Received: 2 October 2020 | Revised: 15 January 2021 | Accepted: 4 February 2021

DOI: 10.1111/bph.15413

RESEARCH PAPER

IL-17-induced inflammation modulates the mPGES-1/PPAR-γ pathway in monocytes/macrophages

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Funding information
MIUR, Grant/Award Number: 2017A95NCJ/2017A95NCJ_002

Background and Purpose: Recent biochemical and pharmacological studies have reported that in several tissues and cell types, microsomal PGE_2 synthase (mPGES) and PPAR-γ expression are modulated by a variety of inflammatory factors and stimuli. Considering that very little is known about the biological effects promoted by IL-17 in the context of mPGES-1/PPAR-γ modulation, we sought to investigate the contribution of this unique cytokine on this integrated pathway during the onset of inflammation.

Experimental Approach: We evaluated effects of PF 9184 (mPGES-1 inhibitor) and troglitazone (PPAR-γ agonist) in vitro, using the mouse macrophage cell line J774A.1. In vivo, the dorsal air pouch model in CD1 mice was used, and inflammatory infiltrates were analysed by flow cytometry. Locally produced cyto-chemokines and PGs were assessed using ELISA assays. Western blots were also employed to determine the activity of various enzymes involved in downstream signalling pathways.

Key Results: PF 9184 and troglitazone, in a time- and dose-dependent manner, modulated leukocyte infiltration, myeloperoxidase activity, and the expression of COX-2/mPGES-1, NF-κB/IκB-α, and mPTGDS-1/PPAR-γ, induced by IL-17. Moreover, both PF 9184 and troglitazone modulated PG (PGE_2, PGD_2, and PGJ_2) production, the expression of different pro-inflammatory cyto-chemokines, and the recruitment of inflammatory monocytes, in response to IL-17.

Conclusions and Implications: Our data suggest that IL-17 may constitute a specific modulator of inflammatory monocytes during later phases of the inflammatory response. The results of this study show, for the first time, that the IL-17/mPGES-1/PPAR-γ pathway could represent a potential therapeutic target for inflammatory-based and immune-mediated diseases.

Abbreviations: 15d-PGJ_2, 15-deoxy-Δ12,14-PGJ_2; C5a, complement component 5a; CD, Crohn's disease; CMC, carboxymethyl cellulose; cPGES-, cytosolic PGE_2 synthase; FCS, fetal calf serum; IMIDs, immune-mediated inflammatory diseases; IκB-α, nuclear factor κ-B inhibitor α; JE, junctional epithelium; KC, keratinocyte chemoattractant; MCSF, macrophage colony-stimulating factor; MIPs, macrophage inflammatory proteins; mPGES-, microsomal PGE_2 synthase-; MPO, myeloperoxidase; NKT, natural killer T; NSAID, nonsteroidal anti-inflammatory drugs; OA, osteoarthritic; PBS-T, PBS Tween; PMN, polymorphonuclear leukocytes; PsA, psoriatic arthritis; PUFA, polyunsaturated fatty acid; RA, rheumatoid arthritis; SpA, spondylarthritis; Th, T-helper; TIMP-1, metallopeptidase inhibitor-1; TREM-1, triggering receptor expressed on myeloid cells-1.

Asif Jilani Iqbal and Francesco Maione share senior authorship.

KEYWORDS
IL-17A, inflammation, monocytes/macrophages, mPGES-1, PGE_2, PPAR-γ

1 | INTRODUCTION

Inflammation is a complex defence mechanism characterised by leukocyte extravasation from the vasculature to local tissue damage resulting from injurious and noxious agents/stimuli (Serhan, 2014). Neutrophils dominate the initial influx of leukocytes followed by monocytes and macrophages. The recruitment of inflammatory monocytes is correlated with a transient increase of pro-inflammatory mediators including cytokines, chemokines, PGs, and LTs (D'Acquisto et al., 2010; Perretti et al., 2017). Indeed, inappropriate monocyte/macrophage survival or overactivation perpetuate inflammatory pathways and strengthen disease activity and duration (Zhou et al., 2009). Therefore, regulating the function of monocytes/macrophages during inflammation is critical to promote resolution and healing. PGs and LTs are potent bioactive lipid mediators involved not only in the onset of inflammation but also in numerous homeostatic functions (Funk, 2001). Their biosynthesis is initialized by two cyclooxygenase isoenzymes (**COX-1** and **COX-2**) that convert **arachidonic acid** to **PGH_2** (Hawkey, 1999) which is subsequently isomerized, by three different **PGE_2** synthases (situated downstream of COXs in the PG synthesis pathway), to **PGE_2** (Koeberle & Werz, 2015). The cytosolic PGE_2 synthase (**cPGES**) and the microsomal PGE_2 synthase (**mPGES)-2** are constitutive enzymes, whereas **mPGES-1** is an inducible isoform (Samuelsson et al., 2007). PGE_2 production can also be indirectly modulated by the alternative pathway of **PPAR-γ**, a member of the nuclear receptor superfamily of ligand-dependent transcription factors, activated by 15-deoxy-$\Delta^{12,14}$-**PGJ_2** (15d-PGJ_2) (Cuzzocrea et al., 2002). Anti-inflammatory effects related to PPAR-γ activation have previously been demonstrated in several studies (Ricote et al., 1998; Tsai et al., 2010) through its ability to increase the expression of **NF-κB inhibitor α (IκB-α)**, an endogenous inhibitor that interferes with the activation of p65 NF-κB (Korbecki et al., 2019), via its natural ligand 15d-PGJ_2. Although a large body of work has been carried out to elucidate the biological function of PPAR-γ activation, this nuclear receptor's role remains poorly defined in the context of monocytes/macrophages activation via the arachidonic acid pathway.

Recently, several biochemical and pharmacological studies demonstrated a molecular interaction between COXs and PGES isoenzymes, which results in preferential functional coupling activity. Specifically, mPGES-2 was shown to utilize COX-1 to generate PGH_2, in contrast to mPGES-1 that uses COX-2 (Samuelsson et al., 2007). Moreover, studies with PGES-deficient mice have shown that induced PGE_2 synthesis is largely and preferentially dependent on mPGES-1 enzyme (Inada et al., 2006). Consistent with such results, the up-regulation of mPGES-1 expression and the involvement of COX-2/mPGES-1/PGE_2 cascade in terms of PGs production have been extensively reported in pathological settings in which PGE_2 is implicated, such as fever, pain, and inflammatory-based diseases (Trebino et al., 2003; Uematsu et al., 2002). In line with these observations, in several tissues and different cell types including fibroblasts, osteoblasts, chondrocytes, and osteoarthritic cartilage, mPGES-1 expression is enhanced by a variety of inflammatory factors including **LPS**, **IL-1β**, **tumour necrosis factor-α (TNF-α)**, and IL-17A, commonly known as **IL-17**, (Li et al., 2005; Stichtenoth et al., 2001) and this last has been used in this study.

In this context, IL-17 has received much attention as a significant driver of autoimmune and auto-inflammatory conditions (Maione, 2016; Maione et al., 2020; Raucci et al., 2020). This cytokine is mainly produced by T-helper (Th)-17 lymphocytes, but it also released by natural killer T (NKT) cells, macrophages, neutrophils, monocytes, $CD8^+$ T cells, γδ T cells, and innate lymphoid cells (Onishi & Gaffen, 2010). We have previously demonstrated that IL-17, compared to other pro-inflammatory cytokines such as IL-1α and TNF-α, sustains chronic inflammation and tissue remodelling rather than initiating it (Maione et al., 2009), through its ability to prime monocytes/macrophages towards an inflammatory phenotype (Maione, 2016; Maione et al., 2011). Considering that very little is known about the biological effects promoted by IL-17 both in vitro and in vivo in the context of mPGES-1/PPAR-γ modulation, we sought here to investigate and characterize the role of IL-17 on this pathway during an ongoing inflammatory response.

What is already known

- mPGES-1 and PPAR-γ expression are modulated by a variety of inflammatory factors and stimuli.

What this study adds

- IL-17 constitutes a specific modulator of inflammatory monocytes during later phases of the inflammatory response.
- IL-17 modulates the mPGES-1/PPAR-γ pathway during the onset of inflammation.

What is the clinical significance

- The IL-17/mPGES-1/PPAR-γ pathway could represent a potential therapeutic target for inflammatory-based diseases.
- IL-17-site-directed antibodies could be used in inflammation-based and immune-mediated diseases.

2 | METHODS

2.1 | Murine cell isolation and culture

Mouse macrophage cell line (J774A.1, ATCC® TIB-67™) was cultured in DMEM supplemented with FBS (ATCC® 30-2020™) to a final concentration of 10%. Cells were seeded in petri culture dishes (100 × 20 mm, Falcon®) at a density of 5×10^5 cells per dish and allowed to grow for 24 h. The medium was then replaced, and cells were treated for 4 and 24 h with recombinant mouse IL-17 (0.5–500 ng·ml^{-1}). In another set of experiments, cells were treated with IL-17 (50 ng·ml^{-1}) in presence or absence of PF 9184 (50 μM) or troglitazone (50 μM) according to previous in vitro studies (Li et al., 2005). Following incubations for 4 and 24 h, cells were collected with a cell scraper, and pellets were lysed at 4°C for 10 min with a buffer containing 1-g/100-ml Triton X-100, 5-mM EDTA in PBS (pH 7.4) containing protease inhibitors. After centrifugation at 14000× *g* for 10 min at 4°C, the supernatant was collected and stored at −80°C for later western blot analysis. Protein concentration was determined by the Bio-Rad protein assay (Bio-Rad, Milan, Italy).

2.2 | Animals

All animal care and experimental procedures were in compliance with the international and national law and policies and approved by the Italian Ministry of Health (EU Directive 2010/63/EU for animal experiments, ARRIVE guidelines, and the Basel declaration including the 3Rs concept). Animal studies are reported in compliance with the ARRIVE guidelines (Percie du Sert et al., 2020) and with the recommendations made by the British Journal of Pharmacology (Lilley et al., 2020). Male CD1 mice (8- to 12-week-old) were purchased from Charles River (Milan, Italy), and housed with ad libitum access to food and water and maintained on a 12-h light/dark cycle. All procedures were carried out to minimize the number of animals used (n = 7 per group) and their suffering. Experimental study groups were randomized and their assessments were carried out by observers, blinded to the treatment groups.

2.3 | Air pouch

Dorsal air pouches were induced by injection of 2.5 ml of air on day 0 and day 3 as previously described (Maione, Iqbal, et al., 2018). On day 6, mice received the following treatments: (i) control (CTRL) 0.25 ml of 0.5% carboxymethyl cellulose (CMC); (ii) IL-17 (1 μg) in 0.25 ml of 0.5% CMC; (iii) IL-17 (1 μg) in 0.25 ml of 0.5% CMC co-treated with PF 9184 (1–9 μg per pouch); and (iv) IL-17 (1 μg) in 0.25 ml of 0.5% CMC co-treated with troglitazone (1–9 μg per pouch) accordingly to previous studies (Li et al., 2005; Maione et al., 2009). In another set of experiment, the inhibitory effect of PF 9184 was compared to AF 3485 (9 μg per pouch). In all experimental conditions, mice were killed after 4, 24, and 48 h from the injection and air pouches washed thoroughly with 2 ml of PBS containing 50 U·ml^{-1} heparin and 3-mM EDTA. Lavage fluids were centrifuged at 220 × *g* for 10 min at 4°C to separate the exudates from the recruited cells. Inflammatory exudates were collected and measured to evaluate the level of inflammatory cyto-chemokines, whereas the cell pellets were analysed by western blot and FACS analysis, as described below. Cell number was determined by TC20 automated cell counter (Bio-Rad, Milan, Italy) using Bio-Rad's automated cell counter uses disposable slides, TC20 Trypan blue dye (0.4% Trypan blue dye w/v in 0.81% sodium chloride and 0.06% potassium phosphate dibasic solution), and a CCD camera to count cells based on the analyses of capture images (Bellavita et al., 2020; Maione, Iqbal, et al., 2018).

2.4 | Myeloperoxidase assay

Leukocyte **myeloperoxidase (MPO)** activity was assessed by measuring the H_2O_2-dependent oxidation of 3,3′,5,5′-tetramethylbenzidine as previously reported (Maione et al., 2009). Cellular lysate, from air pouch experiments, were homogenized in a solution composed of hexadecyltrimethylammonium bromide (0.5% w/v) in 50-mM sodium phosphate buffer at pH 5.4. After homogenization, samples were centrifuged at 1008 × *g* for 10 min and the supernatant used for the assay. Aliquots of 20 μl were incubated with 160 μl of 3,3′,5,5′-tetramethylbenzidine and 20 μl of H_2O_2 (in 80-mM phosphate buffer, pH 5.4) in 96-well plates. Plates were incubated for 5 min at room temperature, and OD was read at 620 nm using a plate-reader (Biorad, Italy). Assays were performed in duplicate and normalized for protein content.

2.5 | ELISA and ELISASpot assay

ELISAS for IL-17, PGE_2, **PGD_2**, and 15d-PGJ_2 were carried out on pouch inflammatory exudates. Briefly, 100 μl of samples, diluted standards, quality controls, and dilution buffer (blank) were added to a pre-coated plate with monoclonal anti-IL-17, PGE_2, PGD_2, or 15d-PGJ_2 for 2 h. After washing, 100 μl of biotin-labelled antibody was added for 1 h. The plate was washed and 100 μl of streptavidin-HRP conjugate was added and the plate was incubated for a further 30-min period in the dark. The addition of 100 μl of the substrate and stop solution represented the last steps before the reading of absorbance (measured at 450 and 405 nm for IL-17, PGE_2, PGD_2, and 15d-PGJ_2, respectively) on a microplate reader. Antigen levels in the samples were determined using a standard curve and expressed as pg per pouch (Raucci, Iqbal, Saviano, Casillo, et al., 2019). For cyto-chemokines protein array, equal volumes (1.5 ml) of pouch inflammatory fluids in all described experimental conditions were incubated with the pre-coated proteome profiler array membranes according to the manufacturer's instructions. Dot plots were detected by using the enhanced chemiluminescence detection kit and Image Quant 400 GE

Healthcare software (GE Healthcare, Italy) and successively quantified using GS 800 imaging densitometer software (Biorad, Italy) as previously described (Cristiano et al., 2019).

2.6 | Flow cytometry

Cells collected from the pouch cavities, at 4 and 24 h, were first washed with PBS and then re-suspended in FACS buffer (PBS containing 1% FCS and 0.02% NaN_2) containing CD16/CD32 FcγIIR blocking antibody (clone 93; eBioscience, London, UK) for 30 min at 4°C. Thereafter, cells were labelled for 30 min at 4°C with the following conjugated antibodies (all from BioLegend, London, UK): CD45 (1:100; clone 30-F11), LY6C (1:100; clone HK1.4), LY6G (1:100; clone 1A8), CD115 (1:100; clone AFS98), CD11b (1:100; clone M1/70), F4/80 (1:100; clone BM8), and CD206 (1:100; clone C068C2), prior to analysis by FACS calibre using CellQuest software (Becton Dickinson, Franklin Lakes, NJ, RRID: SCR_014489). Neutrophils, macrophage, and resident/inflammatory monocytes were defined according to the flow cytometry procedure previously described (Kapellos et al., 2019; Maione, Iqbal, et al., 2018; Podaru et al., 2019). At least 1×10^4 cells were analysed per sample, and determination of positive and negative populations was performed based on the staining obtained with related IgG isotypes. Flow cytometry was performed on BriCyte E6 flow cytometer (Mindray Bio-Medical Electronics, Nanshan, China) using MRFlow and FlowJo software operation (RRID: SCR_008520) (Raucci, Iqbal, Saviano, Casillo, et al., 2019).

2.7 | Western blot analysis

Homogenates of cell pellets (50 μg of protein) from in vitro and in vivo experiments were subjected to SDS-PAGE (10 and 12% gel) using standard protocols, as previously described (Maione, Piccolo, et al., 2018). The proteins were transferred to nitrocellulose membrane (0.2-μm nitrocellulose membrane, Trans-Blot® TurboTM, Transfer Pack, Bio-Rad Laboratories, Hercules, CA, USA, RRID: SCR_008426) in transfer buffer (25-mM Tris–HCl pH 7.4 containing 192-mM glycine and 20% v/v methanol) at 400 mA for 2 h. The membranes were saturated by incubation for 2 h with non-fat dry milk (5% wt/v) in PBS supplemented with 0.1% (v/v) Tween 20 (PBS-T) for 2 h at RT and then incubated with 1:1000 dilution of primary antibodies overnight at 4°C such as mouse monoclonal anti-actin (E-AB-20094), mouse monoclonal anti-COX-2 (E-AB-27666), mouse monoclonal anti-IκB-α (4814), rabbit polyclonal anti-IL-17 Receptor (E-AB-63080), mouse monoclonal anti-NFκB (MAB3026), rabbit polyclonal anti-mPTGDS-1 (TA301420), rabbit polyclonal anti-mPGES-1 (E-AB-32563), and rabbit polyclonal anti-PPAR-γ (NBP2-22106) and then washed three times with PBS-T. In all cases, blots were then incubated with a 1:3000 dilution of related HRP-conjugated secondary antibody for 2 h at room temperature and finally washed three times with PBS-T. Protein bands were detected by using the enhanced chemiluminescence method (ClarityTM Western ECL Substrate, Bio-Rad Laboratories, Hercules, CA, USA) and Image Quant 400 GE Healthcare software (GE Healthcare, Italy). Finally, protein bands were quantified using the GS 800 imaging densitometer software (Biorad, Italy) and normalized with respective actin. The immuno-related procedures used comply with the recommendations made by the *British Journal of Pharmacology* (Alexander et al., 2018).

2.8 | Data and statistical analysis

In this study, statistical analysis complies with the recommendations of *BJP* on experimental design and analysis in pharmacology (Curtis et al., 2018) and data sharing and presentation in preclinical pharmacology (Alexander et al., 2018; George et al., 2017). All data are presented as means ± SD and were analysed using Student's *t* test (two groups) or one-way ANOVA followed by Bonferroni's for multiple comparison test (more than two groups). GraphPad Prism 8.0 software (San Diego, CA, USA, RRID: SCR_002798) was used for analysis. Differences between means were considered statistically significant when $P \leq 0.05$ was achieved. Sample size was chosen to ensure α of 0.05 and power of 0.8. Animal weight was used for randomization and group allocation to reduce unwanted sources of variations by data normalization. No animals and related ex vivo samples were excluded from the analysis. In vivo and in vitro studies were carried out to generate groups of equal size (n = 7 independent values), using randomization and blinded analysis.

2.9 | Materials

PGE_2 ELISA kit, proteome profiler mouse cytokine array kit, and recombinant mouse IL-17 were purchased from R&D System (Milan, Italy). PF 9184 and troglitazone were purchased from Tocris (Milan, Italy) and AF 3485 from Cayman Chemical Company (Michigan, USA), whereas FACS buffer and all conjugated antibodies from BioLegend (London, UK). PGD_2 ELISA kit and the primary antibodies for western blot analysis were obtained from Elabscience (Milan, Italy) whereas the HRP-conjugated IgG secondary antibodies from Dako (Copenhagen, Denmark). 15d-PGJ_2 ELISA kit was purchased from Abcam (Cambridge, UK). Unless otherwise stated, all the other reagents were from BioCell (Milan, Italy).

2.10 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Cidlowski, et al., 2019; Alexander, Fabbro, et al., 2019; Alexander, Kelly, Mathie, Peters, Veale, Faccenda et al., 2019; Alexander, Kelly, Mathie, Peters, Veale, Armstrong et al., 2019).

3 | RESULTS

3.1 | PF 9184 and troglitazone, in a time- and dose-dependent manner, reverse leukocyte accumulation and activation at the site of inflammation

We knew from our previous studies (Maione et al., 2009; Maione, Iqbal, et al., 2018) that the single administration of IL-17 (1 μg per pouch) into a 6-day-old air pouch causes a transient infiltration of leukocytes by 4 h, which peaks at 24 h and then declines by 48 h. To test the potential dose-dependent effect of an mPGES-1 inhibitor and a PPAR-γ agonist at this local site of inflammation, we administered PF 9184 (1–9 μg per pouch) and troglitazone (1–9 μg per pouch) concomitantly with IL-17. All mice were killed at 4, 24, and 48 h time points. Consistent with our previous findings, 4 and 24 h after IL-17 injection, mice showed significant differences in the number of inflammatory leukocytes, compared with vehicle (Figure 1a,b). No significant differences were observed at 48 h (Figure 1c). Interestingly, mice receiving PF 9184 at a dose of 9 μg per pouch showed a marked decrease (∼40%) in inflammatory infiltrates, compared with IL-17-treated mice, at both 4 and 24 h (Figure 1a,b). A similar anti-inflammatory profile was observed after administration of troglitazone (9 μg per pouch), with a marked reduction in infiltrating leukocytes at 4 and 24 h (Figure 1a,b). No biological effects were observed at 48 h (Figure 1c). The inhibitory effect of PF 9184 was also compared to AF 3485 (another selective mPGES-1 inhibitor), and a similar reduction in total leukocyte infiltration was observed (Supporting Information S1). Based on these results, we selected the most effective dose of PF 9184 and troglitazone (9 μg per pouch) for all subsequent experiments. The level of myeloperoxidase (MPO, Figure 1d–f), a peroxidase enzyme most abundantly expressed in polymorphonuclear leukocytes, and different PGs such as PGE_2, PGD_2, and 15d-PGJ_2 were then measured in pouch fluid. Administration of IL-17 (still present in the air pouch at 48 h after a single injection, Supporting Information S2) was correlated with increased levels of MPO (Figure 1d,e) and PGE_2 (Figure 2a,b) at both 4 and 24 h. Conversely, a reduction in PGD_2 at both 4 and 24 h (Figure 2c,d) and 15d-PGJ_2 (Figure 2f) only at 24 h was observed. When co-injected in the presence of PF 9184 and troglitazone, the opposite profile was observed with a marked

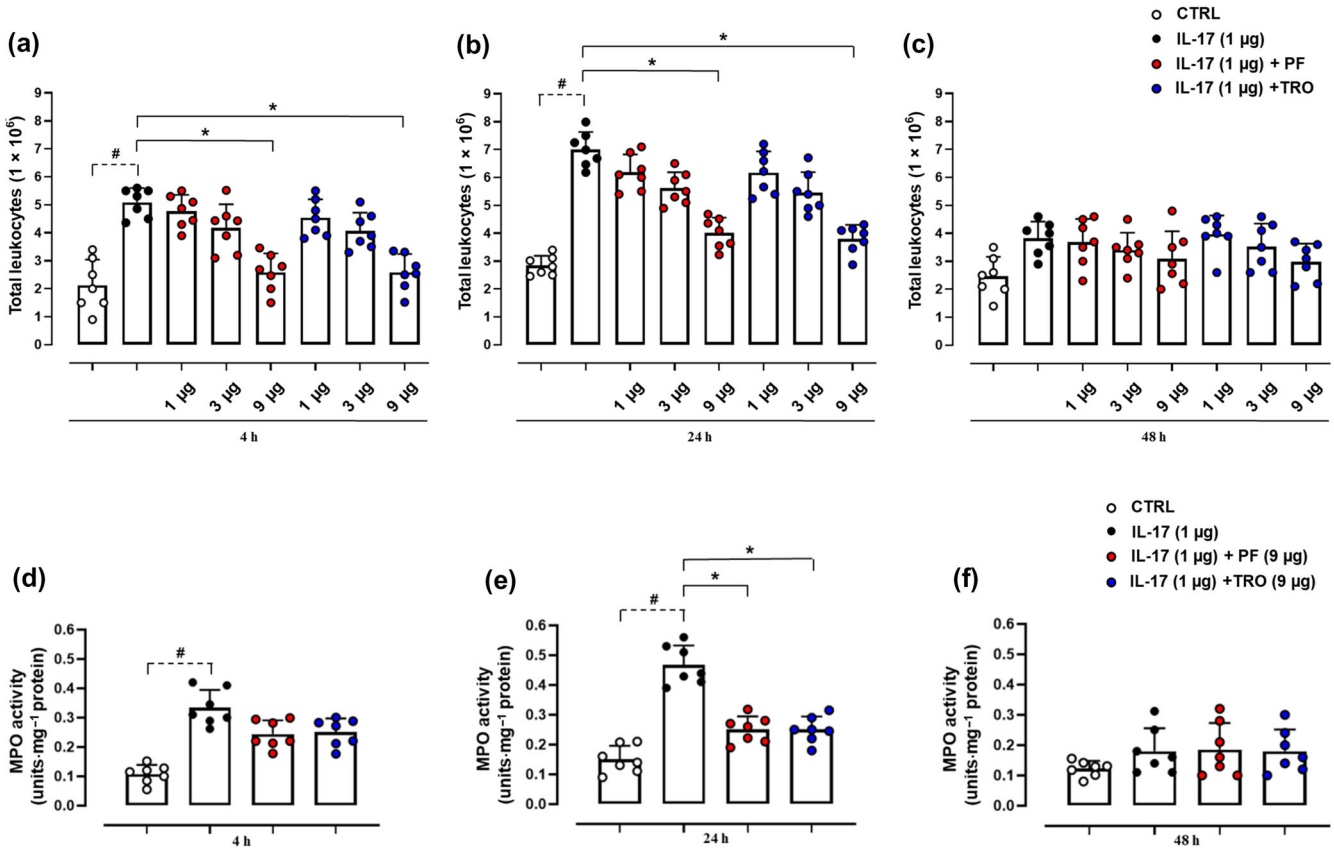

FIGURE 1 PF 9184 and troglitazone, in a time- and dose-dependent manner, reverse the accumulation and activation of leukocyte at the site of inflammation: Mice were treated with IL-17 vehicle (CTRL), IL-17 (1 μg per pouch) alone (IL-17) or co-treated with PF 9184 (PF, 1–9 μg per pouch) or troglitazone (TRO, 1–9 μg per pouch) and thereafter total cell number from the pouch inflammatory exudates was evaluated at 4 h (a), 24 h (b), and 48 h (c). At the same time-point (d–f), supernatants from cell pellet lysate were tested for myeloperoxidase activity. Data were expressed as 10^6 cells for pouch (a–c) or units·mg^{-1} of protein (d–f) and presented as means ± SD; n = 7 mice per group. $^{\#}P \leq 0.05$, significantly different from CTRL group; $^{*}P \leq 0.05$, significantly different from IL-17 group; one-way ANOVA followed by Bonferroni's test for multiple comparisons

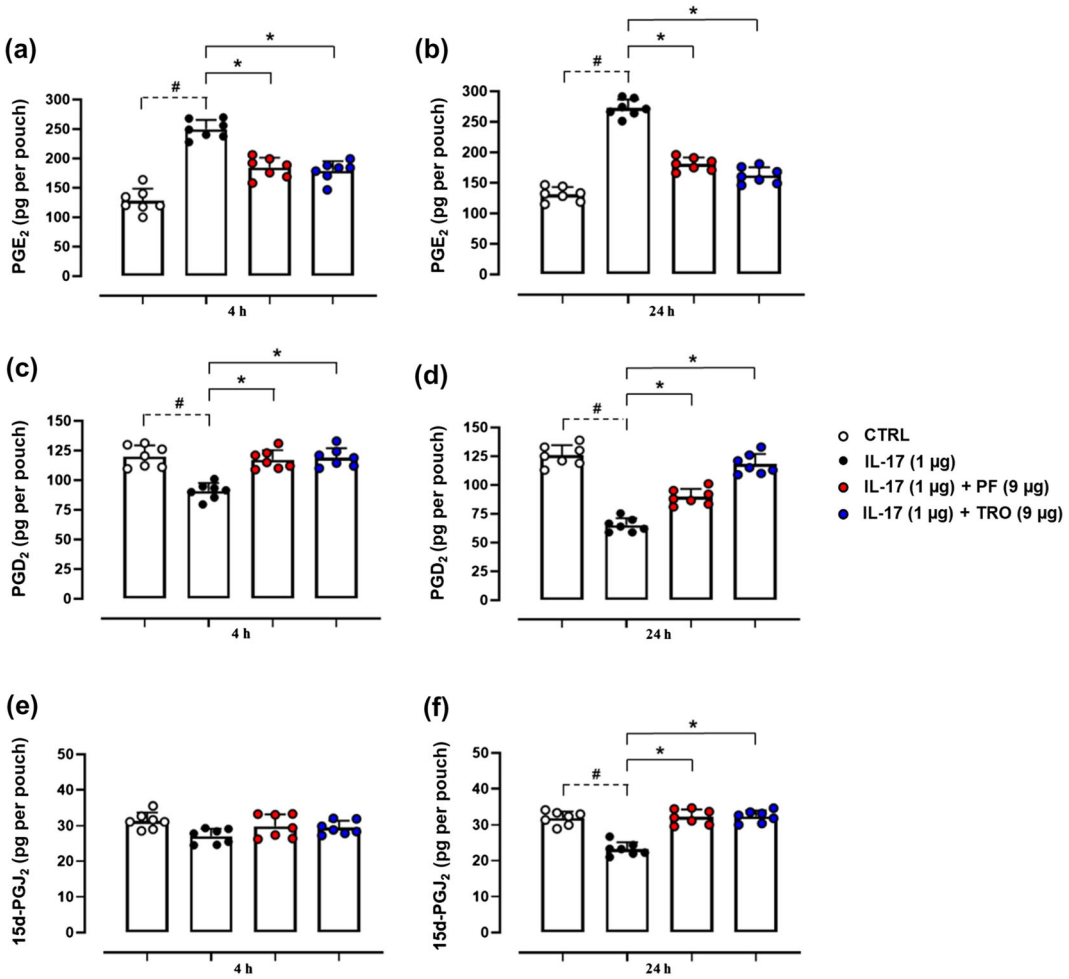

FIGURE 2 PF 9184 and troglitazone selectively modulate the release of pro- and/or anti-inflammatory PGs at site of inflammation: Mice were treated with IL-17 vehicle (CTRL), IL-17 (1 μg per pouch) alone (IL-17) or co-treated with PF 9184 (PF, 9 μg per pouch) or troglitazone (TRO, 9 μg per pouch). Inflammatory fluids from all experimental conditions were assayed by ELISA for PGE_2 (a, b), PGD_2 (c, d), and 15d-PGJ_2 (e, f) levels at both 4 and 24 h. Data were expressed as pg per pouch and presented as means ± SD; n = 7 mice per group. $^{\#}P \leq 0.05$, significantly different from CTRL group; $^{*}P \leq 0.05$, significantly different from IL-17 group; one-way ANOVA followed by Bonferroni's test for multiple comparisons

reduction in MPO (Figure 1e) activity and PGE_2 (Figure 2a,b) and reversal in PGD_2 (Figure 2c,d) and 15d-PGJ_2 levels (Figure 2f). Collectively, these data indicate time- and dose-dependent protective effects of a selective mPGES-1 inhibitor and a PPAR-γ agonist on inflammatory cell recruitment and activation, induced by -IL-17.

3.2 | Modulation of the mPGES-1 and PPAR-γ enzymic pathway, at the onset of ongoing inflammation

Previous studies have shown in various tissues and cell types, both COX-2 and mPGES-1 expression are enhanced in response to a range of inflammatory mediators including LPS, IL-1β, TNF-α, and IL-17 (Maione, Iqbal, et al., 2018). We, therefore, carried out western blot analysis on recruited cells and found that COX-2 (Figure 3b) and mPGES-1 (Figure 3h) were up-regulated following IL-17-induced inflammation and were both significantly reduced at 4 and, in particular, 24 h after PF 9184 and troglitazone treatment. Moreover, we found that expression of **IL-17 receptor**s, which was increased in IL-17-treated animals compared to CTRL group at 24 h, were not altered by treatment with either PF 9184 or troglitazone (Figure 3a). We also observed a substantial increase in NF-κB expression in mice treated with IL-17 (Figure 3c). The endogenous inhibitor of NF-κB (IκB-α) was also measured, and the converse was observed in mice treated with PF 9184 or troglitazone at 4 and 24 h (Figure 3f). Notably, mPTGDS-1 and PPAR-γ expression was low in the IL-17 group, whereas it significantly increased in PF 9184 (only at 24 h) and troglitazone-treated mice (at both 4 and 24 h), confirming the hypothesis of the activation of an alternative molecular pathway following thiazolidinedione administration

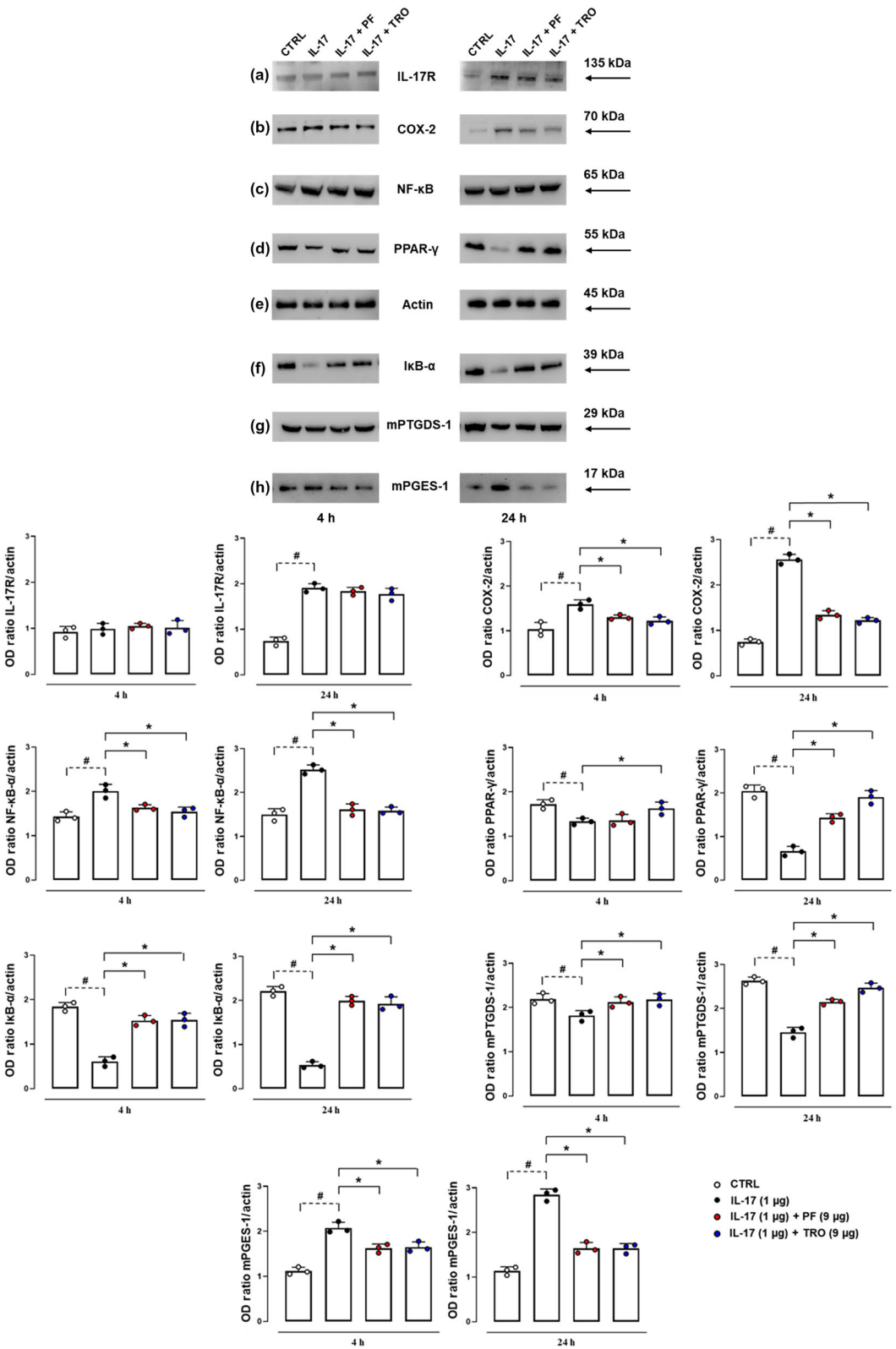

FIGURE 3 Modulation of the mPGES-1 and PPAR-γ enzymic pathway, at the onset of ongoing inflammation: Homogenates of the cell pellets from air pouch experiments in all experimental conditions were assayed by western blot for IL-17 receptor (IL-17R) (a), COX-2 (b), NF-κB (c), PPAR-γ (d), IκB-α (f), mPTGDS-1 (g), mPGES-1 (h) expression at 4 and 24 h. Western blot images are representative of three separate experiments with similar results. Cumulative densitometric values (at the bottom of the figure) are expressed as OD ratio with actin (e) for both 4 and 24 h. Values are presented as means ± SD of three separate independent experiments run each with $n = 7$ mice per group pooled. $^{\#}P \leq 0.05$, significantly different from CTRL group; $^{*}P \leq 0.05$, significantly different from IL-17 group; one-way ANOVA followed by Bonferroni's test for multiple comparisons

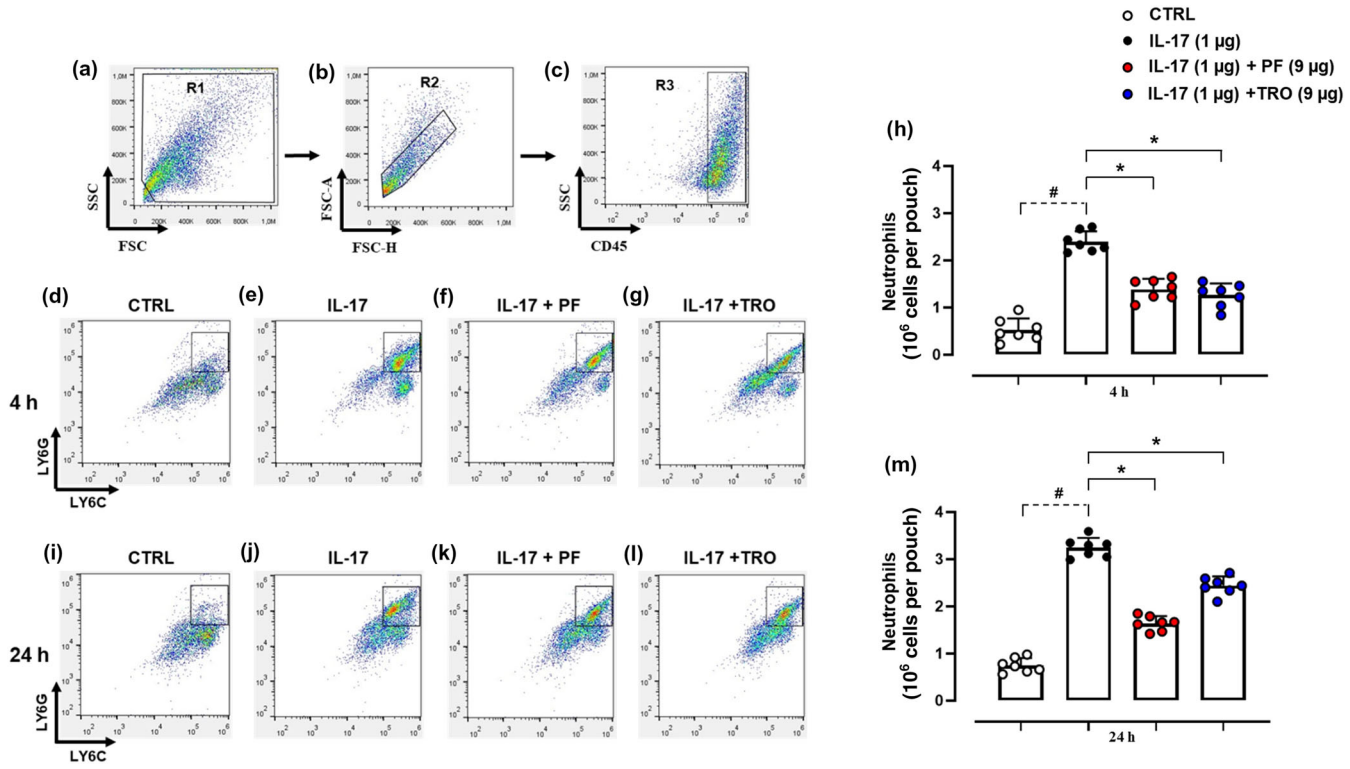

FIGURE 4 Flow cytometry strategy applied to identify the modulation of neutrophils after IL-17 stimulation: Mice were treated with IL-17 vehicle (CTRL), IL-17 (1 μg per pouch) alone (IL-17) or co-treated with PF 9184 (PF, 9 μg per pouch) or troglitazone (TRO, 9 μg per pouch). Cells collected from the pouch cavities were washed, gated in their totality (a, *gate* R1) and singlet (b, *gate* R2) before the identification of CD45 positive (c, $CD45^{+ve}$) population (*gate* R3). $CD45^{+ve}$ cells (c) were then plotted for Ly6C and Ly6G expression at 4 (d–g) and 24 h (i–l) to identify $CD45^{+ve}/Ly6C^{+ve}/Ly6G^{+ve}$ as neutrophils. Histograms values (expressed as 10^6 cells per pouch) indicate the total positive cells, in the different experimental conditions, of $CD45^{+ve}/Ly6C^{+ve}/Ly6G^{+ve}$ (h, m) at 4 and 24 h. FACS pictures are representative of independent experiments with similar results. Values are presented as means ± SD of $n = 7$ mice per group. $^{\#}P \leq 0.05$, significantly different from CTRL group; $^{*}P \leq .05$, significantly different from IL-17 group; one-way ANOVA followed by Bonferroni's test for multiple comparisons

(Figure 3g,d, respectively). The inhibitory effect of PF 9184 was also compared with that of AF, and similar levels of inhibition of the expression of COX-2/mPGES-1 and PPAR-γ were observed (Supporting Information S3). Densitometric values (at the bottom of Figure 3) are expressed as OD ratio with actin (Figure 3e) for both 4 and 24 h. Uncropped and original western blots are presented in Supplementary Figures S1–S12.

3.3 | PF 9184 and troglitazone selectively modulate the recruitment of inflammatory monocytes

We went on to further characterize the phenotype of recruited cells at different time points. Flow cytometry was employed to determine neutrophil and monocyte/macrophage subsets. Specifically, to identify potential differences in leukocyte subpopulations, total cells were gated (Figures 4a and 5a,n, *gate* R1), followed by single cells (Figures 4b and 5b,o, *gate* R2). **CD45** (pan leukocyte/immune cell marker; Figure 4c) and **CD11b** (myeloid marker; Figure 5c,p) were selected ($^{+ve}$, *gate* R3). Neutrophils were identified as $CD45^{+ve}/Ly6G^{Hi}/Ly6C^{Hi}$ as shown both at 4 (Figure 4d–g) and 24 h (Figure 4i–l). Monocytes and macrophages were further delineated based upon a range of markers. $CD11b^{+ve}$ cells were plotted for Ly6C and CD115 at 4 (Figure 5d–g) and 24 h (Figure 5i–l) to distinguish $CD11b^{+ve}/CD115^{+ve}/Ly6C^{lo}$ patrolling monocytes (*gate* R4) from $CD11b^{+ve}/CD115^{+ve}/Ly6C^{hi}$ inflammatory monocytes (*gate* R5) (de-Brito et al., 2019; Kapellos et al., 2019; Raucci, Iqbal, Saviano, Minosi, et al., 2019) and for CD206 and F4/80 (Figure 5q–t and Figure 5v–y at 4 and 24 h, respectively) to identify $CD11b^{+ve}/F480^{+ve}/CD206^{+ve}$ reparative macrophages (Podaru et al., 2019).

Our results show that in IL-17-injected mice, at 4 h, the majority of cells recovered were neutrophils (Figure 4h), which were largely replaced by inflammatory monocytes (Figure 5m) and a lower proportion of reparative macrophages (Figure 5z) at 24 h. Interestingly, both PF 9184 and troglitazone treatments significantly inhibited this selective and time-dependent recruitment of neutrophils and inflammatory monocytes (Figures 4h,m and 5h,m). Moreover, administration of troglitazone at 24 h maintained similar levels of reparative macrophages as the control group (Figure 5z). In all experimental conditions, no significant differences were found in resident monocyte recruitment (*gate* R4). Reported values were strengthened by a low percentage of positive cells found in the staining for the isotype control

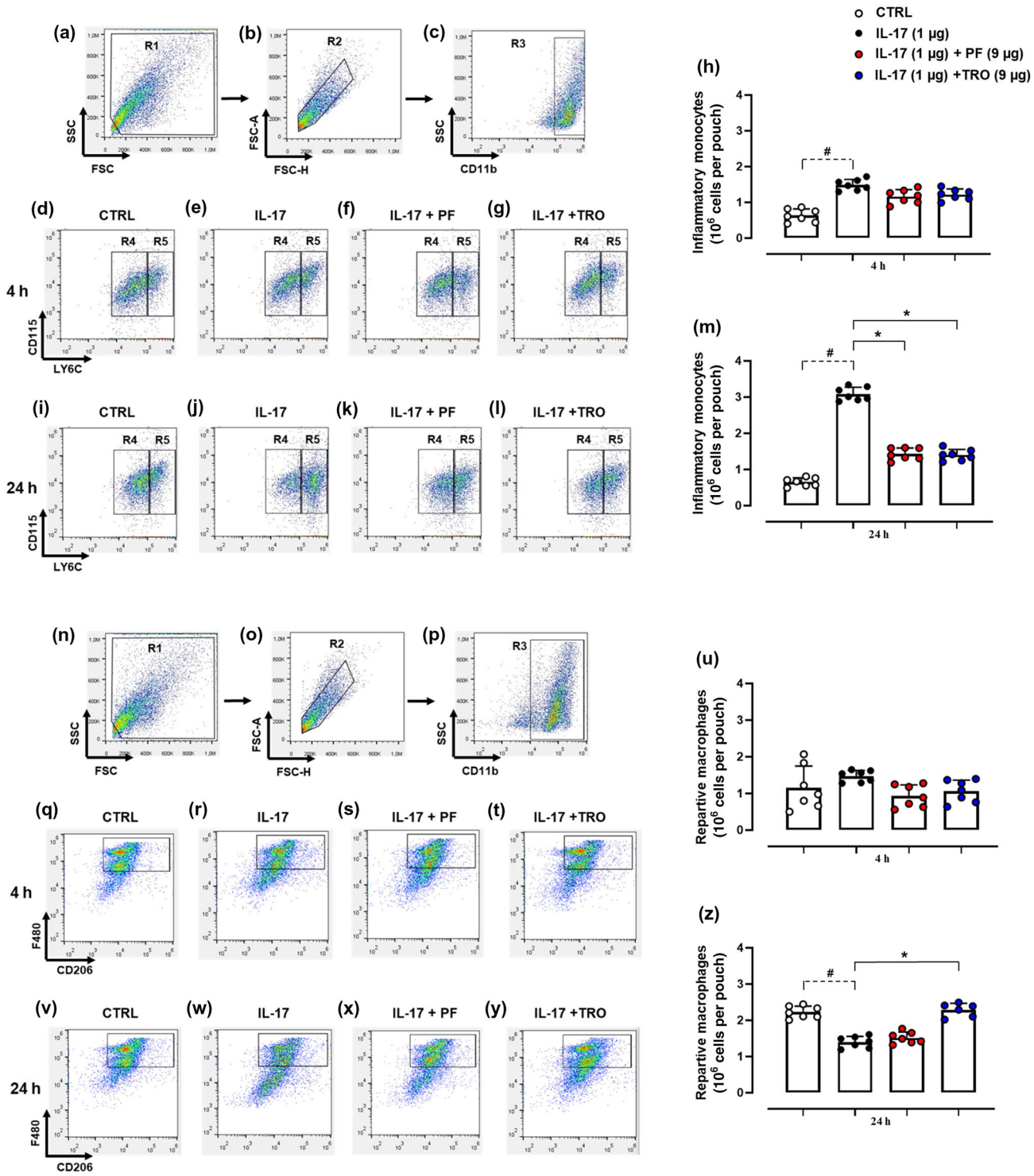

FIGURE 5 PF 9184 and troglitazone selectively modulate the recruitment of inflammatory monocytes and reparative macrophages: Mice were treated with IL-17 vehicle (CTRL), IL-17 (1 μg per pouch) alone (IL-17) or in co-treated with PF 9184 (PF, 9 μg per pouch) and troglitazone (TRO, 9 μg per pouch). Cells collected from the pouch cavities were washed, gated in their totality (a, n, *gate* R1) and singlet (b, o, *gate* R2) before the identification of CD11b positive (c, p, $CD11b^{+ve}$) population (*gate* R3). $CD11b^{+ve}$ (c) cells were then plotted for Ly6C and CD115 expression at 4 (d–g) and 24 h (i–l) to distinguish $CD11b^{+ve}/CD115^{+ve}/Ly6C^{low}$ patrolling monocytes (*gate* R4) from $CD11b^{+ve}/CD115^{+ve}/Ly6C^{hi}$ inflammatory monocytes (*gate* R5). Therefore, $CD11b^{+ve}$ cells were then plotted for CD206 and F480 expression at both 4 (q–t) and 24 h (v–y) to identify $CD206^{+ve}/F480^{+ve}$ population. Histograms values (expressed as 10^6 cells per pouch) indicate the total positive cells, in the different experimental conditions, of $CD11b^{+ve}/CD115^{+ve}/Ly6C^{hi}$ (h, m) and $CD11b^{+ve}/CD206^{+ve}/F480^{+ve}$ (u, z) at 4 and 24 h. FACS pictures are representative of independent experiments with similar results. Values are presented as means ± SD of $n = 7$ mice per group. $^{\#}P \leq 0.05$, significantly different from CTRL group; $^{*}P \leq 0.05$, significantly different from IL-17 group; one-way ANOVA followed by Bonferroni's test for multiple comparisons

antibodies (Supporting Information S4). These results suggest that PF 9184 and troglitazone treatment significantly disrupted the recruitment of inflammatory cells in the first phase of the response and that troglitazone selectively promoted resolution in the subsequent reparative phase.

3.4 | Co-administration of PF 9184 and troglitazone with IL-17 into the air pouch decreases the release of cyto-chemokines in the inflammatory fluids

To gain some insights into other possible differences in the inflammatory response caused by co-administration of an mPGES-1 inhibitor or a PPAR-γ agonist with an IL-17 inflammatory stimulus, we used an unbiased approach (pre-made protein array) based on profiling cytokines and chemokines present in the inflammatory fluids. As shown in Figure 6, the pouch fluid obtained from mice treated with IL-17 only showed a large increase, at 4 (Figure 6a–d) and, in particular, 24 h (Figure 6f–i), of cyto-chemokines compared to vehicle (CTRL group). When comparing pouch fluids from PF 9184 and troglitazone-treated groups with IL-17 (alone), we observed a selective decrease in a range of mediators (Figure 6a–d and Figure 6f–i at 4 and 24 h, respectively). Densitometric analysis revealed that the PF 9184-treated group had a specific modulation, at 4 h (Figure 6e), in the following factors: CXCL13, soluble **ICAM-1**, IL-16, **CXCL10**, keratinocyte chemoattractant (**KC**), macrophage colony-stimulating factor (**M-CSF**), junctional epithelium (JE), **CCL12**, **CXCL9**, macrophage inflammatory proteins (MIPs), **metallopeptidase inhibitor-1 (TIMP-1)**, and triggering receptor expressed on myeloid cells-1 (TREM-1), compared with levels in the IL-17 only group (Figure 6e). This profile was confirmed at the 24-h time-point (Figure 6j) in addition to complement component 5a (**C5a**), IFN-γ, IL-1α, IL-1β, IL-7, CXCL11, and CXCL12 (Figure 6j). A similar inhibitory profile was found in troglitazone-injected mice, but surprisingly, we observed a more prominent modulation of CXCL13, C5a, IL-17, CXCL10, CXCL12, and TIMP-1 at 4 h (Figure 6e) and of CXCL13, soluble ICAM-1, IL-16, IL-17, JE, CCL12, and CXCL9 at 24-h time-point (Figure 6j). The increase or decrease of cyto-chemokines in all experimental conditions is shown in Supporting Information S5.

3.5 | Protective effect of PF 9184 and troglitazone on murine isolated, and IL-17-stimulated, macrophages

To further confirm the validity of our in vivo findings, we carried out in vitro studies using a murine macrophage cell line J774. Stimulation of macrophages with increasing concentrations of IL-17 (0.5–500 $ng \cdot ml^{-1}$) induced a significant increase in IL-17R expression at both 4 and 24 h (Figure 7a). Notably, pretreatment of IL-17 (50 $ng \cdot ml^{-1}$)-stimulated macrophages with PF 9184 or troglitazone (50 μM) reversed the expression of COX-2 and mPGES-1 at 4 and 24 h (Figure 7b). Moreover, PPAR-γ expression was weakly present in IL-17 group, whereas it significantly increased in PF 9184-(only at 24 h) and troglitazone-treated mice (at both 4 and 24 h), further strengthening our hypothesis of activation of an alternative pathway following thiazolidinedione administration (Figure 7b). Densitometric values (at the bottom of the Figure 7a,b) are expressed as OD ratio with actin for both 4 and 24 h. Original western blots are presented in Supplementary Figures S13–S18.

4 | DISCUSSION AND CONCLUSIONS

The integration of inflammatory signals is crucial to controlling the intensity and duration of the immune response. Eicosanoids, particularly PGE_2, are critical molecules in the initiation of inflammation and the transition from innate to acquired immune responses. mPGES-1, an integral membrane enzyme functionally coupled to COX-2, whose regulated expression controls PGE_2 levels at sites of inflammation (Kalinski, 2012; Park et al., 2006), has pleiotropic effects on many cells of the immune system, influencing both the innate and acquired immune responses (Sreeramkumar et al., 2012; Sreeramkumar et al., 2016). PGE_2 can promote the influx and activation of neutrophils, macrophages, and mast cells (Kojima et al., 2008; Westman et al., 2004), but can also suppress NKT cytolytic and granulocyte functions (Jakobsson et al., 1999). In vitro evidence from several groups have shown that the induction of mPGES-1 is increased in response to the pro-inflammatory cytokines IL-1β, TNF, or LPS and that its expression, in certain immune-mediated inflammatory diseases (IMIDs), maybe up-regulated by a wide range of stimuli (Korotkova et al., 2008). Li and colleagues (Li et al., 2005) have shown that expression and regulation of mPGES-1 and PPAR-γ in human osteoarthritic cartilage and chondrocytes are regulated by pro-inflammatory stimuli such as IL-1α and TNF-α and that the concomitant presence of IL-17 displayed a synergistic effect, reversed by troglitazone or exogenous PGE_2. These data suggest that mPGES-1 may prove to be an interesting therapeutic target for controlling PGE_2 synthesis in certain IMIDs such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondylarthritis (SpA) (Jouzeau et al., 2008; Navarini et al., 2020) where IL-17 levels are uniquely situated to amplify inflammation (Maione, 2016).

Self-regulation of the COXs pathway does not consist solely of positive feedback but also involves mechanisms that inhibit the inflammatory response. At the centre of the COXs auto-inhibitory pathway are the PPARs. Activation of inflammatory responses causes an increase in the expression of **PPAR-α** and a decrease in PPAR-γ (García-Alonso et al., 2013; Kapoor et al., 2007). PPARs are nuclear receptors activated by oxidised and nitrated fatty acid derivatives and cyclopentenone PGs (PGA_2 and $15d\text{-}PGJ_2$) during the inflammatory response. Other activators include nonsteroidal anti-inflammatory drugs (NSAID), fatty acids, especially polyunsaturated fatty acid (PUFA) (arachidonic acid, ALA, EPA, and DHA), and thiazolidinedione derivates (Yousefnia et al., 2018). The primary function of PPARs during the inflammatory reaction is to promote the inactivation of NF-κB

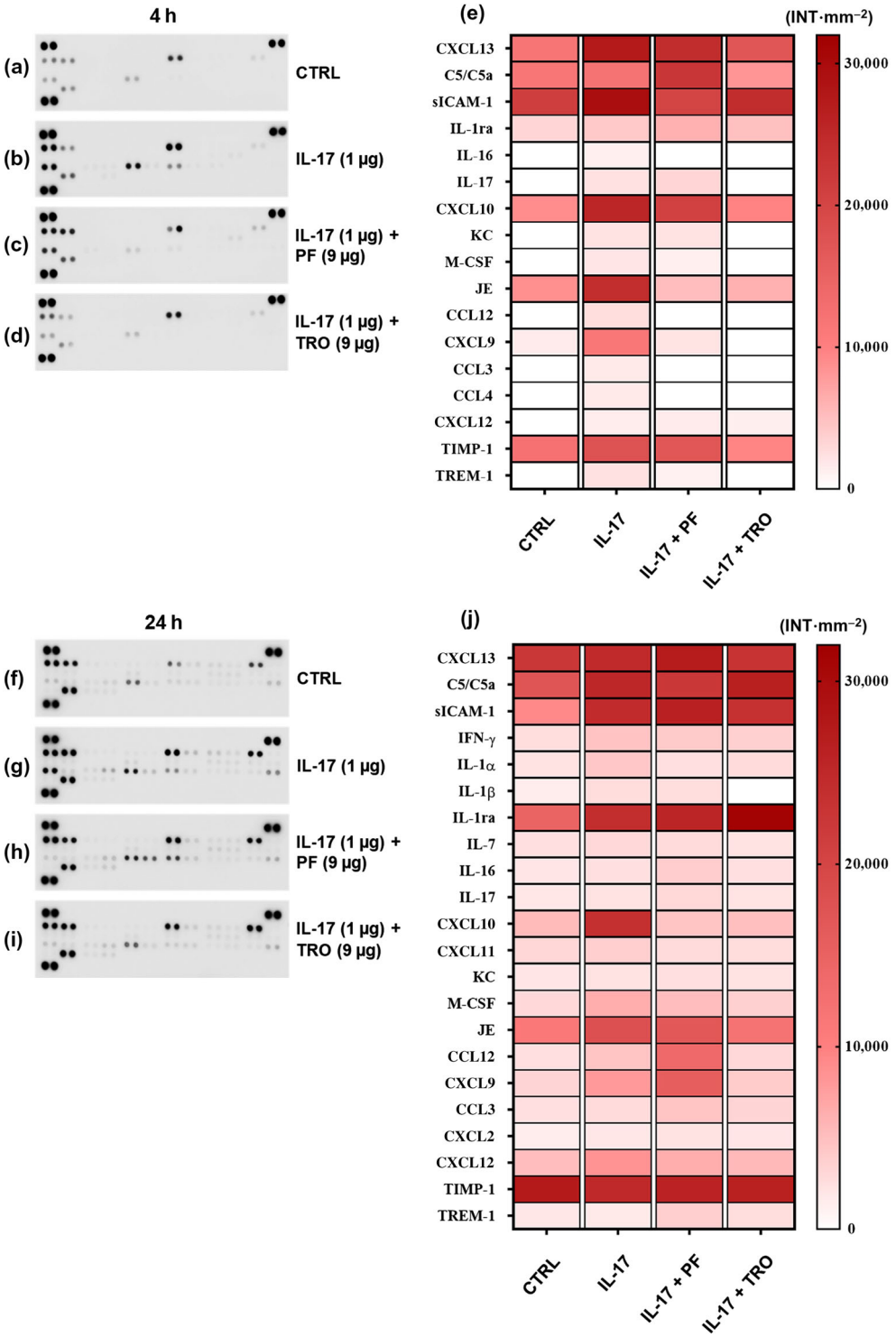

FIGURE 6 Co-treatment with PF 9184 (PF) and troglitazone (TRO) and IL-17 into the air pouch decreases the release of cyto-chemokines in the inflammatory fluid: Inflammatory supernatants obtained from the pouch cavities were assayed using a proteome profiler cytokine array at both 4 and 24 h for CTRL (respectively, a, f), IL-17 (1 μg per pouch, respectively, b, g), IL-17 + PF (9 μg per pouch, respectively, c, h) and IL-17 + TRO (9 μg, respectively, d, i). Densitometric analysis is presented as heatmap at 4 (e) and 24 h (j). Data (expressed as INT·mm^{-2}) are presented as means ± SD of positive spots of three separate independent experiments run, each with n = 7 mice per group pooled

(by direct binding of p65 NF-κB) or the proteolytic degradation of p65 NF-κB. PPARs also cause an increase in the expression of IκB-α, SIRT1, and PTEN, which interfere with the activation and function of NF-κB in inflammatory reactions (Thommesen et al., 1998). From a pathological point of view, it should also be taken into account that IL-1α, TNF-α, IL-17, and PGE_2, which are involved in the pathogenesis and progression of certain IMIDS, also down-regulate PPAR-γ expression in a dose- and time-dependent manner (Afif et al., 2007; Korbecki et al., 2014). Several lines of evidence suggest that PPAR-γ activation may have therapeutic benefits in RA, PsA, and possibly other chronic articular diseases (Korbecki et al., 2019; Murakami, 2011) where all these mediators, and in particular IL-17, are up-regulated (Maione, 2016; Raucci, Iqbal, Saviano, Minosi, et al., 2019).

IL-17 is an archetype molecule for the entire family of IL-17 cytokines. Currently believed to be produced by a specific subset of $CD4^+$ T cells, named Th17 cells, but also by many innate cell components

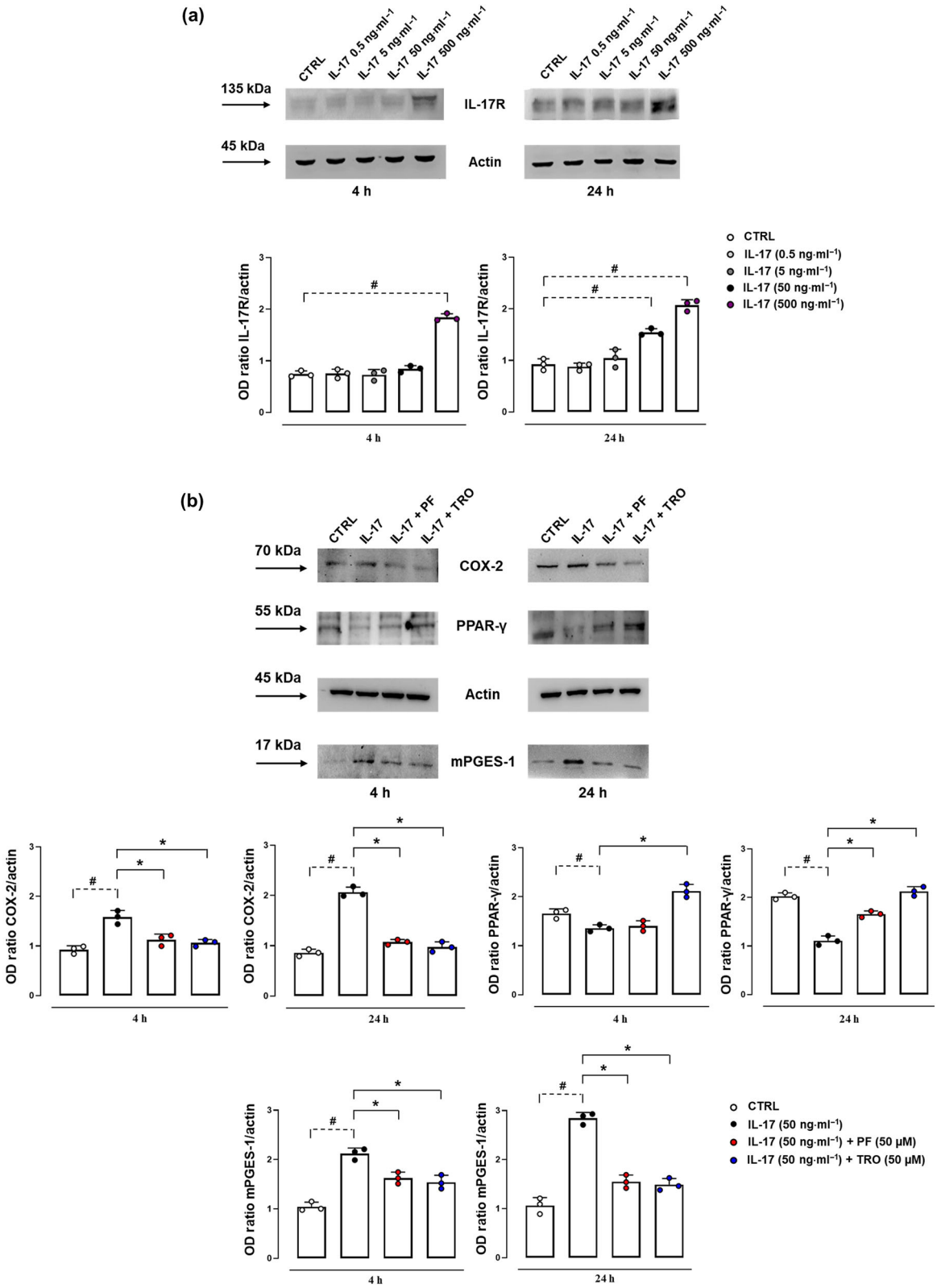

FIGURE 7 Protective effect of PF 9184 and troglitazone on murine isolated, and IL-17-stimulated, macrophage: Whole cellular pellets homogenates from murine macrophages stimulated with increasing concentration of IL-17 (0.5–500 ng·ml^{-1}) (a) or with IL-17 at 50 ng·ml^{-1} in presence or absence of PF 9184 (PF, 50 μM) and troglitazone (TRO, 50 μM) at 4 and 24 h (b) were analysed, by western blot, for IL-17R, COX-2, PPAR-γ, mPGES-1, and actin expression. Western blot images are representative of three separate experiments with similar results. Cumulative densitometric values (at the bottom of figure a, b) are expressed as OD ratio with actin for both 4 and 24 h. Values are presented as means ± SD of three separate independent experiments run each with n = 7 mice per group pooled. $^{\#}P \leq 0.05$, significantly different from CTRL group; $^{*}P \leq 0.05$, significantly different from IL-17 group; one-way ANOVA followed by Bonferroni's test for multiple comparisons

(D'Acquisto et al., 2010), this cytokine is functionally located at the interface of innate and adaptive immunity (Maione, 2016). Specifically, the ability of IL-17 to induce the release of a range of cyto-chemokines and growth factors has led to its emergence as an essential co-ordinator of local inflammatory reactions due to its ability to modulate neutrophil and monocyte accumulation in inflamed tissues. Furthermore, there is growing evidence that suggests targeting IL-17 signalling may prove useful in a variety of inflammatory-based diseases including RA, OA, asthma, Crohn's disease (CD), psoriatic like-disease, and PsA. Here, using a well-established preclinical model of ongoing inflammation, the dorsal air pouch (Maione et al., 2009), we tested the hypothesis that pretreatment with an mPGES-1 inhibitor or PPAR-γ agonist could retard the process of IL-17-induced inflammation. We confirmed the pro-inflammatory action (at 4 and 24 h) of IL-17, but also found a novel protective role for PF 9184 and troglitazone , as exemplified by a reduction in both PMN (polymorphonuclear leukocytes) recruitment (at both 4 and in particular 24 h), MPO activity, and modulation of crucial lipid mediators strictly related to mPGES-1 and PPAR-γ enzymic activity (PGE_2, PGD_2, and PGJ_2). From a mechanistic basis, we demonstrated that IL-17 increased in a time-dependent manner, the levels of its receptor (IL-17R), COX-2, mPGES-1, and NF-κB, and decreased mPTGDS-1, PPAR-γ, and IκB-α expression, in pouch-recruited leukocytes. Moreover, co-administration with PF 9184 and troglitazone was shown to significantly reverse PMN recruitment and MPO activity and reduce the level of lipid mediators and, most importantly, to modulate mPGES-1, mPTGDS-1, PPAR-γ, and NF-κB/IκB-α expression, leaving unchanged the expression of IL-17 receptors. Another exciting aspect of our study is that we provide the first reported evidence of an indirect, co-ordinated functional regulation in both neutrophils and monocytes by mPGES-1 and PPAR-γ. This is most likely related to the presence of complex mechanisms regulating COX-2/mPGES-1 in vivo which go onto to affect PPAR-γ activity (Maione et al., 2020).

This hypothesis is consistent with previous studies showing that pre-adipocytes stably transfected with either COX-1 or COX-2 had lower PPAR-γ expression (Chu et al., 2009) and that mice genetically deficient for mPGES-1 had basal elevations in PPAR-γ expression and transcriptional activity (Kapoor et al., 2007). The mechanisms by which the COX-2/mPGES-1/PGE_2 axis and the nuclear receptor PPAR-γ interact during the inflammatory process are not entirely delineated but may be linked to the ability of PGE_2 (mainly produced by neutrophils at the early stage of inflammation) to decrease the amount of well-known lipid mediators (such as PGD_2 and PGJ_2) which are involved in the induction of PPAR-γ (Maione et al., 2020). It is also possible that the reduction of COX-2/PGE_2 involves trans-repression, via SUMOylation, of PPARγ (Pascual et al., 2005; Zelcer & Tontonoz, 2005). This "off-target" effect has been previously described for other mPGEs-1 inhibitors (Di Francesco et al., 2020) such as AF 3485. In this study, AF 3485 displayed an anti-inflammatory profile similar to that of PF 9184.

This biological event is interconnected with a cellular shift from neutrophils to monocytes as exemplified by the release of specific neutrophil (KC and C5a) and monocytes/macrophages (IFN-γ, IL-16, IL-17, CXCL10, JE, MIPs, TREM-1, ICAM, IL-1α/β, MCPs, CXCL9 and TIMP-1) cyto-chemokines. It is well-established in the literature that (i) PPAR-γ acts as a negative regulator of macrophage activation (Ricote et al., 1998) due to its ability to control polarization of monocyte differentiation between pro-inflammatory (M1) and alternative

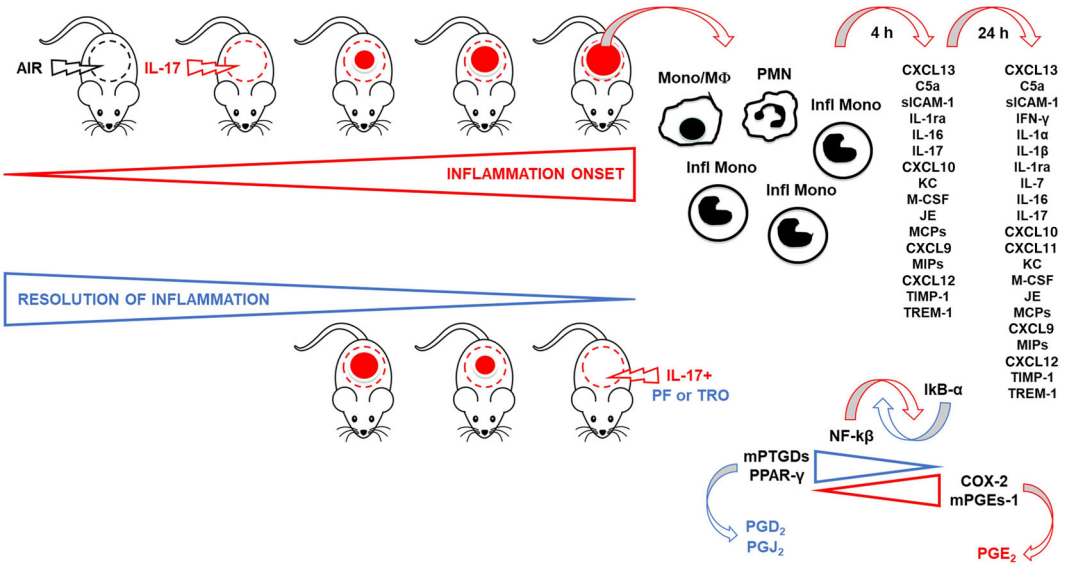

FIGURE 8 Diagram of the involvement of the IL-17/mPGES-1/PPAR-γ pathway on the onset and resolution of inflammation: IL-17 injection into air pouch recruits neutrophils and, more specifically, inflammatory monocytes, producing a massive release of pro-inflammatory cyto-chemokines at both 4 and 24 h. However, the co-administration of IL-17 with an mPGES-1 inhibitor (PF 9184; PF) or PPAR-γ agonist (troglitazone; TRO) shifts the *equilibrium* between COX-2/mPGES-1 and PPAR-γ/mPTGDS-1 pathways, down-regulating PGE_2 and up-regulating PGD_2/PGJ_2 levels via NF-κB

anti-inflammatory (M2) macrophage phenotypes (Tontonoz & Spiegelman, 2008) and to reduce neutrophil migration to sites of injury (Napimoga et al., 2008); (ii) neutrophils are a primary cellular source of mPGES-1, with activated M1, rather than alternatively activated M2 macrophages, a secondary source (Mosca et al., 2007; Posadas et al., 2000). It is clear from this current study that the release of PGE_2 and PGD_2/PGJ_2 related to COX-2/mPGES-1 and PPAR-γ/mPTGDS-1 expression follows the temporal shift from neutrophils to monocytes that are involved in the potential resolution of inflammatory response. This was confirmed by our experiments performed in the presence of either PF 9184 or troglitazone where both compounds were shown to reverse the inflammatory response (Figure 8). To further support this association between IL-17 and mPGEs-1/PPARγ expression and modulation, and in light of the detrimental role of macrophages and macrophage-derived cytokines in RA and SpA synovium (Kabala et al., 2020), we performed in vitro experiments where we used the J774 cell line. Interestingly, we confirmed our in vivo results demonstrating a direct involvement of mPGES-1/PPAR-γ axis in IL-17 stimulated macrophages.

In conclusion, our results reveal a novel interaction between IL-17 and mPGES-1/PPAR-γ generated by macrophages/inflammatory monocytes during inflammation. Therefore, we believe that the IL-17/mPGES-1/PPAR-γ pathway could represent a potential therapeutic target for inflammatory-based and immune-mediated diseases.

ACKNOWLEDGEMENTS

This work was supported by MIUR (PRIN 2017; 2017A95NCJ/201795NCJ_002, "Stolen molecules - Stealing natural products from the depot and reselling them as new drug candidates") and Birmingham Fellowship awarded to A.J.I.

AUTHOR CONTRIBUTIONS

F.R., A.S., G.M.C., M.G.R., A.A.M., M.P., and M.G.F. performed the experiments. E.P., V.V., C.I., F.C., R.S., N.M., M.A., A.J.I., and F.M. performed data analysis and wrote the manuscript. F.R., A.J.I., and F.M. revised the final version of the manuscript for intellectual contents. All authors gave final approval to the publication.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the BJP guidelines for Design & Analysis, Immunoblotting and Immunochemistry, and Animal Experimentation, and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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How to cite this article: Raucci F, Saviano A, Casillo GM, et al. IL-17-induced inflammation modulates the mPGES-1/PPAR-γ pathway in monocytes/macrophages. *Br J Pharmacol*. 2021; 1–17. https://doi.org/10.1111/bph.15413