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Petkovic, F., Lazzarino, G., Engblom, D., Blomqvist, A., (2020), IL-6R expressed on CNS vascular endothelial cells contributes to the development of experimental autoimmune encephalomyelitis in mice, *Journal of Neuroimmunology*, 342, 577211. https://doi.org/10.1016/j.jneuroim.2020.577211

**IL-6R expressed on CNS vascular endothelial cells contributes to the development of experimental autoimmune encephalomyelitis in mice**

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**Abstract**

Experimental autoimmune encephalomyelitis (EAE) is the most common model for studying the molecular mechanisms of multiple sclerosis (MS). Here, we examined the CNS-restricted effects of classical interleukin (IL)-6 signaling on the development of EAE, using mice with cell-type specific deletion of the IL-6 receptor (IL-6R). We found that IL-6R deletion in CNS vascular endothelial cells, but not in microglia, ameliorated symptoms of EAE. The milder clinical symptoms in the gene-deleted mice were associated with less demyelination and immune cell infiltration/activation, and lower mRNA levels of cytokines IL-17 and IL-1β, as well as cell adhesion molecules VCAM-1, ICAM-1 and ICAM-2 than what was seen in WT mice. These findings demonstrate that classical IL-6 signaling via endothelial cells of the CNS contributes substantially to development of MS-like pathology, which should be taken into consideration when conceptualizing future therapeutic approaches.

**Keywords:** Demyelination, Interleukin-6, Microglia, Multiple sclerosis, EAE, Endothelial cells

**List of abbreviations:** EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; IL, interleukin; VCAM-1, vascular cell adhesion molecule 1; ICAM, intracellular adhesion molecule; Th, T helper; PBS, phosphate-buffered saline; Iba1, ionized calcium-binding adapter molecule 1; MOG, myelin oligodendrocyte glycoprotein; IFN, interferon; TNF, tumor necrosis factor.

## 1. Introduction

Multiple sclerosis (MS), an immune-mediated disease of the central nervous system (CNS), remains incurable, largely due to our limited understanding of the molecular mechanisms underlying its complex pathology. In animal models, pathogenesis of MS is usually studied using experimental autoimmune encephalomyelitis (EAE), an autoimmune T helper (Th) lymphocyte-driven model of this disease (Krishnamoorthy and Wekerle, 2009). Interleukin (IL)-6 is one of the proinflammatory cytokines, which generally is increased in MS patients (Malmeström et al., 2006; Stelmasiak et al., 2000) and therefore considered to have a disease-promoting role. Indeed, it was shown that IL-6 plays a key role in the pathogenesis of EAE, principally by contributing to the development of pathogenic Th17 lymphocytes in the peripheral lymphoid organs (Samoilova et al., 1998; Okuda et al., 1999). However, in addition to its effects in the periphery, IL-6 might exert effects on CNS-resident cells as well, considering the increased expression of this cytokine in the CNS of EAE mice (Murphy et al., 2010).

IL-6 can signal either via a membrane-bound receptor or a soluble receptor, thereby triggering classical signaling or trans-signaling, respectively. Even though both IL-6 signaling pathways are dependent on the subsequent activation of the ubiquitously expressed membrane-bound gp130 protein, it is thought that they may activate distinct downstream intra-cellular pathways, resulting in differential cellular responses (Scheller et al., 2011). However, the data on which cell types in the CNS express the membrane-bound IL-6 receptor (mIL-6R), and which thereby could respond to classical IL-6 signaling, are inconsistent. Still, it seems that the mIL-6R is not ubiquitously but rather selectively expressed in certain cell types, therefore limiting the classical IL-6 signaling to particular cell populations, namely endothelial cells of the blood vessels and microglia (Blecharz-Lang et al., 2018; Eskilsson et al., 2014; Lin and Levison, 2009).

Here we studied the CNS-restricted effects of classical IL-6 signaling in EAE, using mice with cell-specific deletion of IL-6R in either endothelial cells of the CNS (IL-6R:Slco1c1) or microglia (IL-6R:Cx3Cr1).

## 2. Material and methods

### 2.1 Animals

Mice with cell-specific deletion of the IL-6R gene were generated by crossing mice possessing loxP sites flanking exons 4-6 of the IL-6R-α chain (*Il6ra*; The Jackson Laboratory) with mice expressing tamoxifen-inducible Cre recombinase ($CreERT^{T2}$) under the Slco1c1 promoter (expressed by cerebrovascular endothelium; Ridder et al., 2011) or the Cx3Cr1 promoter (expressed by myeloid cells; Goldmann et al., 2013). Littermates that did not inherit the $CreERT^{T2}$ gene were designated as wild type (WT) mice. Gene deletion was induced in 6-7-week-old female mice with tamoxifen, as described elsewhere (Eskilsson et al., 2014). The same treatment was given to WT mice. All the experiments were approved by the Linköping Animal Care and Use Committee and followed international guidelines.

Both Cre-lines are well validated. The Slco1c1-$CreER^{T2}$ line results in recombination preferentially in small and medium-sized brain vessels (Eskilsson et al., 2017), although recombination in in epithelial cells of the choroid plexus and some GFAP+ astrocytes also has been reported (Ridder et al., 2011). It has also been demonstrated to attenuate immune-induced IL-6R expression in the brain (Eskilsson et al., 2014). Similarly, the Cx3Cr1-$CreER^{T2}$ line has been extensively validated using reporter lines (Goldmann et al., 2013), and work in this laboratory has demonstrated a pronounced phenotype of the IL-6R:Cx3Cr1 mice in an immune-induced place aversion paradigm.

## 2.2 EAE induction

EAE was induced 4 weeks after the tamoxifen treatment, by giving the mice a 200 µl subcutaneous injection containing 200 µg of myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ (GenScript, New Jersey, USA) in a complete Freund´s adjuvant (InvivoGen, San Diego, CA, USA) containing 300 µg of *M. tuberculosis* (BD, Sparks, MD, USA). Simultaneously and 48 h later, mice were injected intraperitoneally with 300 ng of pertussis toxin (Invitrogen, Carlsbad, CA, USA). Clinical manifestations of EAE were scored as follows: 0, no clinical manifestations; 1, tail paralysis; 2, hind limb paresis; 3, hind limb paralysis; 4, partial-fore limb paralysis. Intermediate 0.5 scores were assigned if the animals displayed the symptoms between the two scores. Tissue for histological and molecular biological analyses was taken from mice that had reached a certain score and remained at that score for 3 consecutive days (considered as peak of the disease). If no symptoms developed, animals were followed for a total of 26 days before they were killed.

## 2.3 Quantitative PCR

For the gene expression analysis, mice were asphyxiated with $CO_2$ and briefly perfused with phosphate-buffered saline (PBS) prior to spinal cord isolation. RNA isolation, reverse transcription and quantitative PCR were performed as described previously (Eskilsson et al., 2014). TaqMan primers used were: IL-17 (Mm00439618_m1), IFN-γ (Mm01168134_m1), IL-1β (Mm01336189-m1), TNF (Mm00443258-m1), Vcam-1 (Mm01320970_m1), Icam-1 (Mm00516023_m1), Icam-2 (Mm00494862_m1) and GAPDH (Mm99999915g1) (Applied Biosystems, Foster city, CA, USA).

## 2.4 Histology

For histological analysis, mice were perfused with cold 4% paraformaldehyde, lumbar spinal cords were isolated, post fixed in the same fixative overnight on 4°C and further processed for paraffin embedding and 5 µm-thick sectioning on a microtome (HM 355S Automatic

Microtome; ThermoFisher, Watham, MA, USA). Luxol fast blue stain for visualization of spinal cord myelin and hematoxylin-eosin stain for visualizing cell nuclei were performed as described previously (Petković et al., 2016). The area of demyelination was measured using ImageJ (www.imagej.nih.gov; version 1.52n; Java 1.8.0_202). Slides were digitized, the lateral funiculus was manually outlined as the region of interest (ROI), and a threshold value was manually set and kept constant across analysis of all slides from all animals. The Luxol Fast Blue-negative area (i.e. area of demyelination) was calculated as percentage of the outlined ROI. Three to four images per animal were examined.

For Iba1 immunohistochemistry, first the activity of endogenous peroxidase was blocked by 5 min incubation with 2% $H_2O_2$ in 70% methanol. **S**ections were then incubated for 1 h in a blocking buffer solution (PBS, pH 7.4, containing 1% bovine serum albumin and 0.1% Triton X-100), followed by incubation with the primary antibody anti-Iba1 (1:1000; 178847; Abcam, Cambridge, UK) overnight at 4ºC. Subsequent steps included 1 h incubation with secondary biotinylated anti-rabbit antibody (1:500, BA-1000; Vector, Burlingame, CA, USA) and 2 h with streptavidin-peroxidase (ABC kit, Vector), both at the room temperature. The peroxidase activity was visualized using 3,3´-diaminobenzidine tetrahydrochloride (Sigma, St Louis, MO, USA).

Infiltration of cytotoxic T cells was determined by immunofluorescence. Antigen retrieval was performed in a PT Link Rinse Station, Code PT200 (Agilent Santa Clara, CA 95051) using EnVision™ FLEX Target Retrieval Solution, High pH (Dako Omnis; Agilent) following the manufacturer's instructions. Sections were then incubated with a monoclonal mouse anti-CD3 antibody (Clone F7.2.38; Dako, Glostrup, Denmark) diluted 1:50 overnight at 4°C followed for 2 h at RT by donkey anti-mouse IgG (H+L) conjugated with Alexa Fluor 555 (A31570, Life Technologies, Invitrogen, Paisley, UK), diluted 1:1000. Quantification of

the number of labeled cells was done manually using the "multi-point" tool in Image J on 3-4 sections per animal.

### 2.5 Statistics

Statistical analysis was performed in GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA), using either Mann-Whitney U test or two-way ANOVA followed by Bonferroni´s *post hoc* test for multiple comparisons. Data are presented as mean ± SEM, if not otherwise stated.

## 3. Results and Discussion

While there was no significant difference in the incidence and the time of onset of EAE symptoms between WT and IL-6R:Sloco1c1 mice (Table 1), IL-6R:Slco1c1 mice developed substantially milder clinical manifestations of EAE than their WT littermates (Fig. 1A, Table 1). In contrast, mice with deletion of IL-6R in microglia did not show any modification of the clinical manifestations of EAE compared to their WT counterparts (Fig. 1B, Table 1). In line with ameliorated clinical symptoms of EAE, IL-6R:Slco1c1 mice presented clearly less demyelination of the spinal cord white matter than WT mice at the peak of EAE (3 ± 2% vs 17 ± 3% in the lateral funiculus, n = 4 and 5 respectively; two-tailed *t*-test $P = 0.0112$; Fig. 1 C, D, I). Relative preservation of the myelin in IL-6R:Slco1c1 mice coincided with less immune cell infiltration (Fig. 1 E, F), and more specifically with less microglia/macrophage activation and infiltration compared to what was seen in WT mice (Fig. 1 G, H). These results demonstrated overall reduction of EAE-associated histopathological changes in the spinal cord of IL-6R:Slco1c1 mice, which coincided with milder clinical manifestations of EAE in these mice.

A caveat in the interpretation of the present data could be that deletion of the IL-6R by the Slco1c1-CreER$^{T2}$ line could have affected the peripheral inflammatory response. However,

although such an affect cannot be excluded, it is unlikely since the Slco1c1-CreER$^{T2}$ line results in recombination almost exclusively in the brain (Ridder et al., 2011; Wilhelms et al., 2014; Fritz et al., 2018), and deletion of inflammatory associated molecules, including IL-6R, by the Slco1c1-CreER$^{T2}$ have shown normal peripheral inflammatory responses (Eskilsson et al., 2017; Fritz et al., 2018).

EAE is an autoimmune model of MS, driven by peripherally primed MOG-specific Th1 and Th17 lymphocytes that infiltrate the CNS and propagate neuroinflammation and tissue damage (Krishnamoorthy and Wekerle, 2009). Gene expression analysis of the most typical proinflammatory cytokines at the peak of EAE in this paradigm, namely IL-17, interferon (IFN)-γ, IL-1β and tumor necrosis factor (TNF)α, showed that the induction of these disease-promoting cytokines was not uniformly attenuated in spinal cords of IL-6R:Slco1c1 (Fig. 2). While the expression of IL-17 and IL-1β was significantly lower than in WT mice, there was no difference in the expression of IFN-γ and TNFα, suggesting that EAE was ameliorated via a specific mechanism and not merely by a general reduction in the expression of proinflammatory, generally disease-promoting, cytokines. The major producers of IL-17 and IFN-γ are Th17 and Th1 lymphocytes, respectively (Bettelli et al., 2007). Therefore, decreased expression of IL-17, but not of IFN-γ, might be a consequence of a reduced permissiveness of the IL-6R-deficient CNS endothelium for transmigration of Th17 but not Th1 lymphocytes.

Further, we detected lower induction of gene expression for cell adhesion molecules involved in immune cell extravasation, namely VCAM-1, ICAM-1 and ICAM-2, in spinal cords of IL-6R:Slco1c1 mice compared to what was found in WT mice at the peak of EAE. (Fig. 2A). In line with these observations we also found less infiltration of CD3 positive cells in the spinal cord in IL-6R:Slco1c1 mice than in WT mice (29 ± 14 vs 117 ± 18 cells per section, n = 4 and 5 respectively; two-tailed *t*-test $P = 0.0077$; Fig. 2B, C). The importance of

CNS endothelial VCAM-1 expression in MS is well established, since one of the drugs used for treating MS, namely natalizumab, is interfering with the ability of immune cells to bind to VCAM-1 and infiltrate the CNS (Shirani and Stüve, 2018). At the same time, the fold induction of ICAM-1 was much higher compared to that of VCAM-1 and ICAM-2, which might point to a specific role of this cell adhesion molecule in facilitating immune cell egress from the blood vessels at the peak of EAE. Indeed, it was recently reported that Th17 cell transmigration is ICAM-1-dependant (Velázquez et al, 2019). In addition, it was shown that EAE-resistant IL-6 deficient mice were unable to upregulate the expression of VCAM-1 and ICAM-1 in the CNS, unlike their WT counterparts (Eugster et al., 1998).

It has been reported that IL-6 trans-signaling contributes to the EAE development as well, by acting on the CNS endothelium (Linker et al., 2008). In that study, systemic inhibition of IL-6 trans-signaling modestly ameliorated the symptoms of EAE, and the effect was linked to reduced expression of VCAM-1 (Linker et al., 2008). These results, together with our data, suggest that the endothelial cells of the CNS may be the key targets of pathological actions of IL-6 in the CSN in this experimental model.

Current immunosuppressive MS treatments are often quite broad in their mode of action, which consequently can lead to various undesirable and serious side effects, in addition to their limited effectiveness. Therefore, there is a need for more specific therapies, which would target individual proteins involved in this self-damaging immune response, perhaps even in a cell-specific manner. Potential targets of such an approach could be cytokines and/or their corresponding receptors, that jointly orchestrate immune cell activation and production of cell-damaging molecules. Having this in mind, we show here that classical IL-6 signaling at the level of CNS endothelium substantially contributes to development of MS-like disease in mice, which, therefore, should be considered when designing new treatments.

**Acknowledgments**

This work was supported by the Swedish Research Council (2016-01301), the Swedish Brain Foundation (FO2019-0033) and the Foundation for Parkinson Research at Linköping University. The authors declare no competing interest.

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**Figure legends**

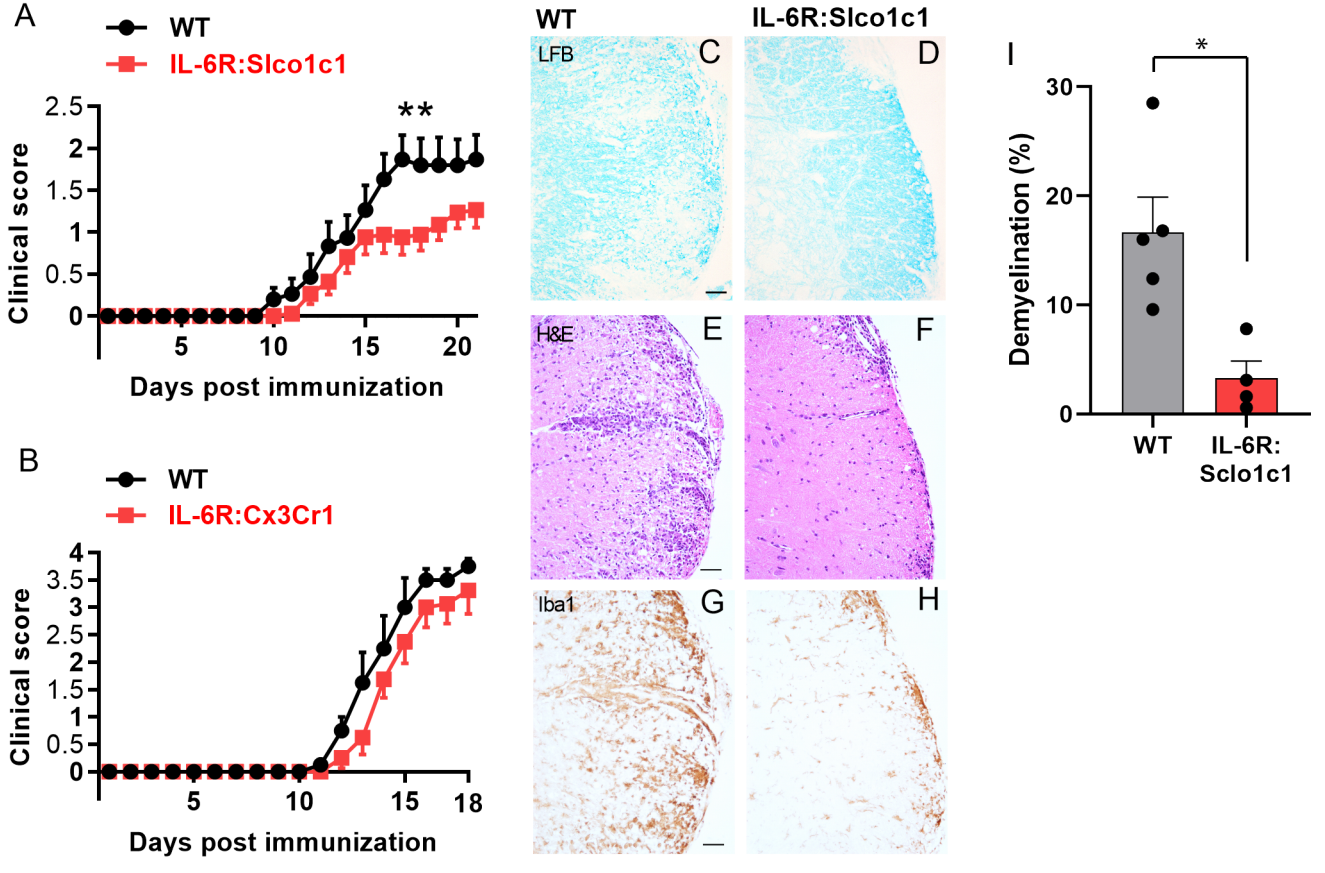
**Figure 1. Deletion of IL-6Rα on CNS endothelial cells ameliorates EAE symptoms and histopathology.** (A) Clinical course of EAE in WT (n = 15) and IL-6R:Slco1c1 (n = 17) mice. (B) Clinical course of EAE in WT (n = 4) and IL-6R:Cx3Cr1 (n = 8) mice. Results are presented as daily mean clinical scores + SEM. * $P < 0.05$, Two-way ANOVA followed by Bonferroni post-hoc test. Representative images of (C, D) Luxol fast blue, (E, F) hematoxylin & eosin, and (G, H) Iba1 immunohistochemistry of lumbar spinal cords of WT (n = 5) and IL-6R:Slco1c1 (n = 4) mice at the peak of EAE. Scale bar = 500 μm. (I) Bar graph showing degree of demyelination in the lateral funiculus of the lumbar spinal cord of WT and IL-6R:Slco1c1 mice.

**Figure 2. Deletion of IL-6R on CNS endothelial cells affects proinflammatory cytokine and cell adhesion molecule gene expression in the spinal cord at the peak of EAE, and infiltration of CD3 positive T cells.** (A) Expression of mRNA for proinflammatory cytokines (IL-17, IL-1β, IFN-γ and TNF) and cell adhesion molecules (VCAM-1, ICAM-1 and ICAM-2) in spinal cord homogenates of WT and IL-6R:Slco1c1 mice at the peak of EAE. The values represent fold induction in mice at the peak of EAE (n = 12) over healthy control mice (n = 4) of the corresponding genotype. Results are presented as mean + SEM from three independent experiments. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; Mann-Whitney U test. (B) Representative images of CD3 immunoreactive cells in the spinal cord of WT (left; n = 5) and IL-6R:Slco1c1 (right; n = 4) mice at the peak of EAE. Scale bar = 100 μm. (C) Bar graph showing average number of infiltrating CD3+ cells in lateral funiculus one side of the lumber spinal cord in WT and IL-6R:Slco1c1 mice.

Table 1. Parameters of EAE symptoms

| **Genotype** | **Incidence** | **Onset** | **Maximal score** |
|---|---|---|---|
| WT | 30/35 (85.7%) | 15.7 ± 4.7 | 2.8 ± 0.9 |
| IL-6R:Slco1c1 | 27/35 (77.1%) | 15.7 ± 4.1 | 1.7 ± 0.9 * |
| WT | 4/5 (80%) | 12.3 ± 1.3 | 3.9 ± 0.3 |
| IL-6R:Cx3Cr1 | 8/8 (100%) | 13.3 ± 0.9 | 3.4 ± 1.2 |

Results are presented as mean ± SD. * $P < 0.05$; Mann-Whitney U test.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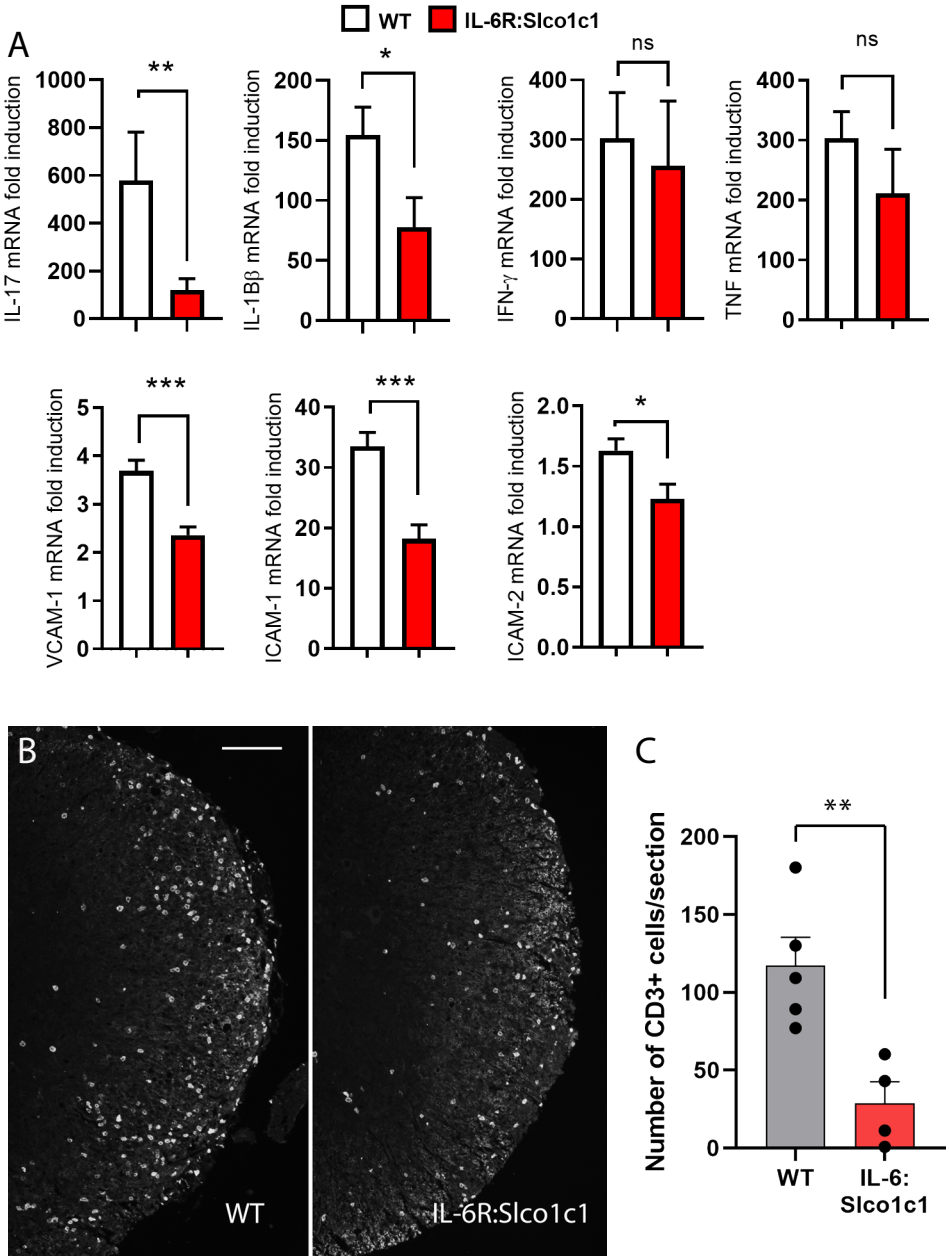
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IFN-γ mRNA fold induction
TNF mRNA fold induction
VCAM-1 mRNA fold induction
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ICAM-2 mRNA fold induction
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B
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IL-6R:Slco1c1
C
Number of CD3+ cells/section
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WT
IL-6:
Slco1c1