 0.162 transcription regulator | 0.00166 | HILA-DQA1,GAPF,HILA-DQB1,NPPA,RAC2 |
| ESR1 | -0.037 kinase | 1.091 | 0.00156 | CCL5,GAPF,HILA-DQA1,GAPF,HILA-DQB1,GAPF,HILA-DQB1,NPPA,RAC2 |

**Endothelin group**

- **VADIMZAN**
  - Chemical drug
  - Fold change: -0.025 bias
  - p-value: 0.000705
  - Associated genes: CCL5,CYBB,GAPF,HLA-DQA1,IRF1,NPPA,RAC2

**Monocrotaline**

- **Monocrotaline**
  - Chemical toxicant
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**L-Carnitine**

- **L-Carnitine**
  - Chemical - endogenous mammalian
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**Prazosin**

- **Prazosin**
  - Chemical drug
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**Geldanamycin**

- **Geldanamycin**
  - Chemical drug
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**Enterotoxin B**

- **Enterotoxin B**
  - Biologic drug
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**NFKB1**

- **NFKB1**
  - Transcription regulator
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**ERBB2**

- **ERBB2**
  - Kinase
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK

**CUX1**

- **CUX1**
  - Transcription regulator
  - Fold change: -1.281
  - p-value: 0.000837
  - Associated genes: CCL5,GFAP,HLA-DQA1,HLA-DQB1,IGF1,NPPA,NPTX2,PENK
| Gene | Class | Description | Log2 | P-value |
|------|-------|-------------|------|---------|
| NOS2 | enzyme |            | 1.387 | 0.00166 |
| C6   | complex | Activated  | 2.213 | 0.00167 |
| PPARA| ligand-dependent nuclear receptor | -0.577 | 0.00167 |
| CCK  | other   |            | -0.93 | 0.00173 |
| liparabinomannan | chemical - endogenous non-mammalian | 0.00173 |
| ilomastat | chemical drug | CCL5, ERRB4 |
| LCN2 | transporter | CCL5, Cxcl9, IGF1, LGALS3BP, SERPINA3 |
| IL1β | cytokine | -0.33 bias | 0.0018 |
| ZFHX3 | transcription regulator | 0.00183 |
| SB220680 | other | C4A/C4B, TLH, IGF1 |
| HDXAS | transporter regulator | 0.00186 |
| mifepristone | chemical drug | CCL5, Cxcl9, GFAP, NPPA |
| SAMSN1 | other | 0.00186 |
| SLC13A1 | transporter | GBP2, IGF1, LGALS3BP, NPPA, PENK |
| IKBK | kinase | 0.00195 |
| ZFP36 | transcription regulator | 0.00201 |
| PPIF | enzyme | -0.21 bias | 0.00201 |
| SLPI | other | 0.00204 |
| levodopa | chemical - endogenous mammalian | -0.964 |
| dactin | chemical drug | 0.0022 |
| HRAS | enzyme | 0.00222 |
| PDGF-αA | complex | CCL5, CTSS, IGF1, IRF1 |
| CDC73 | other | 0.388 |
| TIGAM2 | other | 0.00221 |
| Saa3 | other | 0.259 |
| SPRY1 | other | 0.00221 |
| Fus | transcription regulator | 0.00221 |
| bee venom | chemical - endogenous non-mammalian | 0.00233 |
| NFATC2 | transcription regulator | 0.00236 |
| NFIX | transcription regulator | 0.00238 |
| wortmannin | biological drug | CCL5, IGF1, IRF1, IRF8 |
| vancomycin | biologic drug | CCL5, CTSS, C4A/C4B, LGALS3BP, SERPINA3 |
| ZNF503 | other | -1.487 |
| dimethyl lactonate | chemical reagent | 0.00256 |
| CCR1 | G-protein coupled receptor | 0.00256 |
| Mx2 | other | 1.807 bias | 0.00259 |
| N-acetyl-D-glucosamine methyl ester | chemical drug | 0.00261 |
| Gm20504 | other | 0.00268 |
| CAMTA2 | transcription regulator | 0.00268 |
| CAMTA1 | other | 0.00268 |
| SNORD21 | other | 0.00268 |
| CYTL1 | cytokine | 0.00268 |
| TPH2 | enzyme | 0.00268 |
| ENO2 | enzyme | 0.00268 |
| GATA | other | 0.00268 |
| GLP1D1 | enzyme | 0.00268 |
| CORN | peptidase | 0.00268 |
| Rait16/Rait1e | other | 0.00268 |
| GDN | other | 0.00268 |
| GPD | enzyme | 0.00268 |
| NOS1 | G-protein coupled receptor | 0.00268 |
| BNP | chemical drug | 0.00268 |
| anthraquinone | chemical toxicant | 0.00268 |
| SCH 39370 | chemical - protease inhibitor | 0.00268 | NPPA |
| 10-hydroxydecanoic acid | chemical - endogenous non-mammalian | 0.00268 | IGF1 |
| thiorphan | chemical - protease inhibitor | 0.00268 | NPPA |
| deoxyorticosterone acetate/potassium chloride/sodium chloride | chemical reagent | 0.00274 | CCL5,CYBB |
| TKB1 | enzyme | 0.522 | kinase |
| FTO | enzyme | 0.048 | other |
| BAK1 | other | 0.562 | other |
| MX2-3 | ligand-dependent nuclear receptor | 0.348 | inhibited |
| RARA | enzyme | -0.108 | other |
| HAVCR1 | enzyme | -3.413 | other |
| ST4 | microRNA | 1.981 | bias |
| CARD9 | enzyme | 0.0313 | other |
| CXCL10 | cytokine | 2.616 | other |
| PTX3 | enzyme | 0.0313 | other |
| colletin | biologic drug | 0.0315 | other |
| INSIG1 | enzyme | -0.009 | other |
| kanamy c-A | enzyme | 0.0331 | other |
| TIRAP | enzyme | -3.413 | other |
| CBF | enzyme | 0.0333 | other |
| mir-23 | microRNA | 0.0333 | other |
| FAS | microRNA | 1.333 | other |
| NCF1 | enzyme | 1.123 | other |
| CGAS | enzyme | 4.151 | other |
| KDM8 | enzyme | 0.284 | other |
| CNG | enzyme | 0.0354 | other |
| BNE1 | enzyme | -0.037 | other |
| NFIC | enzyme | 0.108 | other |
| TAB1 | enzyme | 0.226 | other |
| ROR | enzyme | 0.0357 | other |
| SYK | enzyme | 1.298 | kinase |
| INSR | enzyme | 0.0369 | kinase |
| cholesterol | enzyme | -0.019 | kinase |
| melonodazole | enzyme | 0.0375 | other |
| TNFSF14 | cytokine | 0.0376 | other |
| SUMO1 | enzyme | 0.231 | other |
| PBX1 | enzyme | 0.225 | other |
| TR | enzyme | 0.0384 | other |
| TSRC | enzyme | 0.0398 | other |
| PTPA | enzyme | 0.523 | other |
| PRDM16 | enzyme | 0.568 | other |
| CTBB | enzyme | 4.356 | other |
| HSFG2 | enzyme | 0.901 | other |
| Kik1 | enzyme | 0.042 | other |
| vinblastine | enzyme | 0.042 | other |
| Alpha catenin | enzyme | 0.042 | other |
| indomethacin | enzyme | 0.042 | other |
| mir-130 | enzyme | 1.91 | other |
| UBE2I | enzyme | 0.78 | other |
| RAD21 | enzyme | 0.185 | other |
| FOS | enzyme | 0.184 | other |
| tetradecanoylphorbol acetate | enzyme | -0.581 | other |
| genistein | enzyme | -1.3 | other |
| **Thioacetamide** | chemical toxicant | 0.00481 | C4A/C4B,GFAP,IGF1,LGALS3BP |
| **Bortezomib** | chemical drug | 0.849 | 0.00488 | CCL5,GFAP,IGF1,SERPINA3 |
| **SMARC5** | transcription regulator | 0.368 | 0.00505 | B2M,HLA-A,UNK358B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| **15-keto-13,14-dihydroprostaglandin E2** | chemical - endogenous mammalian | | |
| **MEK3C** | enzyme | 0.34 | 0.00536 | GFAP |
| **ARLT6** | other | -0.999 | 0.00536 | CCL5 |
| **ADGRG1** | G-protein coupled receptor | -0.16 | 0.00536 | GFAP |
| **ADH1C** | enzyme | -0.975 | 0.00536 | NPPA |
| **SERPINE2** | other | -0.202 | 0.00536 | HLA-A |
| **SMARCA5** | transcription regulator | 0.368 | 0.00536 | B2M,HLA-A,UNC93B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| **15-keto-13,14-dihydroprostaglandin E2** | chemical - endogenous mammalian | | |
| **MEK3C** | enzyme | 0.34 | 0.00536 | GFAP |
| **ARLT6** | other | -0.999 | 0.00536 | CCL5 |
| **ADGRG1** | G-protein coupled receptor | -0.16 | 0.00536 | GFAP |
| **ADH1C** | enzyme | -0.975 | 0.00536 | NPPA |
| **SERPINE2** | other | -0.202 | 0.00536 | HLA-A |
| **SMARCA5** | transcription regulator | 0.368 | 0.00536 | B2M,HLA-A,UNC93B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| **15-keto-13,14-dihydroprostaglandin E2** | chemical - endogenous mammalian | | |
| **MEK3C** | enzyme | 0.34 | 0.00536 | GFAP |
| **ARLT6** | other | -0.999 | 0.00536 | CCL5 |
| **ADGRG1** | G-protein coupled receptor | -0.16 | 0.00536 | GFAP |
| **ADH1C** | enzyme | -0.975 | 0.00536 | NPPA |
| **SERPINE2** | other | -0.202 | 0.00536 | HLA-A |
| **SMARCA5** | transcription regulator | 0.368 | 0.00536 | B2M,HLA-A,UNC93B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| **15-keto-13,14-dihydroprostaglandin E2** | chemical - endogenous mammalian | | |
| **MEK3C** | enzyme | 0.34 | 0.00536 | GFAP |
| **ARLT6** | other | -0.999 | 0.00536 | CCL5 |
| **ADGRG1** | G-protein coupled receptor | -0.16 | 0.00536 | GFAP |
| **ADH1C** | enzyme | -0.975 | 0.00536 | NPPA |
| **SERPINE2** | other | -0.202 | 0.00536 | HLA-A |
| **SMARCA5** | transcription regulator | 0.368 | 0.00536 | B2M,HLA-A,UNC93B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| **15-keto-13,14-dihydroprostaglandin E2** | chemical - endogenous mammalian | | |
| **MEK3C** | enzyme | 0.34 | 0.00536 | GFAP |
| **ARLT6** | other | -0.999 | 0.00536 | CCL5 |
| **ADGRG1** | G-protein coupled receptor | -0.16 | 0.00536 | GFAP |
| **ADH1C** | enzyme | -0.975 | 0.00536 | NPPA |
| **SERPINE2** | other | -0.202 | 0.00536 | HLA-A |
| **SMARCA5** | transcription regulator | 0.368 | 0.00536 | B2M,HLA-A,UNC93B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| **15-keto-13,14-dihydroprostaglandin E2** | chemical - endogenous mammalian | | |
| **MEK3C** | enzyme | 0.34 | 0.00536 | GFAP |
| **ARLT6** | other | -0.999 | 0.00536 | CCL5 |
| **ADGRG1** | G-protein coupled receptor | -0.16 | 0.00536 | GFAP |
| **ADH1C** | enzyme | -0.975 | 0.00536 | NPPA |
| **SERPINE2** | other | -0.202 | 0.00536 | HLA-A |
| **SMARCA5** | transcription regulator | 0.368 | 0.00536 | B2M,HLA-A,UNC93B1 |
| **PLAUR** | transmembrane receptor | 0.00517 | CCL5,CYBB | 19 (5) |
| Gene | Description | Expression | Associated Genes |
|------|-------------|------------|------------------|
| JAK  | Group       | 0.00595    | CCL5,IGF1        |
| USP22| Peptidase   | 0.00595    | CCL5,LYZ        |
| pristane | Chemical toxicant | 0.00595 | CCL5,GBP2,PENK |
| IL22 | Cytokine    | 0.00621    | CCL5,Cxcl9,SERPINA3 |
| DPP4 | Peptidase   | 0.00623    | CCL5,Cxcl9      |
| FLT3 | Kinase      | 0.00651    | CYBB,LYZ     |
| HBB  | Transporter | 0.00651    | CCL5,Cxcl9   |
| SOD1 | Enzyme     | 0.00656    | B2M,C1QA,GFAP,IGF1 |
| PI3  | Complex     | 0.00671    | IGF1,IRF1,PENK  |
| Sox11 | Transcription regulator | 0.00671 | CCL5,ERBB4,HLA-DRB5 |
| PRKACA | Kinase | 0.00679 | IGF1,PENK |
| temozolomide | Chemical drug | 0.00679 | CCL5,Cxcl9 |
| pristane | Chemical toxicant | 0.00685 | CCL5,Cxcl9,IRF1,IFITM3,IGF1 |
| fulvestrant | Chemical drug | 1.869 | CCL5,CD74,IGF1,IRF1 |
| SMAD1 | Transcription regulator | 0.00704 | C1QA,C1QB,CCL5,Cxcl9,IRF1 |
| C3AR1 | G-protein coupled receptor | 0.00708 | CCL5,IGF1 |
| IFIH1 | Enzyme     | 0.00708    | B2M,CCL5      |
| calcitriol | Chemical drug | 0.00709 | CCL5,Cxcl9,CYBB,IGF1,PENK,TAP1 |
| quinolinic acid | Chemical - endogenous mammalian | 0.00737 | GFAP,PENK |
| N-formylMet-Leu-Ph | Chemical reagent | 0.00737 | CYBB,RAC2 |
| IL-12 (family) | Group | 0.00751 | CCL5,IRF1,IRF8 |
| EBF1 | Transcription regulator | 0.00765 | CCL5,Cxcl9,IRF1 |
| PAF1 | Other      | 0.00767    | CCL5,IFITM3    |
| halofuginone | Chemical drug | 0.00779 | C4A/C4B,CCL5,Cxcl9,IRF1,IFITM3 |
| estrogen | Chemical drug | 0.055 | bias |
| IL15 | Cytokine   | 0.00791    | CCL5,CD74,IRF1,NPTX2,RAC2 |
| Ack28 | Transcription regulator | 0.00798 | B2M,IGF1 |
| istradefylline | Chemical drug | 0.00803 | PENK |
| HS-243 | Chemical - kinase inhibitor | 0.00803 | CCL5 |
| SXNT01959 | Chemical reagent | 0.00803 | IGF1 |
| drotrecogin alfa | Biologic drug | 0.00803 | NPPA |
| Os1/213 | Group | 0.00803 | IGF1 |
| psipentofylline | Chemical drug | 0.00803 | GFAP |
| SLC4A5 | Transporter | 0.00803 | NPPA |
| DPP10 | Peptidase | 0.00803 | KCNIP1 |
| LRRK2E | Ion channel | 0.00803 | CCL5 |
| ASPAT1 | Enzyme | 0.00803 | IGF1 |
| HP1BP3 | Other | 0.348 | IGF1 |
| ABRA | Other | 0.00803 | NPPA |
| SF3BP1 | Other | 0.915 | NPPA |
| PCDH17 | Other | 0.209 | NPPA |
| Ap1 gamma | Group | 0.00803 | HLA-A |
| GLO1 | Enzyme | 0.00803 | GFAP |
| GNL4 | Other | 0.00803 | CCL5 |
| INPP1 | Other | -1.374 | NPPA |
| Tardp | Transcription regulator | 0.00803 | ERBB4 |
| ostami | Chemical drug | 0.00803 | IGF1 |
| ZNRD1ASP | Other | 0.00803 | HLA-A |
| S100A1 | Other | -0.082 | NPPA |
| IFNGR2 | Transmembrane receptor | 0.00803 | IRF1 |
| MBP5 | Other | -0.14 | IGF1 |
| MYOZ2 | Other | 0.00803 | NPPA |
| DDX4 | Enzyme | 1.602 | IFTM3 |
| Lycium barbarum polysaccharides | Chemical - endogenous non-mammalian | 0.00803 | IGF1 |
| LIFR | Transmembrane receptor | 0.00803 | GFAP |
| Gene/Drug | Type | Description |
|-----------|------|-------------|
| Herc5     | enzyme|             |
| fomepizole| chemical drug |             |
| desmazole | chemical drug |             |
| chlorothamidine | chemical-drug |             |
| CRTCL-MAM-2 | fusion | product     |
| (+)gallic+chinate | gallic acid | enzyme-protase inhibitor |
| 2,5'-dideoxadenosine | chemical reagent |             |
| proline zinc insulin | biologic drug |             |
| 2R,4R-4-aminoypymidine-2,4-dicarboxylic acid | chemical reagent |             |
| aflatoxin B1 | chemical - endogenous | non-mammalian |
| IFNA4 | cytokine |             |
| JUNB | 1.227 | transcription regulator group |
| cytokine | group |             |
| carrageenan | chemical drug |             |
| DIO2 | -0.134 | enzyme |
| IGK | 3.578 | enzyme |
| glucocorticoid | chemical reagent |             |
| budesonide | chemical drug |             |
| TSC2 | 0.123 | other |
| HSL | complex |             |
| APLN | 0.503 | other |
| DCN | 0.422 | other |
| TNFRSF11A | 0.505 | transmembrane receptor |
| galactosylceramide-alpha | chemical reagent |             |
| SMPD1 | 0.103 | enzyme |
| PTP1E | 1.712 | phospholase |
| ninflutacin | chemical drug |             |
| SP600125 | chemical drug | -0.152 |
| Insulin | group | -1.732 |
| progesterone | chemical - endogenous | mammalian |
| MAP2K7 | 0.831 | kinase |
| APOA1 | transporter |             |
| MAP2K4 | -0.014 | kinase |
| Ro 25-6760 | chemical toxicant |             |
| sargamostim | biologic drug |             |
| cholinase | group |             |
| CACTIN | 0.965 | other |
| ROBO3 | 0.191 | transmembrane receptor |
| G100H71 | 1.224 | other |
| SLCO1C3 | -0.456 | transporter |
| endothelin receptor | group |             |
| ITPRB2 | -0.074 | other |
| LRG3 | 1.061 | other |
| ALX3 | -1.162 | transcription regulator |
| calhepstin L inhibitor | chemical drug |             |
| TNIL | 0.429 | other |
| GALNS | 0.755 | enzyme |
| KCNBD3 | 0.034 | ion channel |
| PKA | 0.361 | other |
| UFD1 | 0.28 | peptidase |
| RGL2 | 0.523 | other |
| miR-384 | microRNA |             |
| K-604 | chemical drug |             |
| TAAT2 | 0.229 | transcription regulator |
| NILC4 | 0.195 | other |
| A4GALT | enzyme |             |
| CSTB | 1.037 | peptidase |
| SCIN | other |             |
| Compound                                      | Type                          | Other                          | p-value | Modulation  |
|-----------------------------------------------|--------------------------------|--------------------------------|---------|-------------|
| phenylacetic acid                             | chemical - endogenous mammalian | other                          | 0.0107 | GFAP        |
| arzoxifene                                    | chemical drug                 |                                | 0.0107 | IGF1        |
| nabumetone                                    | chemical drug                 |                                | 0.0107 | NPPA        |
| cromakalin                                    | chemical drug                 |                                | 0.0107 | NPPA        |
| sodium phosphate                              | chemical drug                 |                                | 0.0107 | NPPA        |
| AC0033537.1                                   | other                          |                                | 0.0107 | CCL5        |
| succinylacetone                               | chemical - endogenous mammalian | other                          | 0.0107 | CYBB        |
| CDP-choline                                   | chemical - endogenous mammalian | other                          | 0.0107 | GFAP        |
| tamoxifen                                     | chemical drug                 |                                | 1.521  | ERBB4,IGF1,IRF1,SERPINA3 |
| DO3                                           | enzyme                        |                                | 0.0113 | HLA-A,IRF1,Ngn |
| PPP2CA                                        | phosphatase                   |                                | 0.0113 | Cck1,IRF1   |
| PTGES                                         | enzyme                        |                                | 0.0113 | CYBB,NPPA   |
| anisomycin                                    | chemical - endogenous non-mammalian | other                          | 0.0113 | CYBB,IRF1   |
| DNMT3A                                        | enzyme                        |                                | 0.0114 | CYBB,IRF1,NRF8 |
| STUB1                                         | enzyme                        |                                | 0.0117 | CTSS,NPPA   |
| Ap1                                           | complex                       |                                | 0.0118 | CCL5,GFAP,IGF1 |
| IRF1A                                         | transcription regulator       | 0.562                          | 0.012  | CCL5,Cxcl9,ERBB4,IGF1,NPPA |
| DNMT3B                                        | enzyme                        |                                | 0.012  | CCL5,HLA-DQB1,PTN |
| dopamine                                      | chemical - endogenous mammalian |                                | 0.012 | CCL5,Cxcl9,PENK |
| CS11L1                                        | growth factor                 |                                | 0.0121 | IGF1,IRF1   |
| IL6ST                                         | transmembrane receptor        |                                | 0.0124 | GFAP,IRF1   |
| FOXP3                                         | transcription regulator       |                                | 0.0127 | CCL5,GFAP,HLA-A |
| rotenone                                      | chemical toxicant             |                                | 0.0128 | CYBB,GFAP   |
| MAPK8                                         | kinase                        |                                | 0.0129 | CCL5,CYBB,NPPA |
| S100A8                                        | other                         |                                | 0.0131 | C1QB,Cxcl8,IGF1 |
| IL19R1                                        | transmembrane receptor        | -1.964                         | 0.0133 | Bax2,GBP2,GFAP,IGF1,1LGAL3BP,PARP14 |
| CF102                                         | chemical drug                 |                                | 0.0133 | CCL5        |
| davusenlan                                    | chemical drug                 |                                | 0.0133 | NPPA        |
| teniposide                                    | chemical drug                 |                                | 0.0133 | CCL5        |
| ILX-23-7553                                   | chemical drug                 |                                | 0.0133 | NPPA        |
| RAN7R1                                        | complex                       |                                | 0.0133 | IRF1        |
| SMPD3                                         | enzyme                        |                                | 0.0133 | GF1         |
| IRF3-IRF7                                     | complex                       |                                | 0.0133 | CCL5        |
| propolis                                      | biologic drug                 |                                | 0.0133 | CCL5        |
| Fk                                            | other                         |                                | 0.0133 | NPPA        |
| G6PC3                                         | phosphatase                   |                                | 0.0133 | CYBB        |
| S100A1                                        | group                         |                                | 0.0133 | NPPA        |
| MCOLN2                                        | ion channel                   |                                | 0.0133 | CCL5        |
| TAF9                                          | transcription regulator       |                                | 0.0133 | IRF1        |
| Nc2                                           | complex                       |                                | 0.0133 | HLA-A       |
| RAP1B                                         | enzyme                        |                                | 0.0133 | CCL5        |
| KON12                                         | ion channel                   |                                | 0.0133 | KCNIP1      |
| NBR1                                          | other                         |                                | 0.0133 | CYBB        |
| CTS5                                          | peptidase                     |                                | 0.0133 | NPPA        |
| DGX                                           | peptidase                     |                                | 0.0133 | GFAP        |
| ADAM8                                         | peptidase                     |                                | 0.0133 | CCL5        |
| AQP3                                          | transporter                   |                                | 0.0133 | CCL5        |
| talazoparib                                   | chemical drug                 |                                | 0.0133 | CCL5        |
| RIYANK                                         | transcription regulator       |                                | 0.0133 | HLA-A       |
| Z-endoxifen                                   | chemical - endogenous mammalian | other                          | 0.0133 | IGF1        |
|Idegakalin                                     | chemical drug                 |                                | 0.0133 | GF1         |
| fluticasone                                   | chemical drug                 |                                | 0.0133 | CCL5        |
| H3B-8810                                      | chemical drug                 |                                | 0.0133 | CCL5        |
| Chemical/Protein | Category | Description | Log2 Fold Change | Associated Genes |
|-----------------|----------|-------------|-----------------|------------------|
| Gabapentin      | Chemical | Drug        | 0.0133          | GFAP             |
| Naloxone        | Chemical | Drug        | 0.0133          | PNK              |
| Fenoldopam      | Chemical | Drug        | 0.0133          | CYBB             |
| Nor-binaltorphimine | Chemical | Reagent     | 0.0133          | CYBB             |
| Celecoxib       | Chemical | Drug        | 0.0133          | GFAP             |
| 5-Hydroxydecanoic acid | Chemical | -Endogenous mammalian | 0.0133 | NPPA             |
| Halofuginol     | Chemical | Reagent     | 0.0133          | CCL5             |
| FLJ13191        | 0.185    | Transcription regulator | 0.0138 | CCL5, Cxcl9      |
| MRTFA           | 0.542    | Transcription regulator | 0.0139 | CCL5, HLA-A, NPPA |
| Cytarabine      | Chemical | Drug        | 0.0140          | CCL5             |
| IRF4            | 0.803    | Cytoplasm   | 0.0143          | CCL5, GFAP, IGF1 |
| Topotecan       | Chemical | Drug        | 0.0143          | CCL5, GFAP, IGF1 |
| 3,3'-Diindolylmethane | Chemical | Drug      | 0.0144          | NLA-A, TAP1      |
| ANXA7           | 0.299    | Ion channel | 0.0148          | Cc9              |
| Folic acid      | Chemical | Drug        | 0.0148          | CCL5, CYBB       |
| INHBA           | 0.294    | Growth factor | 0.0151         | ERBB4, IGF1, IGF1 |
| USF2            | 0.293    | Transcription regulator | 0.0152 | B2M, LGALS3BP    |
| PRKD1           | 0.377    | Kinase      | 0.0152          | CCL5, Cc9        |
| CD28            | Transmembrane receptor | Activated | 0.0153         | B2M, HLA-DQB1, IGF1, IGF2, IGF3 |
| MAPK14          | 0.494    | Kinase      | 0.0153          | CCL5, Cc9, NPPA  |
| PDX1            | 0.054    | Transcription regulator | 0.0153 | ERBB4, FABP7, GFAP |
| SRF              | 0.054    | Kinase      | 0.0153          | CCL5, Cc9        |
| SHH             | 0.437    | Peptidase   | 0.0156          | CVA, ERBB4, IGF1 |
| SASH1           | -0.78    | Other       | 0.0156          | IGF1             |
| RORA            | -0.238   | Ligand-dependent nuclear receptor | 0.0159 | CCL5, Cc9, IGF1  |
| MCEB613         | 0.016    | Chemical reagent | 0.0165          | Cc9              |
| Pervanadate     | 0.016    | Chemical reagent | 0.0164          | IGF1             |
| SHH1            | 0.054    | Other       | 0.0166          | NPPA             |
| F-Actin         | 0.016    | Complex     | 0.0166          | CTSS             |
| 5R-Hydroxytriptolide | Chemical | Drug    | 0.0166          | IGF1             |
| BCC1            | 0.016    | Other       | 0.0166          | ERBB4            |
| PKCAP1          | 0.016    | Other       | 0.0166          | IGF1             |
| Ampa Receptor   | Complex   | Protein complex | 0.0166         | ERBB4            |
| PRKACB          | 0.143    | Kinase      | 0.0166          | PENK             |
| Msx3            | 0.932    | Peptidase   | 0.0166          | IGF1             |
| ERAP1           | 1.747    | Phosphatase | 0.0166          | CCL5             |
| PTPN1           | 0.311    | Transcription regulator | 0.0166 | ERBB4, GFAP     |
| BLC18A1         | 0.138    | Transporter | 0.0166          | CYBB             |
| mir-320b (and other miRNAs w/ seed AAAGCUG) | Mature microRNA | 0.0166 | IGF1             |
| 190 nucleobase  | Biologic drug | 0.0166 | CCL5             |
| MOV10L1         | 0.016    | Enzyme      | 0.0166          | NPPA             |
| TAF10           | 0.394    | Transcription regulator | 0.0166 | IGF1             |
| LRG1            | 0.927    | Other       | 0.0166          | ERBB4            |
| RNF17           | 0.22     | Other       | 0.0166          | SERPIN A3        |
| NOCT            | 0.315    | Transcription regulator | 0.0166 | IGF1             |
| EPHA4           | 0.533    | Kinase      | 0.0166          | IGF1             |
| SBB       | 1.439    | Other       | 0.0166          | PENK             |
| Nru4r           | 0.016    | G-protein coupled receptor | 0.0166 | IGF1             |
| Lasentib        | 0.016    | Chemical drug | 0.0166          | CCL5             |
| ERC2            | 0.145    | Enzyme      | 0.0166          | IGF1             |
| U 50488H        | 0.016    | Chemical reagent | 0.0166          | CYBB             |
| Icatibat         | 0.016    | Chemical drug | 0.0166          | CYBB             |
| Amlactin         | 0.016    | Chemical drug | 0.0166          | PTN              |
| BB-Cl-amidine   | 0.016    | Chemical reagent | 0.0166          | IGF1             |
| Gene/Protein          | Type                 | Z-score | p-value   |
|----------------------|----------------------|---------|-----------|
| zimelidine           | chemical drug        | 0.0186  | SERPINA3  |
| lysophosphatidylcholine | chemical - other       | 0.0186  | CCL5,EDN4 |
| IFI16                | transcription regulator | 2.645   | 0.0191    |
| CCL5                 | cytokine             | 4.542   | 0.0191    |
| PLX5E22              | chemical drug        | 0.0191  | B2M,CCL5  |
| GATA6                | transcription regulator | 0.0191  | C3A/C4B,IRF8,NPPA |
| CHUK                 | kinase               | 0.192   | 0.0196    |
| miR-16-5p (and other miRNAs with seed AGCAAGCA) | mature microRNA | 0.0196  | IG1,LMATOR5,NPPA |
| cisplatin            | chemical drug        | 1.747   | 0.0199    |
| Fos                  | group                | 0.02     | IG1,NPPA,PCDH1,PTN |
| PPARβ                | other                | 0.02     | CCL5,IGF1 |
| FFAO3                | G-protein coupled receptor | 0.0205  | Cc9,GGBP2 |
| TGFA                 | growth factor        | 0.0205  | CCL5,GFAP |
| C3                   | peptidase            | 0.0205  | CTD,CCL5 |
| PPP3CA               | phosphatase          | 0.0205  | GFAP,NPPA |
| epinephrine          | chemical - endogenous mammalian | 0.0205  | NPPA,PTN |
| ANGPT2               | growth factor        | 0.0206  | CCL5,CYBB,NPPA |
| metformin            | chemical drug        | 0.0206  | IGF1,PARP14 |
| E2F2                 | transcription regulator | 0.0206  | CCL5,ERBB4,IGF1,PTN |
| UCA1                 | other                | 0.0213  | NPPA |
| cyanidin 3-O-glucoside | chemical - endogenous non-mammalian | 0.0213  | CCL5 |
| PPT1                 | enzyme               | 0.0213  | GFAP |
| ABCC1                | transporter          | 0.0213  | CYBB |
| LITAF                | transcription regulator | 0.0213  | CCL5 |
| U1 snRNP             | complex              | 0.0213  | CCL5 |
| CDSL                 | transmembrane receptor | 0.0213  | CCL5 |
| ERC4                 | enzyme               | 0.0213  | IGF1 |
| RLNT1                | other                | 0.0213  | NPPA |
| miR-192-5p (and other miRNAs with seed UGACUCAU) | mature microRNA | 0.0213  | IGF1 |
| POU3F3               | transcription regulator | 0.182   | FABP7 |
| SCN1A                | ion channel          | 0.0213  | CYBB |
| SMN1/SMN2            | other                | 0.677   | IGF1 |
| GRP1                 | transcription regulator | 0.373   | IGF1 |
| HEYL                 | transcription regulator | 2.188   | NPPA |
| TPP1                 | phosphatase          | 0.015   | IGF1 |
| DSG2                 | other                | 2.627   | NPPA |
| MTPN                 | transcription regulator | 0.073   | NPPA |
| Rho1                 | other                | 0.013   | HLA-A |
| CAPN2                | peptidase            | 0.013   | GFAP |
| NCR3                 | transmembrane receptor | 0.013   | CCL5 |
| CCL-34               | chemical reagent     | 0.013   | Cc9 |
| JUNB                 | transmembrane receptor | 0.013   | HLA-A |
| cariporide           | chemical drug        | 0.013   | NPPA |
| domoic acid          | chemical toxicant    | 0.013   | GFAP |
| ETV6-NTRK3           | fusion gene/product  | 0.013   | IGF1 |
| epoxyeicosatrienoic acid analog B | chemical reagent   | 0.013   | CYBB |
| epoxyeicosatrienoic acid analog A | chemical reagent   | 0.013   | CYBB |
| tosyllysine chloromethyl ketone | chemical - protease inhibitor | 0.013   | IGF1 |
| USF1                 | transcription regulator | 1.174   | B2M,CTSS |
| TRAF2                | enzyme               | 2.953   | CCL5,MEG1 |
| romidepsin           | biologic drug        | 0.0214  | CCL5,Cc9 |
| pimpyrrolidoneuric acid | chemical drug       | 0.0218  | C1QB,IGF1,TUBB2B |
| TFK                  | kinase               | 0.0219  | CCL5,HLA-A |
| IFN1                 | cytokine             | 0.0224  | HLA-DQβ1,NPTX2 |
| MAPK3                | kinase               | 0.0224  | HLA-DQβ1,NPTX2 |
| Chemical | Type | Regulation | Z-score |
|----------|------|------------|---------|
| Histamine | Chemical - endogenous mammalian | 0.0224 | CCL5, PENK |
| TGM2     | Enzyme | 0.0228 | CD74, PARP14, TAP1 |
| IRF5     | Transcription regulator | 0.0234 | CCL5, IFITM3 |
| NCOA3    | Transcription regulator | 0.0239 | IGFI, IRF1 |
| FGF19    | Growth factor | 0.0239 | HLA-DQB1, SERPINA3 |
| Haloperidol | Chemical drug | 0.0239 | GFAP, PENK |
| Ck2      | Complex | 0.0239 | CYBB |
| IRF-3 dimer | Complex | 0.0239 | CCL5 |
| BVRD-2A  | Enzyme | 0.0239 | CCL5 |
| ZBD2     | Transcription regulator | 0.0239 | HLA-A |
| RUBCN    | Other | 0.0239 | GBP2 |
| AIF4     | Transcription regulator | 0.0239 | WRAP58 |
| MARCHF2  | Enzyme | 0.0239 | CCL5 |
| Salmonella typhimurium lipopolysaccharide | Chemical - endogenous non-mammalian | 0.0239 | CCL5 |
| CD58P1   | Phosphatase | 0.0239 | NPPA |
| PHF6     | Transcription regulator | 0.0239 | IGFI |
| MHC CLASS I (family) | Group | 0.0239 | CCL5 |
| Farnitin | Complex | 0.0239 | CCL5 |
| Nicotin | Chemical reagent | 0.0239 | GFAP |
| GADD45G  | Other | 0.0239 | NPTX2 |
| TRG      | Other | 0.0239 | HLA-DQB1 |
| DUSP16   | Phosphatase | 0.0239 | IFI |
| TPM3     | Other | 0.0239 | IGFI |
| Cc6      | Cytokine | 0.0239 | CT5 |
| NB       | Transporter | 0.0239 | NPPA |
| YB6X3    | Transcription regulator | 0.0239 | HLA-DQB1 |
| Benazepril | Chemical drug | 0.0239 | NPPA |
| ammonium trichloro(dioxoethylene O,O'-)tellurate | Chemical drug | 0.0239 | HLA-DQB1 |
| Brimonidine | Chemical drug | 0.0239 | GFAP |
| PD 168393 | Chemical drug | 0.0239 | CCL5 |
| IL14     | Chemical reagent | 0.0239 | HLA-A |
| 3-beta, 17-beta-androstenediol | Chemical - endogenous mammalian | 0.0239 | LYZ |
| TPT3     | Transcription regulator | 0.0239 | B2M, LYZ, SERPINA3, TAP1 |
| ERBB4    | Kinase | 0.0239 | ERBB4, SERPINA3 |
| Ascorbic acid | Chemical - endogenous mammalian | 0.0244 | IGFI, NPPA |
| SOC3     | Phosphatase | 0.0254 | IRF1, NPPA |
| RGS4     | Enzyme | 0.0259 | IGFI, NPPA |
| ATPI     | Transcription regulator | 0.0259 | NPPA, PENK |
| To-901317 | Chemical reagent | 0.0261 | IFI, MPE1G1, SERPINA3 |
| CCL2     | Cytokine | 0.0264 | CCL5, IGFI |
| Trinitrobenzenesulfonic acid | Chemical reagent | 0.0264 | CCL5, Cxcl9 |
| Stat1-Stat2 | Complex | 0.0265 | IRF1 |
| RNASEH2B | Other | 0.0265 | CCL5 |
| PARP14   | Enzyme | 0.0265 | CCL5 |
| Rhesus theta-defensin 1 | Chemical - endogenous mammalian | 0.0265 | CCL5 |
| DAZ2     | Translation regulator | 0.0265 | IFITM3 |
| L2HGDH   | Enzyme | 0.0265 | CYBB |
| PHLP2    | Enzyme | 0.0265 | NPPA |
| Necrostatin-1 | Chemical reagent | 0.0265 | GFAP |
| EEFA2    | Translation regulator | 0.0265 | CYBB |
| CD244    | Transmembrane receptor | 0.0265 | CCL5 |
| KCNN4    | Ion channel | 0.0265 | CCL5 |
| LGALS8   | Other | 0.0265 | CCL5 |
| HLA-DQB1 | Other | 0.0265 | HLA-DQA1 |
| Gene/Chemical | Expression Value | Function/Type | Expression Value | Associated Genes |
|--------------|-----------------|---------------|-----------------|------------------|
| SEMA4D       | 1.399           | transmembrane receptor | 0.0265 | HLA-DQB1 |
| ITGA4        | 0.717           | transmembrane receptor | 0.0265 | HLA |
| PDK2         | 0.278           | kinase          | 0.0265 | IRF8 |
| NCR1         | 0.451           | transmembrane receptor | 0.0265 | CCL5 |
| RNF41        | 0.275           | phosphatease    | 0.0265 | IRF |
| RELN         | -0.151          | peptidase       | 0.0265 | FABP7 |
| CD200R1      | 0.075           | transmembrane receptor | 0.0265 | Cxcl9 |
| L1RB1        | 0.715           | other           | 0.0265 | Cxcl9 |
| ICN1T1       | 0.392           | ion channel     | 0.0265 | NPPA |
| CTTN         | 0.152           | other           | 0.0265 | CCL5 |
| TDGF4        | 0.225           | growth factor   | 0.0265 | NPPA |
| clomipramine | 0.875           | chemical drug   | 0.0265 | NPPA |
| IGBP1        | 0.875           | other           | 0.0265 | NPPA |
| RELN         | -0.225          | peptidase       | 0.0265 | CCL5 |
| (5-(4-N-methyl-N2-pyridyl)amino)ethoxybenzyl thiazolidine-2,4-dione | 0.225 | chemical reagent | 0.0265 | CTSS |
| OGA          | 0.027           | enzyme          | -0.152 | C1QA,C1QB,FABP7,IGF1 |
| TRA4         | 0.153           | transcription regulator | 0.0265 | PENK,PTN |
| FOX2A2       | 0.374           | kinase          | 0.0265 | CCL5,MPEG1 |
| methotrexate | 0.618           | chemical drug   | 0.0265 | CIGF1,LYTZ,NPTX2 |
| EGF          | 0.74            | growth factor   | -0.548 | bias |
| YBX1         | 0.4             | transcription regulator | 0.0265 | CCL5,HLA-DQB1 |
| RHA          | 0.225           | enzyme          | 0.0265 | NPPA |
| N-acetyl-L-cysteine | 0.225 | chemical drug | 0.0265 | CCL5,HLA-A |
| ADIPQ2       | 0.029           | other           | 0.0265 | CCL5,CYBB,NPPA |
| EIF2AK2      | 0.374           | kinase          | 0.0265 | IRF1,LGAL53BP |
| CTSV         | 0.153           | peptidase       | 0.0265 | PENK |
| mGluR        | 0.374           | group           | 0.0265 | ERBB4 |
| apolipoprotein B | 0.374 | biologic drug | 0.0265 | CCL5 |
| APOL1        | 0.153           | transporter      | 0.0265 | Cxcl9 |
| FBXO42       | 0.731           | other           | 0.0265 | CCL5 |
| Y001         | 0.4             | enzyme          | 0.0265 | CCL5 |
| IRX4         | 0.731           | transcription regulator | 0.0265 | NPPA |
| DHTK1        | 0.731           | enzyme          | 0.0265 | NPPA |
| HTR2B        | 0.731           | G-protein coupled receptor | 0.0265 | NPPA |
| PRPF19       | 0.517           | enzyme          | 0.0265 | NPPA |
| SARM1        | 0.923           | transmembrane receptor | 0.0265 | CCL5 |
| Taq18        | 0.923           | other           | 0.0265 | CCL5 |
| G0s1         | 0.923           | group           | 0.0265 | B2M |
| astroglia   | 0.923           | chemical - endogenous non-mammalian | 0.0265 | GFAP |
| BM66-7548057 | 0.923           | chemical drug   | 0.0265 | ERBB4 |
| TAF5         | 0.852           | transcription regulator | 0.0265 | IGF1 |
| ITL1RD       | 1.149           | other           | 0.0265 | Cxcl9 |
| MED14        | 0.331           | transcription regulator | 0.0265 | IRF8 |
| mIR-193a-3p (and other mature miRNAs w/seed ACUGGCC) | 0.331 | mature microRNA | 0.0265 | ERBB4 |
| m1520        | 0.331           | microRNA        | 0.0265 | IGF1 |
| docosahexaenoic acid | 0.331 | chemical reagent | 0.0265 | CCL5 |
| PLCB1        | 0.259           | enzyme          | 0.0265 | NPPA |
| WWP2         | 0.136           | enzyme          | 0.0265 | CCL5 |
| MMP7         | 0.136           | peptidase       | 0.0265 | ERBB4 |
| LB-205       | 0.136           | chemical reagent | 0.0265 | GFAP |
| ISG15        | 1.698           | other           | 0.0265 | IFTM3 |
| Gene      | log2FC | Description          | log10(p) | Genes                     |
|-----------|--------|----------------------|----------|---------------------------|
| TNF3      | -0.008 | transporter          | 0.0291   | CCL5                      |
| AFF1      | -0.101 | transcription regulator | 0.0291  | IGF1                      |
| CAMK2G    | 0.287  | kinase               | 0.0291   | NPPA                      |
| OSTM1     | -0.379 | other                | 0.0291   | IRF6                      |
| MYZAP     | 0.076  | other                | 0.0291   | NPPA                      |
| CYBA      | 0.416  | enzyme               | 0.0291   | CYBB                      |
| Ifn (includes others) | cytokine  |                      | 0.0291   | IGF1                      |
| emactuzumab | biologic drug | 0.0291  | PTN                      |
| sesame oil | chemical reagent  | 0.0291   | GFAP                     |
| aldosterone | chemical drug |         | 0.0291   | CCL5                      |
| cidofovir | chemical drug | 0.0291   | NPPA                     |
| SD6       | -0.379 | chemical reagent     | 0.0291   | CCL5                      |
| 2,2-bis(4-hydroxyphenyl)-1,1,1-trichloroethane | chemical - endogenous mammalian | 0.0291   | IGF1                      |
| terbutaline | chemical drug   | 0.0291   | GFAP                     |
| phoslopholid | chemical - endogenous mammalian | 0.0291   | CCL5                      |
| CA074-methyl ester | chemical reagent | 0.0291   | GFAP                     |
| theophylline | chemical drug  | 0.0291   | GFAP                     |
| progesterone | chemical drug | 0.0291   | GFAP                     |
| allopregnanolone | chemical - endogenous mammalian | 0.0291   | PENK                      |
| testolone | chemical drug | 0.0291   | IGF1                      |
| erlotinib | chemical drug | 0.0307   | CCL5,CYBB                |
| EP300     | 0.081  | transcription regulator | 0.0312  | IGF1                      |
| THPO      | 0.263  | cytokine             | 0.0313   | IRF1,TAP1                 |
| CEBP8     | 0.263  | transcription regulator | 0.0313  | GFAP,IGF1                 |
| NS399     | 0.263  | chemical reagent     | 0.0313   | CCL5,IGF1                 |
| estrogen receptor | group | 0.0314   | ERBB1,IGF1,PCDH1         |
| PPARC1A   | 0.088  | transcription regulator | 0.106   | IGF1,NPPA,PTN,SERPINA3    |
| L-Lysine  | chemical - endogenous mammalian | 0.0317   | IGF1                      |
| chlorcyclizine | chemical drug | 0.0317   | SERPINA3                 |
| ATP6AP2   | -0.004 | transporter          | 0.0317   | CYBB                      |
| SLC7A2    | -0.001 | transporter          | 0.0317   | Cx9                      |
| BV6       | -0.001 | chemical reagent     | 0.0317   | CCL5                      |
| PTGDR2    | 0.081  | G-protein coupled receptor | 0.0317  | CCL5                      |
| DEPTOR    | -0.012 | other                | 0.0317   | CCL5                      |
| AFAP1-AS1 | -0.012 | other                | 0.0317   | RAC2                      |
| PEL1      | 0.268  | enzyme               | 0.0317   | CCL5                      |
| STAR      | 0.211  | transporter          | 0.0317   | CCL5                      |
| CST3      | 0.431  | other                | 0.0317   | IRF6                      |
| AVPR1A    | -3.835 | G-protein coupled receptor | 0.0317  | NPPA                      |
| CAV3      | -0.106 | enzyme               | 0.0317   | NPPA                      |
| CCR3      | -0.106 | G-protein coupled receptor | 0.0317  | NPPA                      |
| PIAS2     | 0.277  | transcription regulator | 0.0317  | IGF1                      |
| RB105C1   | -0.002 | other                | 0.0317   | CCL5                      |
| DORZ      | 0.344  | kinase               | 0.0317   | HLA-A,a                   |
| NPY2R     | 0.143  | kinase               | 0.0317   | NPPA                      |
| ARF6      | 0.085  | transporter          | 0.0317   | CCL5                      |
| DAT5      | 0.085  | transporter          | 0.0317   | NPPA                      |
| MAS1      | 0.135  | G-protein coupled receptor | 0.0317  | CYBB                      |
| KASGRF1   | 0.135  | other                | 0.0317   | IGF1                      |
| NGFI     | 0.575  | other                | 0.0317   | PENK                      |
| **riluzole** | chemical drug | 0.0317 | **GFAP** |
| **threonine** | chemical drug | 0.0317 | **GF1** |
| **Mt** | group | 0.0317 | **GFAP** |
| **KITLG** | -0.759 | growth factor | 0.0321 | **B2M**, **GFAP**, **NPPA** |
| **primac acid** | chemical toxicant | 0.0321 | **CCL5**, **HLA-DQA1**, **IRITM3**, **IRIF8** |
| **GATA4** | transcription regulator | 0.0324 | **IRF8**, **NPPA**, **SERPINA3** |
| **cyclosporin A** | biologic drug | 0.152 | 0.0328 | **CA4/C4B**, **CCL5**, **GFAP**, **NPPA** |
| **LMNA** | 0.406 | other | 0.0333 | **IRF1**, **IRIF8**, **NPPA** |
| **Mapk** | group | 0.0341 | **CYBB**, **IGF1** |
| **MYF6** | transcription regulator | 0.0341 | **Cxcl9**, **IGF1** |
| **neomycin** | chemical drug | 0.0343 | **CCL5** |
| **perhexiline** | chemical drug | 0.0343 | **SERPINA3** |
| **ISGF3** | complex | 0.0343 | **IRF1** |
| **TRIM18** | enzyme | 0.0343 | **CCL5** |
| **harmine** | chemical - endogenous non-mammalian | 0.0343 | **NPPA** |
| **ANG** | 1.432 | enzyme | 0.0343 | **CCL5** |
| **PPP3CB** | 0.226 | phosphatase | 0.0343 | **CYBB** |
| **CCL21** | cytokine | 0.0343 | **Cxcl9** |
| **GNB3** | enzyme | 0.0343 | **CX3G13** |
| **PDE4B** | 0.022 | enzyme | 0.0343 | **CCL5** |
| **BGLAP** | other | 0.0343 | **CD74** |
| **GHSR** | G-protein coupled receptor | 0.0343 | **IGF1** |
| **PLAZOG2E** | enzyme | 0.0343 | **CCL5** |
| **EDNRB** | 0.116 | G-protein coupled receptor | 0.0343 | **NPPA** |
| **ACO1** | enzyme | 0.0343 | **GFAP** |
| **MA-602** | chemical reagent | 0.0343 | **IGF1** |
| **6-aminopyrazolopyrimidine derivative compound II** | chemical drug | 0.0343 | **FITM3** |
| **RV 838** | chemical reagent | 0.0343 | **GFAP** |
| **hormone** | chemical drug | 0.0343 | **IGF1** |
| **[D-Ala2,N-Me-Phe4,Gly5-ol]-Enkephalin** | chemical reagent | 0.0343 | **CCL5**, **CYBB**, **IGF1** |
| **6-aminopyrazolopyrimidine derivative compound II** | chemical drug | 0.0353 | **C4A/C4B**, **CYBB** |
| **peptidoglycan** | chemical - endogenous non-mammalian | 0.0358 | **HLA-A**, **MPEG1** |
| **ciprofloxacin** | chemical drug | 0.0358 | **HG1-A**, **MPEG1** |
| **cyclic AMP** | chemical - endogenous mammalian | 0.036 | **IGF1**, **LGALS3BP**, **PENK** |
| **TNFSF11** | cytokine | 0.036 | **CCL5**, **CYBB**, **GFAP**, **SERPINA3** |
| **CDK11A** | 0.219 | kinase | 0.0363 | **Cxcl9**, **FITM3**, **LGALS3BP** |
| **NPEUL2** | 0.67 | transcription regulator | 0.0364 | **CL5**, **CYBB**, **GFAP**, **SERPINA3** |
| **mexinidine** | chemical drug | 0.0369 | **NPPA** |
| **Ginkgo biloba** | chemical drug | 0.0369 | **CCL5** |
| **4-nonylphenol** | chemical toxicant | 0.0369 | **IGF1** |
| **[N2-(gamma-D-glutamyl)-meso-2,2'-diaminopimelic acid]** | chemical reagent | 0.0369 | **CCL5** |
| **SCAVENGER receptor CLASS A** | group | 0.0369 | **CCL5** |
| **DNAJC3** | 0.149 | other | 0.0369 | **Ngn** |
| **mir-302** | microRNA | 0.0369 | **CCL5** |
| **PLCE1** | enzyme | 0.0369 | **GFAP** |
| **PTP8E** | phosphatase | 0.0369 | **Cxcl9** |
| **PIAS3** | 0.289 | transcription regulator | 0.0369 | **SERPINA3** |
| **TRAF4** | -0.408 | other | 0.0369 | **CCL5** |
| **CSF3R** | 2.887 | transmembrane receptor | 0.0369 | **Lyz** |
| **ZBTB32** | transcription regulator | 0.0369 | **HLA-DQ8** |
| **RALA** | enzyme | 0.0369 | **NPPA** |
| Gene/Protein | Type                  | Expression | Change | Functions/Properties                                                                 |
|-------------|-----------------------|------------|--------|--------------------------------------------------------------------------------------|
| ADAM15      | peptidase             | -0.139     |        | CCL5                                                                                 |
| SOCS2       | other                 | 0.0369     |        | IGF1                                                                                 |
| picrox chloride | chemical toxicant   | 0.0369     |        | HLA-DQA1, IGF1, NRPA3                                                              |
| metoprolol  | chemical drug         | 0.037      |        | GFAP, IGF1, IGF1, NPPA                                                                |
| streptozocin | chemical drug         | 0.037      |        | GFAP, IGF1, IGF1, NPPA, NRPA3                                                       |
| GNA15       | enzyme                | 0.037      |        | GP2, SERPINA3                                                                      |
| pseudoxyalumin | chemical drug   | 0.037      |        | IGF1, NPPA                                                                          |
| LDL         | complex               | 0.0373     |        | CCL5, CYBB, IGF1                                                                   |
| hyaluronic acid | chemical - endogenous mammalian | 0.0376 |        | CCL5, CyIβ                                                                   |
| 5-N-ethylcarboxyamido adenosine | chemical reagent | 0.0388 |        | HLA-DQA1, HLA-DQB1                                                                |
| L-glutamic acid | chemical - endogenous mammalian | 0.0388 |        | B2M, TAP1                                                                         |
| arsenite     | chemical toxicant     | 0.0388     |        | IGF1, IRF1                                                                          |
| 5-hydroxytryptamine | chemical - endogenous mammalian | 0.0394 |        | CYBB, IGF1                                                                         |
| estrone      | chemical - endogenous mammalian | 0.0395 |        | IGF1                                                                               |
| TIFA         | other                 | 0.0395     |        | CCL5                                                                               |
| IFNL2        | other                 | 0.0395     |        | CyIβ                                                                               |
| TLR5         | other                 | 0.0395     |        | B2M                                                                                |
| TAP1         | ion channel           | 0.0395     |        | HLA-A                                                                              |
| TLR5         | other                 | 0.0395     |        | IFN                                                                              |
| PTBP1        | enzyme                | 0.0395     |        | SERPINA3                                                                           |
| SPTLC2       | enzyme                | 0.0395     |        | NPPA                                                                               |
| BTK          | transcription regulator | 0.0395 |        | NPPA                                                                               |
| MGEA8        | other                 | 0.0395     |        | NPPA                                                                               |
| CAPN4        | peptidase             | 0.0395     |        | CCL5                                                                               |
| DRA5A3       | other                 | 0.0395     |        | IGF1                                                                                |
| PRRA         | other                 | 0.0395     |        | IRF1                                                                               |
| CCL19        | cytokine              | 0.0395     |        | CyIβ                                                                               |
| HRNRPD       | transcription regulator | 0.0395 |        | PENK                                                                               |
| Pigs2d2      | other                 | 0.0395     |        | CCL5                                                                               |
| RGS1         | enzyme                | 0.0395     |        | CyIβ                                                                               |
| SIRPA        | phosphatase           | 0.0395     |        | CCL5                                                                               |
| intralipid   | chemical drug         | 0.0395     |        | PENK                                                                               |
| FITC         | chemical reagent      | 0.0395     |        | CyIβ                                                                               |
| hydroxylflumide | chemical drug        | 0.0395 |        | IGF1                                                                               |
| N-ethyl-N-nitosourea | chemical toxicant | 0.0395 |        | CyIβ                                                                               |
| zinc protoporphyrin IX | chemical - endogenous mammalian | 0.0395 |        | IGF1                                                                               |
| NUP98-KDMSA  | fusion gene/product   | 0.0395     |        | LYZ                                                                                |
| NUP98-NSD1   | fusion gene/product   | 0.0395     |        | LYZ                                                                                |
| abulmin      | chemical drug         | 0.0395     |        | CCL5                                                                               |
| NAD+         | chemical - endogenous mammalian | 0.0395 |        | NPPA                                                                               |
| aixistatin   | chemical - protease inhibitor | 0.0395 |        | CD74                                                                               |
| cyprotonene acetate | chemical drug    | 0.0395 |        | IGF1                                                                               |
| Histone H3   | group                 | 0.0398     |        | B2M, CCL5, CYBB, IGF1                                                                  |
| diphtheria toxin | chemical - endogenous non-mammalian | 0.0401 |        | C1QA, PENK                                                                       |
| THR8        | ligand-dependent nuclear receptor | 0.0404 |        | LY2, NPPA, PENK                                                                   |
| melatonin    | chemical - endogenous mammalian | 0.0407 |        | GFAP, IGF1                                                                       |
| STAT5B       | transcription regulator | 0.0408 |        | IGF1, IRF1, NPPA                                                                  |
| LDB1        | transcription regulator | 0.0419 |        | IGF1, TAP1, UNC93B1                                                                |
| PTEN         | phosphatase           | 0.0419     |        | CCL5, IGF1, NPPA, PTN, UN493B1                                                      |
| prostaglandin A2 | chemical - endogenous non-mammalian | 0.0421 |        | IGF1                                                                               |
| 2-chloroadenosine | chemical reagent      | 0.0421 |        | NPPA                                                                               |
| salbutrimil | chemical reagent      | 0.0421 |        | NPPA                                                                               |
| salbutrimil | chemical reagent      | 0.0421 |        | CCL5                                                                               |
| Term                  | Type                  | Value  | Associated Terms                  |
|----------------------|-----------------------|--------|-----------------------------------|
| DPH5                 | enzyme                | 0.157  | IGF1                              |
| Retna                | other                 | 0.0421 | NPPA                              |
| CABIN1               | other                 | 0.0421 | NPPA                              |
| NTF4                 | growth factor         | 0.477  | PENK                              |
| PURA                 | transcription regulator| -0.11  | GFAP                              |
| SLC18A3              | transporter           | 0.477  | PENK                              |
| POU3F2               | transcription regulator| -0.287 | FBAP2                             |
| LY96                 | transmembrane receptor| 1.927  | CCL5                              |
| DPY14                | transcription regulator| -1.135 | NPPA                              |
| MRT101               | group                 | 0.0421 | IGF1                              |
| IGHE                 | other                 | 0.0421 | CCL5                              |
| CSK                  | kinase                | 0.0421 | PENK                              |
| GFBP4                | other                 | 0.0421 | IGF1                              |
| TNGFIP2              | other                 | 0.0421 | IGF1                              |
| IFT57                | other                 | 0.0421 | PENK                              |
| TNFRF12A             | transmembrane receptor| 0.0285 | CCL5                              |
| CXCL2                | cytokine              | 1.487  | NPPA                              |
| BGL10                | transcription regulator| -0.129 | CCL5                              |
| CAMK2D               | kinase                | 0.013  | NPPA                              |
| DMH1                 | chemical reagent      | 0.0421 | CCL5                              |
| aroclor 1254         | chemical toxicant     | 0.0421 | Nrgn                              |
| tranylcypromine      | chemical drug         | 0.0421 | CCL5                              |
| glyburide            | chemical drug         | 0.0421 | NPPA                              |
| LXN2                 | transcription regulator| 0.206  | NCL1,TAP1,UNC9381                 |
| STAT5A               | transcription regulator| 2.503  | IGF1,IRF1,SERPINA3                |
| FGF2                 | growth factor         | 0.0427 | GFAP,IGF1,NPPA,PENK                |
| staurosporine        | chemical drug         | 0.0422 | IGF1,SERPINA3,PENK                 |
| interferon beta-1a   | biologic drug         | 0.0438 | HLA-DRB5,IRF1                      |
| E2F                  | group                 | 0.0444 | IGF1,NPPA                          |
| deoxy corticosterone | chemical endogenous mammalian | 0.0447 | CYBB                              |
| picropodophyllin     | chemical drug         | 0.0447 | GFAP                              |
| triclosan            | chemical drug         | 0.0447 | CYBB                              |
| VDR                  | other                 | 0.0447 | CCL5                              |
| FZD9                 | G-protein coupled receptor | 1.961  | CCL5                              |
| GSDE1                | enzyme                | 0.0447 | FABP2                             |
| IL17F oligomer       | complex               | 0.0447 | CCL5                              |
| MYT1                 | transcription regulator| 0.94   | Bcl2                              |
| ARG1                 | enzyme                | 0.0447 | IGF1                              |
| NRP1                 | transmembrane receptor| -0.45  | HLA-DRB5,CCL5                     |
| DDX3X                | enzyme                | 0.033  | CCL5                              |
| NBEAL2               | other                 | 0.0447 | IGF1                              |
| TOT1A                | enzyme                | 0.0447 | Nrgn                              |
| S1PR3                | G-protein coupled receptor | 0.696  | IGF1                              |
| IRF2                 | other                 | 0.0447 | CCL5                              |
| premarin             | chemical drug         | 0.0447 | IGF1                              |
| 7-nitroindazole      | chemical reagent      | 0.0447 | GFAP                              |
| phenoxin             | chemical drug         | 0.0447 | CCL5                              |
| cemazolin            | chemical drug         | 0.0447 | CCL5                              |
| STAT3s              | group                 | 0.0451 | IGF1,IRF1                         |
| ILPE                 | enzyme                | 0.0451 | CD74,HLA-DOA1                     |
| Cs                   | cytokine              | 0.0451 | CCL5,CYBB                         |
| 8-bromo-cAMP         | chemical reagent      | 0.469  | bias                              |
| HMOX1                | enzyme                | 0.0454 | GFAP,IGF1,NPPA,RAG2               |
| PI3K (complex)       | complex               | 0.0463 | CYBB,IGF1,NPPA                    |
| AKT1                 | kinase                | 0.0467 | CCL5,CD74,NPPA                    |
| mw-155               | microRNA              | 0.047  | CCL5,IRF2                         |
| SB-431542            | chemical reagent      | 0.047  | GFAP,IGF1                         |
| N(R)-3-kohobilinyl)-S-N-methylcarboxamidoadenosine | chemical drug | 0.0472 | NPPA                              |
| alpha-amanitin       | chemical toxicant     | 0.0472 | GFAP                              |
| Ren2                 | peptidase             | 0.0472 | CYBB                              |
| Gene | Function | Expression Value | Gene | Function | Expression Value |
|------|----------|------------------|------|----------|------------------|
| c-Src | group | 0.0472 | GFAP | | |
| NMDA Receptor | complex | 0.0472 | PENK | | |
| LRBA | other | 0.157 | CCL5 | | |
| ghrelin | biologic drug | 0.0472 | IGF1 | | |
| GRK2 | kinase | 0.008 | NPPA | | |
| Sl100b | other | -0.631 | GFAP | | |
| TAF1 | transcription regulator | 0.328 | IGF1 | | |
| mir-322 | microRNA | 0.0472 | NPPA | | |
| mir-208 | microRNA | 0.0472 | NPPA | | |
| SLC6A3 | transporter | 0.726 | GFAP | | |
| CD46 | transmembrane receptor | 1.487 | LAMTOR5 | | |
| PTGFR | G-protein coupled receptor | 2.131 | NPPA | | |
| CXCL3 | cytokine | 0.0472 | CCL5 | | |
| PDK4 | kinase | 0.0472 | IGF8 | | |
| GAB1 | other | 0.592 | CCL5 | | |
| PCSK1 | peptidase | -0.584 | IGF1 | | |
| pimozide | chemical drug | 0.0472 | IGF8 | | |
| quinpirole | chemical reagent | 0.0472 | NPPA | | |
| piperine | chemical drug | 0.0472 | IGF1 | | |
| iloprost | chemical drug | 0.0472 | CCL5 | | |
| NR5A2 | ligand-dependent nuclear receptor | 0.381 | C1QB,Cxcl8 | | |
| RB1 | | 0.049 | CCL5,Cxcl8,IFITM3,IGF1 | | |
| Rp-cAMPS | chemical - kinase inhibitor | 0.0493 | NPPA | | |
| RHOJ | enzyme | 0.302 | PTN | | |
| CBX7 | other | 0.713 | CTS5 | | |
| XRC6 | enzyme | 0.27 | CCL5 | | |
| PTPN2 | phosphatase | 0.02 | Cxcl9 | | |
| STAT5 inhibitor V1 | chemical reagent | 0.0498 | NPPA | | |
| ITGB4 | transmembrane receptor | 0.826 | CCL5 | | |
| S1PR2 | G-protein coupled receptor | 1.921 | CCL5 | | |
| AICDA | enzyme | 0.0498 | CD74 | | |
| KCNIP3 | transcription regulator | 0.105 | GFAP | | |
| PAEP | other | 0.0498 | CCL5 | | |
| EM2 | other | 1.158 | IGF1 | | |
| NRTN | growth factor | -1.111 | PENK | | |
| KLF13 | transcription regulator | 0.443 | CCL5 | | |
| CEP-1347 | chemical drug | 0.0498 | CCL5 | | |
| thioridazine | chemical drug | 0.0498 | SERPINA3 | | |

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