

SHORT COMMUNICATION **OPEN ACCESS**

Allergy and Inflammation

IL1R2 Acts as a Negative Regulator of Monocyte Recruitment During Inflammation

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Correspondence: Elodie Segura (elodie.segura@inserm.fr)**Received:** 21 August 2024 | **Revised:** 13 November 2024 | **Accepted:** 18 November 2024**Funding:** This work was funded by INSERM, Institut Curie (core funding), Agence Nationale de la Recherche (Grant ANR-10-LABX-0043, ANR-10-IDEX-0001-02 PSL), Wellcome Sanger Institute, Institut National de la Santé et de la Recherche Médicale (core funding), and Fondation ARSEP (Grant #1277).**Keywords:** IL1- β | IL1R2 | inflammation | leukocyte trafficking | monocyte

ABSTRACT

IL1- β plays a central role in inflammation but its biological action needs to be tightly controlled. Such negative regulation can be exerted by the decoy receptor IL1R2. However, IL1R2 biology in immune cells remains poorly characterized, in particular in monocytes. Using conditional deficient mice, we show that *Il1r2* deficiency in monocytes does not affect their steady-state life cycle but dysregulates their trafficking to inflamed tissues in models of peritonitis and neuro-inflammation. Mechanistically, we found that *Il1r2* deficiency in monocytes increases CCL2 secretion in the inflamed peritoneum, thereby amplifying monocyte recruitment from blood. In autoimmune neuro-inflammation, *Il1r2* deficiency in monocytes exacerbates disease severity. Our findings suggest that the specific action of IL1R2 in monocytes contributes to a feedback mechanism for fine-tuning the numbers of recruited monocytes during inflammation.

1 | Introduction

IL1- β plays a central role in inflammation and immune responses [1]. However, dysregulation of the IL1- β pathway can induce tissue damage and is associated to various human inflammatory pathologies [2]. Therefore, IL1- β biological action needs to be tightly regulated. A major player in IL1- β negative regulation is the decoy receptor IL1R2 [3, 4]; however, a full understanding of its biology in immune cells is lacking.

IL1R2 can be expressed on the cell surface or released in a soluble form and acts as a dominant negative and scavenger [5]. At steady-state, IL1R2 is highly expressed by neutrophils but is also found on monocytes [6–8]. In vivo studies of IL1R2 biology in myeloid cells remain scarce. In models of rheumatoid arthritis, *Il1r2* deficiency increased disease symptoms [8, 9], and it was further shown that

neutrophil-expressed IL1R2 dampened inflammatory cytokine secretion by fibroblasts [9]. By contrast, the role of IL1R2 in monocytes is poorly understood, in particular in physiological settings.

Monocytes originate from the bone marrow and circulate in the blood [10, 11]. Two main populations of monocytes have been described, with a precursor–product relationship [10, 11]. In the mouse, classical Ly6C⁺ monocytes convert into nonclassical Ly6C^{low}CD43⁺ monocytes, which mostly remain in the vasculature [12, 13]. Monocyte egress from the bone marrow is dependent on the chemokine receptor CCR2 and its ligand CCL2 [14–16]. Ly6C⁺ circulating monocytes can then migrate into peripheral tissues where they differentiate into macrophages or dendritic cells (DC), both in steady-state and during inflammation [10, 17, 18]. Monocyte migration from blood into inflamed tissues has been

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found to be mostly dependent on CCL2 and/or CCL5, depending on inflammatory contexts [16, 19–21]. During inflammation, monocytes recruited to inflamed tissues not only act as precursors for macrophages and DC but also secrete large amounts of pro-inflammatory or pro-repair mediators depending on the context [10]. Dysregulation of monocyte trafficking can lead to tissue damage or pathology, including chronic inflammatory disorders and fibrosis [10]. Yet, how numbers of recruited monocytes are fine-tuned during inflammation remains unclear. Here, we show that IL1R2 acts as a negative regulator of monocyte recruitment to inflamed tissues.

2 | Results and Discussion

To address the role of IL1R2 in monocytes, we generated mice with a conditional deletion of *Il1r2* in monocytes, using a strain with YFP expression and tamoxifen-inducible Cre recombinase expression under the control of the *Cx3cr1* promoter. To assess whether *Il1r2* deficiency had an impact on monocyte homeostasis, we evaluated monocyte abundance in steady-state conditions using flow cytometry. We also included neutrophils for comparison. We found no difference between *Cx3cr1***Il1r2*-deficient and WT mice in Ly6C⁺ monocytes numbers in the bone marrow (Figure 1A,B) and blood (Figure 1C,D), showing that their generation and maintenance were unchanged. There was also no difference in CD43⁺ monocytes numbers, suggesting that Ly6C⁺ monocytes conversion into CD43⁺ monocytes was unaffected by *Il1r2* deficiency. CCR2 expression was also similar between *Il1r2*-deficient and WT monocytes (Figure 1E). Collectively, these results indicate that the homeostatic life cycle of *Il1r2*-deficient monocytes is unaltered.

We then sought to address the potential role of IL1R2 in monocytes during inflammation. We first used a sterile peritonitis model, on the basis of the thioglycolate intraperitoneal injection. In this model, IL1- β is secreted by recruited neutrophils within 4 h [22]. In addition, we have previously evidenced in this model the recruitment of Ly6C⁺ monocytes in 24–48 h and their progressive differentiation into monocyte-derived macrophages (mo-Mac) or monocyte-derived DCs (mo-DC) [23]. We verified which cell populations were targets of *Il1r2* deletion in the inflamed peritoneum by taking advantage of YFP expression in Cre⁺ cells. We assessed YFP staining by flow cytometry in cells from the peritoneal lavage (Figure 2A and Figure S1). We detected YFP as expected in monocytes and monocyte-derived cells, but not in neutrophils. We also detected YFP in around 50% of cDC2, suggesting that cDC2 may be partially deleted for *Il1r2*. Nevertheless, because cDC2 represent a minor cell population compared to monocytes (Figure 2B), the contribution to the observed phenotype of *Il1r2* deficiency in cDC2 should be negligible. Neutrophils abundance in inflamed peritoneum was similar in *Cx3cr1***Il1r2*-deficient and WT mice (Figure 2B), suggesting that their recruitment during the early phase of inflammation was unaffected. By contrast, monocytes, mo-DC, and mo-Mac were significantly more abundant in *Cx3cr1***Il1r2*-deficient mice compared to WT littermates, whereas resident macrophages were unchanged (Figure 2B). These results indicate an increased recruitment of *Il1r2*-deficient monocytes into the inflamed peritoneum. Consistent with this, CCL2 concentration in the inflamed peritoneum was higher in *Cx3cr1***Il1r2*-deficient

mice compared to WT littermates (Figure 2C), whereas IL-1 β was virtually undetectable at this time point in the peritoneum (Figure 2D). We then assessed cell numbers in blood during peritonitis. We found no difference in neutrophils, Ly6C⁺ monocytes or CD43⁺ monocytes numbers (Figure 2E), suggesting that monocyte egress from bone marrow was similar between *Cx3cr1***Il1r2*-deficient or WT mice. Blood concentration of CCL2 and IL-1 β was unchanged between *Cx3cr1***Il1r2*-deficient mice and WT littermates (Figure 2F,G). Collectively, these results support the idea that *Il1r2* deficiency in infiltrating monocytes augments CCL2 production specifically in the inflamed peritoneum, thereby amplifying monocyte recruitment from blood.

In our previous work [23], we observed that *Il1r2* expression was increased during human monocyte differentiation specifically in cells committed to DC differentiation. In addition, reanalysis of transcriptomic data showed that *Il1r2* was also more expressed in vivo in peritoneal mo-DC compared to mo-Mac, in both mouse (Immgen dataset) and human [24] (Figure S2A). These observations could indicate a role for IL1R2 in monocyte differentiation into mo-DC. However, we found no difference between *Cx3cr1***Il1r2*-deficient and WT mice in the relative proportion of mo-DC versus mo-Mac, neither in steady-state nor inflamed peritoneum (Figure S2B). These results suggest that *Il1r2* expression is not involved in monocyte fate commitment toward mo-DC versus mo-Mac. Instead, *Il1r2* may be part of a gene program preferentially expressed in DC populations. Consistent with this hypothesis, *Il1r2* was found in transcriptomic signatures of various DC populations in single-cell RNA-seq studies [25–28].

Finally, we addressed the impact of *Il1r2* deficiency in monocytes in a model of neuro-inflammation, experimental autoimmune encephalomyelitis (EAE), in which monocyte recruitment [29–31] and IL1- β production [32, 33] play major roles in the pathology. We first analyzed immune cell populations in lymph nodes draining the site of autoantigen immunization during the initiation phase, before disease onset. We verified which cell populations were targets of *Il1r2* deletion in the inflamed lymph nodes by assessing YFP expression (Figure 3A and Figure S3A). Similar to the peritoneum, we detected YFP expression in monocytes and mo-DC and at low levels in cDC2. Monocyte and mo-DC numbers into lymph nodes 7 days after induction were increased in *Cx3cr1***Il1r2*-deficient mice compared to WT mice (Figure 3A,B), whereas other cell types were unaffected (Figure S3B). The abundance of autoantigen-specific CD4 T cells was also increased in the lymph nodes of *Cx3cr1***Il1r2*-deficient mice (Figure 3C), indicating enhanced priming of pathogenic T cells in deficient mice. This is consistent with the fact that monocyte-derived cells are the main antigen-presenting cells involved in this model [34, 35]. These observations suggest that *Il1r2* deficiency in monocytes increases monocyte recruitment into inflamed lymph nodes. Finally, *Cx3cr1***Il1r2*-deficient mice were more sensitive to pathology than WT littermates, with higher incidence and more severe symptoms (Figure 3D,E). Overall, these results demonstrate that *Il1r2* deficiency in monocytes dysregulates their recruitment into inflamed lymph nodes and exacerbates pathogenesis in a model of autoimmune inflammation.

In conclusion, we show that *Il1r2* deficiency in monocytes does not affect their steady-state life cycle but dysregulates their

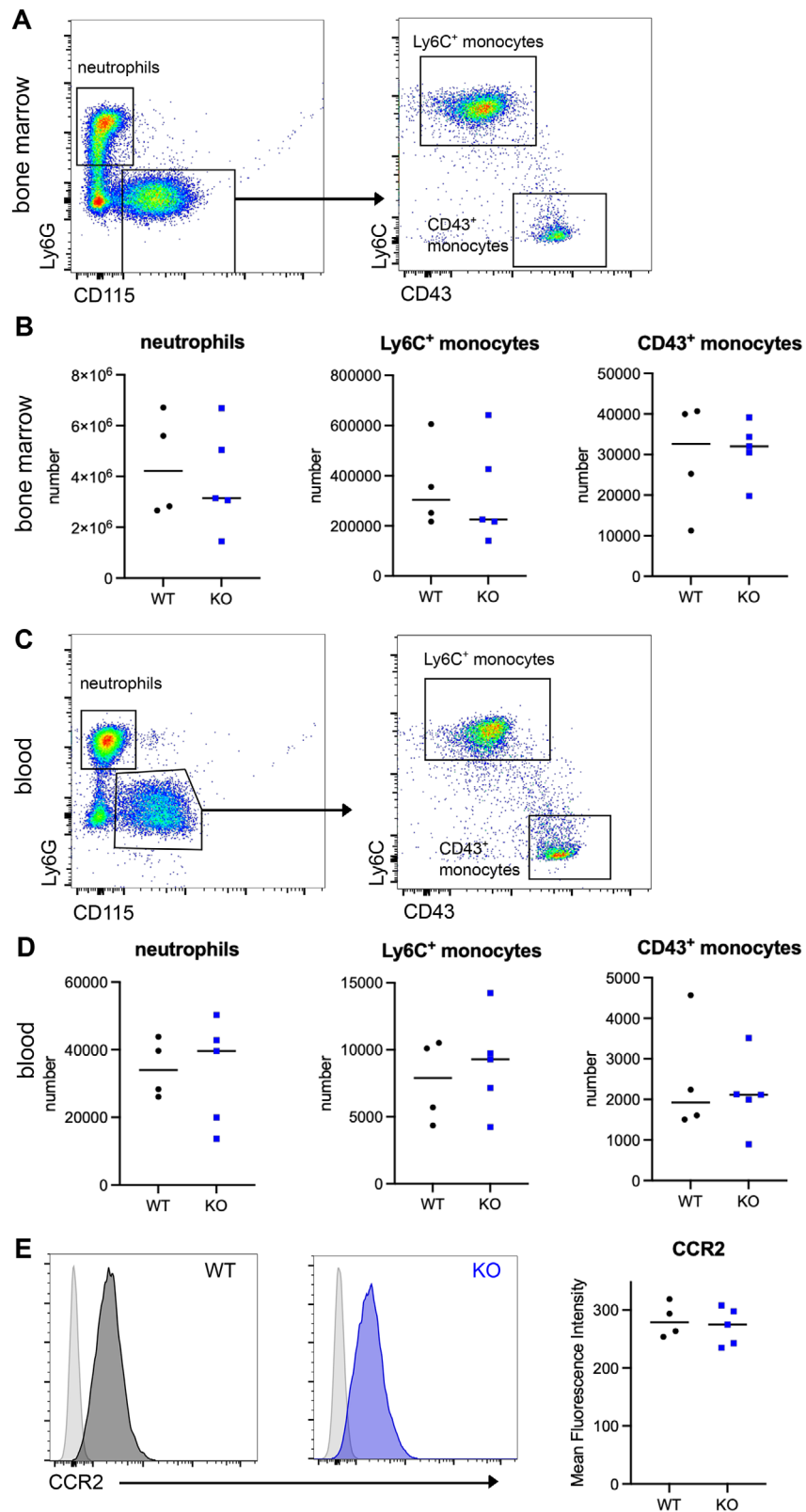


FIGURE 1 | Lack of IL1R2 expression in monocytes does not impact their steady-state life cycle. Bone marrow (A, B, E) and blood (C and D) from Cx3cr1*Il1r2-deficient mice or WT littermates were analyzed. (A and C) Gating strategy. Gated on live singlets TCR- β ⁻CD19⁻CD11b⁺ cells. Representative results are shown. (B) Number of monocytes and neutrophils in bone marrow from one leg. Median is shown ($n = 4-5$ mice in two independent experiments). (D) Number of monocytes and neutrophils in 50 μ L of blood. Median is shown ($n = 4-5$ mice in two independent experiments). (E) CCR2 expression on Ly6C⁺ monocytes from bone marrow. Representative results are shown. Light gray histograms represent fluorescence-minus-one controls. Mean fluorescence intensity, median is shown ($n = 4-5$ mice in two independent experiments).

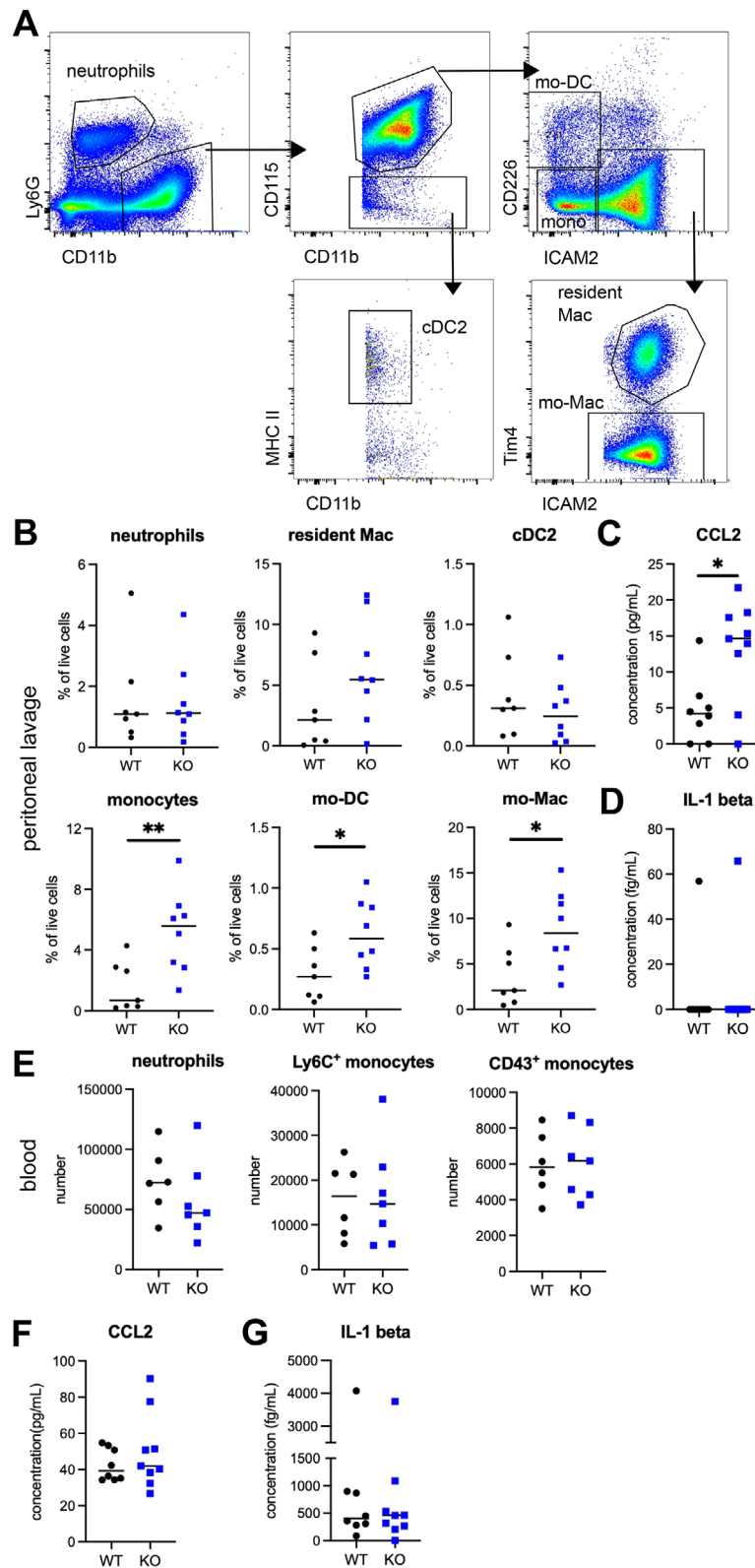


FIGURE 2 | *Il1r2*-deficient monocytes show increased recruitment into inflamed peritoneum. Peritonitis was induced in Cx3cr1**Il1r2*-deficient mice and WT littermates by injection of thioglycolate. (A) Gating strategy for peritoneal lavage analysis. Neutrophils were gated as Ly6G⁺CD11b⁺. CD11b⁺CD115⁺ cells were separated into monocytes, mo-DC, mo-Mac (ICAM2⁺Tim4⁻), and resident macrophages (Res Mac, ICAM2⁺TIM4⁺). cDC2 were gated as CD11b⁺CD115⁻MHCII⁺ cells. (B) Abundance of indicated cell types in peritoneal lavage (B) after 48 h. Median is shown ($n = 6-8$ mice in two independent experiments). Mann-Whitney test, $*p < 0.05$, $**p < 0.01$. (C and D) CCL2 and IL-1 β concentration in peritoneal lavage after 48 h. Median is shown ($n = 8-9$ mice in two independent experiments). (E) Abundance of indicated cell types in 50 μ L of blood after 48 h. Median is shown ($n = 6-8$ mice in two independent experiments). (F and G) CCL2 and IL-1 β concentration in peritoneal lavage after 48 h. Median is shown ($n = 8-9$ mice in two independent experiments). mo-DC, monocyte-derived dendritic cell.

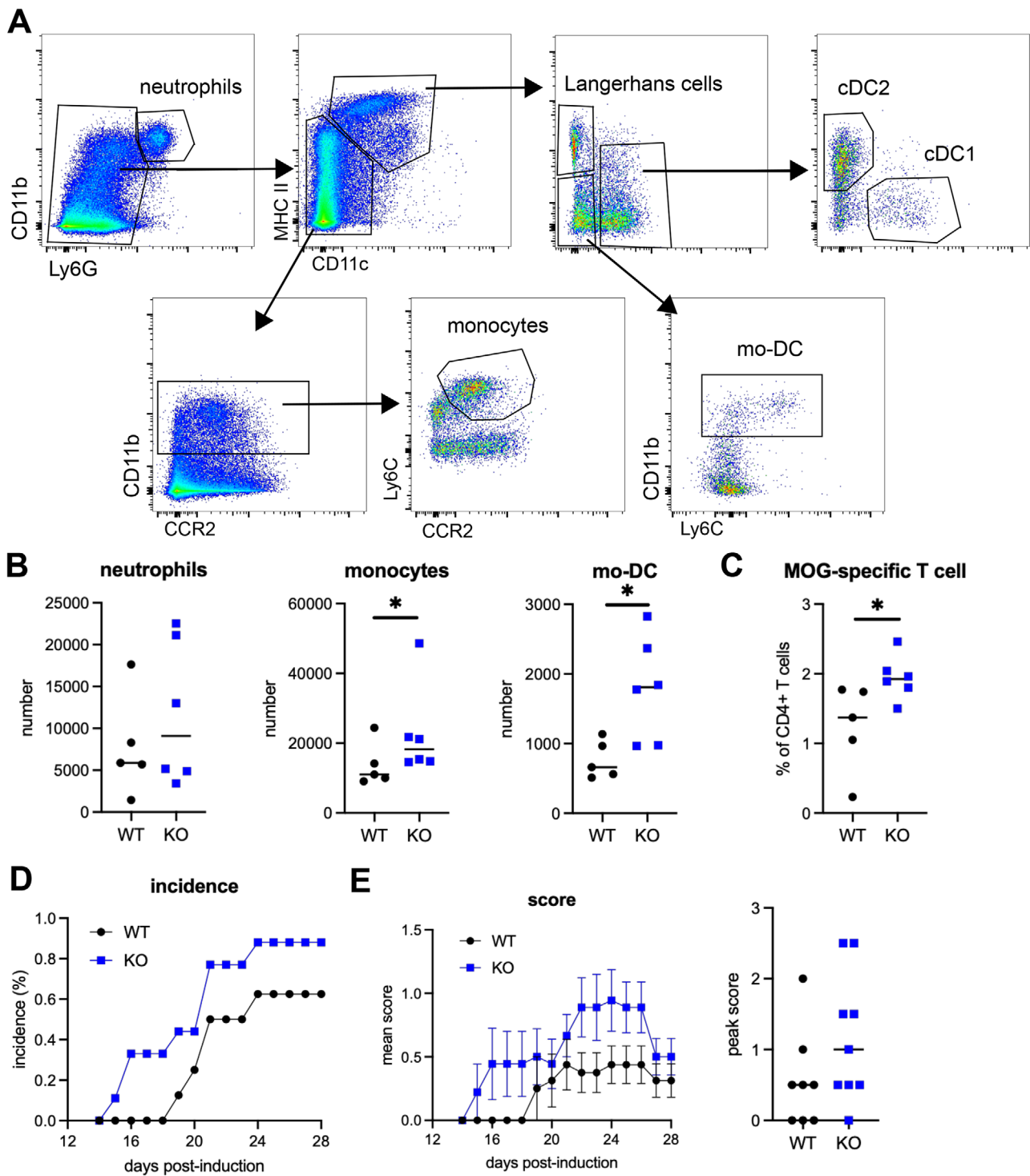


FIGURE 3 | Lack of IL1R2 expression in monocytes worsens autoimmune neuro-inflammation. Experimental autoimmune encephalomyelitis (EAE) was induced in Cx3cr1^{fl}Il1r2-deficient mice or WT littermates by injection of MOG peptide. (A–C) Lymph nodes draining the site of MOG injection were analyzed 7 days after immunization. (A) Gating strategy for lymph node cells. (B) Numbers of indicated cell types in lymph nodes. Median is shown ($n = 5–6$ mice in two independent experiments). Mann–Whitney test, $*p < 0.05$. (C) Abundance of MOG-specific CD4 T cells in lymph nodes. Median is shown ($n = 5–6$ mice in two independent experiments). Mann–Whitney test, $*p < 0.05$. (D) Percentage of mice having developed symptoms. (E) Mean clinical score over time. Bars represent SEM. Peak clinical score ($n = 8–9$ mice in two independent experiments). DC, dendritic cells; mo-DC, monocyte-derived DCs; MOG, myelin oligodendrocyte glycoprotein.

trafficking to inflamed tissues, potentially aggravating monocyte-driven inflammatory damage. On the basis of our results, we propose a model whereby monocytes, following their recruitment to inflamed tissues, participate through IL1R2 expression in the local dampening of IL1- β activity, thereby limiting the production of chemo-attractants and the infiltration of additional monocytes, and ultimately favoring the resolution of inflammation. Of note, IL1- β signaling was shown to induce CCL2 production in multiple cell types in vivo [36]. Mechanistically, IL1- β activity may be neutralized by decreasing IL1- β local availability. Indeed, inflammatory mediators were shown to induce IL1R2 shedding from the cell surface of monocyte ex vivo [7].

Our findings reveal a new facet of the anti-inflammatory actions of IL1R2 [3–5] and shed light onto its specific role in monocyte biology.

3 | Data Limitations and Perspectives

Because the expression of the Cre recombinase is not entirely restricted to monocytes and monocyte-derived cells, we cannot exclude that the observed phenotype may be influenced by partial *Il1r2* deficiency in cDC2, especially in inflamed lymph nodes where cDC2 are present in the same order of magnitude as monocytes. In addition, because microglia are also targeted in this genetic construction [12] and express IL1R2 [37], we cannot exclude that *Il1r2* deficiency in microglia might also contribute to the observed exacerbated neuro-inflammation. Finally, another limitation of the study is the fact that we could not detect IL1- β in the inflamed peritoneum at the time point analyzed. Further work would be needed to definitely demonstrate that *Il1r2* deficiency in monocytes affects IL1- β production, by analyzing shorter time points after the induction of inflammation.

4 | Materials and Methods

4.1 | Animals

Cx3cr1-creERT2 (B6.129P2(Cg)-*Cx3cr1*^{tm2.1(cre/ERT2)}*Litt*/WganJ) mice were obtained from Jackson Laboratory (strain 021160) [38]. *Il1r2-flox* mice (C57BL/6N-A<tm1Brd>*Il1r2*<tm1c(EUCOMM)Wtsi>/WtsiPh) were obtained from the INFRAFRONTIER/EMMA consortium (strain EM:14887, www.infrafrontier.eu) [39, 40], and associated primary phenotypic information can be found at www.mousephenotype.org. *Cx3cr1*Il1r2* strain was generated in-house by crossing *Cx3cr1-creERT2* and *Il1r2-flox* mice. All mice were on C57BL/6J background. Mice were maintained under specific pathogen-free conditions at the animal facility of Institut Curie in accordance with institutional guidelines. Mice were housed in a 12 h light/12 h dark environment, with ad libitum access to water and food. *Cx3cr1*Il1r2* female and male mice (*Il1r2*^{flox/flox} Cre \pm and Cre $-/-$ littermates) were used and sacrificed at age 8–14 weeks. All animal procedures were in accordance with the guidelines and regulations of the French Veterinary Department and have been approved by the local ethics committee (authorization APAFIS #25217-2020042522586261 v1). To avoid confounding effects of circadian rhythms on monocyte biology, mice were always sacrificed for analysis at the same time of day (90 min after light onset).

4.2 | Flow Cytometry

Cells were stained for 30–45 min on ice with indicated antibody cocktails supplemented with Fc block (BD Biosciences) in sterile FACS buffer: PBS (Eurobio Scientific, #CS1PBS01-01) containing 0.5% BSA (Euromedex, #04-100-812-C) and 2 mM EDTA (Invitrogen, #15575-038). After washing with FACS buffer, cells were resuspended in FACS buffer containing DAPI (Fischer Scientific, 100 ng/mL). Cells were acquired on a ZE5 instrument (Bio-Rad) using volumetric counting. Supervised analysis was performed using FlowJo software v10 (FlowJo LLC).

4.3 | Bone Marrow and Blood Cells Analysis

For steady-state analysis, all mice (Cre \pm and Cre $-/-$ littermates) were treated with 5 mg of tamoxifen (Sigma, #T5648) resuspended in corn oil (Sigma, #C8267) by oral gavage, on Days 0 and 3 and sacrificed on Day 4. Bone marrows were flushed out from leg bones and filtered using 40 μ m cell strainers. Blood of 50 μ L was analyzed. Bone marrow and blood cell suspensions were treated with sterile red blood cells lysis buffer Hybri-Max (Sigma, #R7757) for 3 min at room temperature.

Cells were stained with anti-TCR β BUV737 (BD Bioscience, clone H57-597), anti-CD19 BV480 (BD Bioscience clone 1D3), anti-Ly6G APC-Cy7 (Biolegend, clone 1A8), anti-CCR2 BV711 (BD Bioscience, clone 475301), anti-CD43 BB700 (BD Bioscience, clone S7), anti-CD11b PeDazzle594 (BD Bioscience, clone M1/70), anti-Ly6C PeCy7 (Biolegend, clone HK1.4), and anti-CD115 APC (BD Bioscience, clone AFS98).

4.4 | Peritoneal Cells Analysis

For experimental peritonitis, all mice (Cre \pm and Cre $-/-$ littermates) were treated with 5 mg of tamoxifen resuspended in corn oil by oral gavage, on Days 0 and 3. On Day 5, mice received a third gavage of tamoxifen and were injected intraperitoneally with 1 mL of sterile 3.8% brewer's thioglycolate medium (Sigma, #B2551). Thioglycolate was sterilized by autoclaving at 15 lbs. pressure (121°C) for 15 min. Mice were analyzed on Day 7 (48 h after thioglycolate injection). Peritoneal lavage was recovered by intraperitoneal injection of 3 mL of sterile PBS.

Cells were stained with anti-CD115 BUV 395 (BD Bioscience, clone AFS98), anti-Ly6G APC-Cy7 (Biolegend, clone 1A8), and anti-ICAM2 biotin (Biolegend, clone 3C4) followed by staining with streptavidin-BV605 (BD Bioscience), anti-MHC II BV650 (Biolegend, clone M5/114.15.2), anti-CD226 PE-Dazzle594 (Biolegend, clone 10E5), anti-CD11b PerCP-Cy5.5 (BD Bioscience, clone M1/70), and anti-TIM4 Alexa647 (Biolegend, clone RMT4-54).

4.5 | Experimental Autoimmune Encephalomyelitis

All mice (Cre \pm and Cre $-/-$ littermates) were treated with 5 mg of tamoxifen resuspended in corn oil by oral gavage on Days 0, 3, 5, and 7. On Day 5, mice were immunized subcutaneously in the back with 100 μ g myelin oligodendrocyte glycoprotein (MOG)

35–55 peptide (sb-PEPTIDE) emulsified in Incomplete Freund's Adjuvant (Invivogen) supplemented with 4 mg/mL desiccated *Mycobacterium tuberculosis* (H37RA, Sigma). Mice were injected intraperitoneally with 200 ng of pertussis toxin from *Bordetella pertussis* (Calbiochem) on Days 5 and 7 (0 and 48 h after immunization). Mice were examined daily for clinical signs. In agreement with the local ethics committee, mice were scored as follows: 0 healthy; 0.5 tail weakness; 1 limp tail; 1.5 tail paralysis and hindlimb weakness; 2 tail paralysis and limping of one hindlimb; 2.5 tail paralysis and limping of both hindlimbs; 3 paralysis of tail and both hindlimbs; 3.5 paralysis of tail and both hindlimbs, and weakness in forelimbs. Score 3 was predefined as the humane endpoint of the experiment.

4.6 | Lymph Node Cells Analysis

EAE was induced as above. Inguinal lymph nodes were collected 7 days post MOG immunization. For tetramer staining, lymph nodes were dissociated by forcing through a 40 μ m cell strainer. Cells were incubated for 3 h at 37°C in RPMI GlutaMax (Gibco, #61870-010) containing 10% fetal calf serum (Biosera, #FB-1001/500) in the presence of PE-conjugated MOG tetramer (I-A(b) GWYRSPFSRVVH, 2.7 mg/mL) or control tetramer (I-A(b) PVSKMRMATPLLMQA, 2.7 mg/mL) (both obtained from the NIH tetramer core facility). After washing, cells were stained with anti-CD8 BUV395 (BD Bioscience, clone 53-6.7), anti-TCR β BUV737 (BD Bioscience, clone H57-597), anti-CD19 BV480 (BD Bioscience clone 1D3), anti-CD4 PerCPCy5.5 (BD Bioscience, clone RM4-5), and anti-CD11b PeCy7 (BD Bioscience, clone M1/70). Cells were gated on live single CD19⁻CD11b⁻CD8⁻TCR β ⁺CD4⁺ cells.

For flow cytometry of myeloid cells, lymph nodes were cut into small pieces and incubated for 30 min at 37°C in sterile digestion mix: RPMI containing 0.4 mg/mL DNase I (Sigma) and 0.5 mg/mL collagenase D (Roche). Cell suspensions were then filtered using 40 μ m cell strainers. Cells were stained with anti-CCR2 BV711 (BD Biosciences, clone 475301), anti-CD19 BV480 (BD Biosciences, clone 1D3), anti-CD3 BV480 (BD Biosciences, clone 500A2), anti-NK1.1 BV480 (BD Bioscience, clone PK136), anti-SiglecF BV480 (BD Bioscience, clone E50-2440), anti-CD11c BV785 (Biolegend, clone N418), anti-Ly6G BV605 (Biolegend, clone 1A8), anti-CD11b PerCP-Cy5.5 (BD Bioscience, clone M1/70), anti-MHC II BV650 (Biolegend, clone M5/114.15.2), anti-Ly6C Alexa700 (Biolegend, clone HK1.4), anti-XCR1 AF647 (BioLegend, clone ZET), anti-CD26 PE (BioLegend, clone H194-112), and anti-EpCAM APCFire750 (BioLegend, clone G8.8). Cells were gated on live single NK1.1⁻SiglecF⁻CD19⁻TCR β ⁻ cells.

4.7 | Cytokine Measurement

Blood was collected in micro-sample tubes with lithium heparin (Sarstedt, #41.1393.005) and left at room temperature for 3 h. After centrifugation (450 g, 10 min), serum was collected for analysis and kept at -20°C. CCL2 concentration was measured in serum and in peritoneal lavage using CBA (BD Biosciences). The limit of detection was 10 pg/mL. IL1- β concentration was measured using Enhanced Sensitivity CBA (BD Biosciences). The limit of detection was 274 fg/mL.

4.8 | Analysis of Public Datasets

Datasets were downloaded from GEO and Immgen (www.immgen.org).

4.9 | Statistical Analysis

Statistical tests were performed using Prism v10 (GraphPad Software). Mann-Whitney test was used for all data. Absence of stars indicates “not significant.” N corresponds to the number of independent biological replicates analyzed.

Author Contributions

Adeline Cros: investigation, writing–review and editing. **Elodie Segura:** investigation, conceptualization, formal analysis, supervision, writing–original draft, writing–review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1002/eji.202451468>.

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