IFN-\(\lambda\) resolves inflammation via suppression of neutrophil infiltration and IL-1\(\beta\) production

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The most studied biological role of type III interferons (IFNs) has so far been their antiviral activity, but their role in autoimmune and inflammatory diseases remains largely unexplored. Here, we show that treatment with IFN-\(\lambda2/IL-28A\) completely halts and reverses the development of collagen-induced arthritis (CIA) and discover cellular and molecular mechanisms of IL-28A antiinflammatory function. We demonstrate that treatment with IL-28A dramatically reduces numbers of proinflammatory IL-17-producing Th17 and \(\gamma\delta\) T cells in the joints and inguinal lymph nodes, without affecting T cell proliferative responses or levels of anticollagen antibodies. IL-28A exerts its antiinflammatory effect by restricting recruitment of IL-1\(\beta\)-expressing neutrophils, which are important for amplification of inflammation. We identify neutrophils as cells expressing high levels of IFN-\(\lambda\) receptor 1 (IFNLR1)–IL-28 receptor \(\alpha\) (IL28RA) and targeted by IL-28A. Our data highlight neutrophils as contributors to the pathogenesis of autoimmune arthritis and present IFN-\(\lambda\)s or agonists of IFNLR1–IL28RA as putative new therapeutics for neutrophil-driven inflammation.

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RESULTS AND DISCUSSION

Treatment with IL-28A halts and reverses the development of CIA

Male DBA/1 mice were subcutaneously immunized with type II bovine collagen (CII) emulsified in CFA. Approximately 3 wk later, the mice developed a systemic polyarthritic disease affecting multiple joints, including those of the paw. On the day of onset of disease, defined as the first day at least one paw reached a clinical score of one or more, mice were treated with daily intraperitoneal administration of either recombinant IL-28A or PBS control (Fig. 1 a). Using a wide range of doses (0.004–4 mg/kg/d), we demonstrated that therapeutic administration of IL-28A was able to affect the progression of the disease at as low as 0.004 mg/kg/d, as shown by overall clinical score (unpublished data). In all subsequent experiments, we used a 0.4 mg/kg/d dose and noted that disease progression was halted around day 4, and then reverted back to almost baseline levels as judged by clinical score (Fig. 1 b). Individual paw swelling was also reduced (Fig. 1 c). Histologically, mice treated with IL-28A showed significantly reduced cellular infiltrate into the joint, reduced synovial thickening, and decreased joint destruction (P = 0.003; Fig. 1 d). When the optimized CIA model using chicken type II collagen (Inglis et al., 2008) was conducted in the IL28RA-deficient mice (IL28RA−/−) on C57BL/6 background, we observed no significant difference in clinical score (Fig. 1 e). With no endogenous IL-28A mRNA expression detected in either DBA or C57BL/6
Figure 2. Treatment with IL-28A dramatically reduces proinflammatory IL-17–producing Th17 and γδ T cells in the joints. (a) Total numbers of Th17 and IL-17–producing γδ T cells in the hind paw arthritic joints of mice on the 10th day of treatment with IL-28A (0.4 mg/kg/day) or PBS control. The data are mean and SEM derived from eight mice treated with IL-28A and eight mice treated with PBS in a representative of three CIA experiments. Fold induction of (b) IL-17A, IL-1β, and IL-23a mRNA in dissociated cells from arthritic joints of mice treated with IL-28A or control. The data are mean and SEM derived from 19 mice treated with IL-28A and 19 mice treated with PBS from 3 independent CIA experiments. (c) Total numbers of CD4+ T cells and γδ T cells in the lymph nodes and blood of PBS and IL-28A–treated mice. The data are mean and SEM derived from 15 mice that developed arthritis, 8 treated with IL-28A, in a representative of three late CIA experiments. (d) Levels of IFN-γ, IL-1β, IL-6, and CXCL1 in the serum of mice on the 10th day of treatment with IL-28A or PBS control. The data are shown as mean with 95% confidence interval using 16 mice treated with IL-28A and 16 mice treated with PBS, from 3 independent late CIA experiments. (e) Proliferation of lymphocytes after 48-h stimulation with αCD3 or bovine CII. The data are mean and SEM derived from nine independent lymphocyte cultures from LNs of arthritic mice, four of which were treated with IL-28A. Statistical analysis was performed by one-tailed paired Student’s t test. (f) Levels of collagen-specific IgG1 and IgG2a in the serum. The data are mean and SEM using eight mice treated with IL-28A and eight mice treated with PBS, from a representative out of three independent late CIA experiments. (g) Total number of B cells in the lymph nodes. The data are mean and SEM derived from nine independent lymphocyte preparations from LNs of arthritic mice, four treated with IL-28A. Statistical analysis was performed by two-tailed Mann-Whitney U test. *, P < 0.05; **, P < 0.01; ***, P < 0.001.
mice during the course of CIA, we concluded that there was no endogenous IL-28A–mediated suppression of arthritis in this model.

**Treatment with IL-28A reduces proinflammatory IL-17–producing Th17 and γδ T cells in the joints, but has no systemic effect**

IL-17 produced by CD4+ (Th17) cells or γδ T cells plays an important role in the pathogenesis of many murine autoimmune diseases, including CIA (Nakae et al., 2003; Ito et al., 2009). Thus, we analyzed the number of IL-17–producing Th17 and γδ T cells in the joints of mice after 10 d of IL-28A treatment. Both cell populations were significantly reduced (Fig. 2 a), and so was the level of IL-17A mRNA expression (Fig. 2 b). IL-23p19 plays a critical role in the development of CIA via generation of IL-17–producing CD4+ cells (Murphy et al., 2003) and is aided by IL-1β in induction of IL-17 production by γδ T cells independently of T cell receptor (Ito et al., 2009). Therefore, we examined the expression levels of both IL-23p19 and IL-1β in affected joints by quantitative RT-PCR and revealed that treatment with IL-28A caused reduction in their expression (Fig. 2 b).

Interestingly, therapeutic administration of IL-28A caused a major reduction in the total number of CD4+ and γδ T cells, as well as in IL-17–producing T cells, in draining lymph nodes but not in the peripheral blood (Fig. 2 c), indicating that treatment with IL-28A does not cause lymphopenia. Moreover, IL-28A had no effect on neutrophil (GR1+), dendritic cell (CD11b+CD11c+), and B cell (CD19+) counts in
IL-28A targets neutrophils

The IFNLR1–IL28RA subunit has a limited distribution which for a long time was thought to be mainly restricted to cells of epithelial origin, such as lung epithelial cells (Ank et al., 2008; Mordstein et al., 2010). Recent genome-wide gene expression datasets from a diverse array of normal tissues, organs, and cell lines released by the Immunological Genome Project (ImmGen) indicated the highest level of Il28ra mRNA expression is found on CD11b+GR1+-sorted neutrophils from bone marrow. To test whether Il28ra mRNA expression on this cell population results in a functional protein, we stimulated Percoll-purified neutrophils (Fig. S1 a) with IL-28A (and IFN-β used as a positive control) and measured phosphorylation of STAT1, which is in the peripheral blood (not depicted) or on the levels of inflammatory cytokines and chemokines in the serum (Fig. 2 d), ruling out a side effect of the treatment. To further assess T cell responses, we stimulated LN cells from CIA mice with CII or with anti-CD3, and measured proliferation. Both stimulation with anti-CD3 and CII resulted in a significant increase in T cell proliferation in the control PBS treated group (P = 0.0007 and P = 0.034, respectively). Proliferative responses to anti-CD3 and CII were unaffected by IL-28A treatment (Fig. 2 c).

As IL-17 activates both autoantigen-specific cellular and humoral immune responses (Nakae et al., 2003) and B cells appear to play a critical role in arthritis pathogenesis (Dörner and Lipsky, 2014), we examined B cell function in mice treated with IL-28A. CII-specific B cell (IgG1 and IgG2a) responses were assessed at day 10 after IL-28A treatment but revealed no significant changes (Fig. 2 f). This lack of a suppressive effect on antibody responses to type II collagen, together with the unchanged number of total B cells in peripheral blood (not depicted) and LN (Fig. 2 g), indicated that therapeutic administration of IL-28A does not perturb the humoral phase of the autoimmune response generated during CIA.

**Treatment with IL-28A restricts neutrophil infiltration into joint at the early stages of arthritis**

Because disease progression was halted at approximately day 4, which differs from other treatments, such as anti-TNF (Williams et al., 1992), we sought to gain a better understanding of the cellular changes occurring during the early course of treatment by analyzing the cell content of the joints at that point using flow cytometry. Unexpectedly, we found that the number of neutrophils but not other cell types was reduced with IL-28A treatment (Fig. 3 a). This finding was confirmed by immunostaining of histological slides for GR1+ cells, which demonstrated a clear reduction (P = 0.0012) in synovial neutrophil infiltrate in IL-28A-treated animals also at day 10 (Fig. 3 b). Moreover, the mRNA expression of key adhesion molecules involved in different stages of the neutrophil recruitment cascades, such as P-selectin glycoprotein ligand 1 (PSLG1), lymphocyte function-associated antigen 1 (LFA1), and integrin α M (MAC-1; Kolaczkowska and Kubes, 2013), was also reduced in IL-28A–treated animals (Fig. 3 c). Furthermore, we detected a substantial reduction in the levels of leukotriene B4 receptor 1 (LTB4R1), which was previously shown to be absolutely required for effective neutrophil recruitment into the joint in the K/BxN model of inflammatory arthritis (Kim et al., 2006; ig. 3 c). IL-1β secretion by neutrophils is believed to be critical for amplification of arthritis in this model through further induction of neutrophil-active chemokines by synovial cells (Chou et al., 2010). Interestingly, we found that the serum levels of IL-1β, but not other inflammatory cytokines and chemokines, such as IFN-γ, IL-6, or CXCL1 (Fig. 3 d), were transiently reduced at the early stage of treatment.
express IL28RA and therefore can indeed be targets of IL-28A treatment, CD11b+ cells were isolated from the arthritic joints of mice and subjected to a subsequent adhesion step to separate macrophage and neutrophil populations (Fig. S1 b). qPCR analysis of these cell populations revealed Il28ra mRNA levels to be highest in the neutrophil-enriched fraction compared with macrophages or the CD11b− population of cells (Fig. 4 c). Similar results were obtained for circulating blood neutrophils (not depicted). Notably, we also observed pSTAT1 induction was comparable in both IL-28A– and IFN-β–stimulated neutrophils (Fig. 4 a), whereas IFN-β was a stronger inducer of STAT1 phosphorylation in the whole bone marrow (Fig. 4 b), suggesting that IL-28A function is indeed limited to specific populations of immune cells, i.e., neutrophils. We observed no IL-28–induced STAT1 signaling in neutrophils or in the whole bone marrow of IL28RA−/− mice (Fig. 4, a and b). To examine whether synovial neutrophils signaling pathway (Kotenko et al., 2003; Sheppard et al., 2003). pSTAT1 induction was comparable in both IL-28A– and IFN-β–stimulated neutrophils (Fig. 4 a), whereas IFN-β was a stronger inducer of STAT1 phosphorylation in the whole bone marrow (Fig. 4 b), suggesting that IL-28A function is indeed limited to specific populations of immune cells, i.e., neutrophils. We observed no IL-28–induced STAT1 signaling in neutrophils or in the whole bone marrow of IL28RA−/− mice (Fig. 4, a and b). To examine whether synovial neutrophils

Figure 5. Treatment with IL-28A reduces neutrophil recruitment in the air pouch model of acute inflammation by limiting neutrophil migratory capacity. (a) Schematic timeline of the air pouch model showing subcutaneous air injections, treatment with IL-28A or PBS, and challenge with zymosan. (b) Total number of neutrophils per milliliter of wash recovered from the air pouches of mice that had been treated with IL-28A or PBS control before inflammatory challenge. The data are mean and SEM from 12 mice treated with IL-28A and 12 mice treated with PBS from 2 independent experiments. (c) Center-zeroed tracks of air pouch neutrophilic infiltrate in an EZ-Taxiscan migrating toward LTB4; scale is shown in micrometers. (d) The tracks presented in c were analyzed to show the Euclidean distance each cell traveled in a 45-min time period. Data shown are the average and SEM of three independent experiments, each including 9–20 movies per treatment. (e) Percentage of cells infiltrating into the air pouch staining positive for PI and Annexin V. The data are mean and SEM using 12 mice treated with IL-28A and 12 treated with PBS, from 2 independent experiments. (f) Percentage of neutrophils that were positive for pro–IL-1β and infiltrated into the air pouch space of mice. (g) Levels of IL-1β secreted into the air pouch after challenge with zymosan. (h) Percentage of neutrophils or macrophages lining the air pouch membrane that were positive for pro–IL-1β. (i) Expression of IL28RA mRNA in cells infiltrating into the air pouch space compared with cells lining the air pouch, as well as in Percoll-purified neutrophils. (f–i) The data are mean and SEM derived from six mice treated with IL-28A and six mice treated with PBS, in a representative out of two experiments. Statistical analysis was performed by two-tailed Mann-Whitney U test. *, P < 0.05; **, P < 0.01; ***, P < 0.001.
high levels of IL28RA mRNA expression in circulating neutrophils purified from the blood of human donors (unpublished data).

**IL-28A limits neutrophil migratory capacity**

To further confirm the role of IL-28A in neutrophil recruitment, we used the air pouch model of acute inflammation, which provides a robust and reliable method to quantify early neutrophil infiltration into the air pouch cavity and in vivo cytokine production by both infiltrating cells and cells from the granulation tissue lining (Tessier et al., 1997). In this model, a cavity is created on the dorsal surface of the mice, and granulation tissue is allowed to form over a period of 6 d, before challenge with zymosan, a ligand for dectin-1 and TLR 2/6 (Fig. 5 a). Using a range of zymosan doses, we found that injection of 100 µg of zymosan into the pouch cavity resulted in infiltration of ~3 × 10^6 cells/ml 4 h after injection, ~80% of which were CD11b+GR1+ neutrophils (Fig. S1 c). Mice that were pretreated with an intraperitoneal injection of IL-28A before inflammatory challenge with zymosan showed a decrease in the number of neutrophils infiltrating into the air pouch (Fig. 5 b). As a decrease in neutrophil number may come about via a decrease in recruitment or an increase in apoptosis, we measured the chemotactic response and apoptosis in neutrophil infiltrates obtained from IL-28A-treated and control animals. To assess chemotaxis toward the neutrophil chemotactic agent LTB4, we used the EZ-Taxiscan system, which allows visualization of cell migration in shallow, linear gradients and provides real time analysis of neutrophil movement (Nitta et al., 2007). Cells from PBS-treated mice demonstrated good velocity and directionality; however, migration was impaired in cells obtained from IL-28A-treated mice as demonstrated by the reduced Euclidean distance traveled in a 45-min time period (Fig. 5, c and d; and Videos 1–4). Additionally, neutrophils obtained from IL-28A-treated mice exhibited reduced basal migration (Fig. 5, c and d). We also detected an impaired migratory capacity of bone marrow neutrophils treated with IL-28A ex vivo (unpublished data). These data indicate that systemic IL-28A treatment inhibits local neutrophil migratory capacity. No difference was observed in neutrophil apoptosis (Fig. 5 e).

Furthermore, the levels of pro–IL-1β in infiltrating neutrophils (Fig. 5 f) and in neutrophils from within the air pouch lining tissue (Fig. 5 h) significantly decreased in response to IL-28A, as did the levels of IL-1β secreted into the air pouch (Fig. 5 g). We observed no differences in the levels of pro–IL-1β in macrophages (Fig. 5 h) or monocytes (unpublished data) from the lining tissue, indicating that IL-28A is likely to act directly on neutrophils. Indeed, the analysis of IL28RA mRNA expression demonstrated that it was chiefly expressed in Percoll-purified neutrophils (Fig. S1 d) and neutrophil-enriched infiltrates (Fig. 5 i).

Together, these data point to at least one mechanism of IL-28A antiinflammatory function in arthritis, i.e., IL-28A blocks synovial neutrophil IL-1β production and recruitment via limiting LTB4R1 expression at early stages of arthritis. This prevents amplification of further neutrophil recruitment and chemokine/cytokine release that would otherwise lead to activation of synovial tissue cells, such as synoviocytes, endothelial cells, and macrophages leading to reduced numbers of Th17 and γδ T IL-17+ cells. Several recent reports implicated type I IFNs in regulating neutrophil recruitment after viral and bacterial infections, and in tumors (Seo et al., 2011; Brzoz-Brzozowa et al., 2012; Jablonska et al., 2014; Stock et al., 2014). Despite some differences in the proposed mode of action, with type I IFN appearing to work via repressing CXCL1/CXCL2 production by monocytes and macrophages without having an effect on neutrophils themselves (Jablonska et al., 2014; Stock et al., 2014), it is exciting to speculate that the mammalian antiviral system has evolved to control excessive destructive inflammation.

Neutrophils are by far the most abundant immune cell in the synovial fluid of RA patients, but can also be observed at the pannus/cartilage interface in synovial tissue (Mohr et al., 1981). Due to the high levels of antiapoptotic cytokines found in the early rheumatoid joint, the life span of neutrophils is extended (Hotta et al., 2001; Raza et al., 2006) and thereby they have an enhanced potential to contribute to the pathogenesis of inflammation. Notably, many current antiinflammatory drugs used in the treatment of RA, such as a methotrexate, exert inhibitory effects on neutrophils by restoring delayed neutrophil apoptosis and decreasing neutrophil chemotaxis (Kraan et al., 2000; Weinmann et al., 2007). Here, we show that a molecule that appears to specifically target neutrophil function may impact upon pathology of inflammatory arthritis. Our data, together with already demonstrated good safety and tolerability of IFN-α in early clinical studies for the treatment of hepatitis C virus infection (Miller et al., 2009), call for its trial in RA as well as in conditions in which neutrophils are known to play an important role, such as small-vessel vasculitis, gout, and familial Mediterranean fever.

**MATERIALS AND METHODS**

**Study approval.** All work was performed in compliance with UK Home Office guidelines for animal welfare based on the Animals (scientific procedures) act 1986 and under the Home Office approved project license.

**CIA.** The IL28RA−/− mice were provided by ZymoGenetics and bred in-house. Male DBA/1OlaHsd mice (Harlan) were purchased at ~8 wk of age and allowed to acclimatize for at least 2 wk before immunization. The target sample size was n = 5 in each treatment group in each experiment. As the incidence for CIA varies between experiments, enough mice were immunized to ensure minimal arthritic mice were obtained. To induce arthritis, bovine (DBA) or chicken (IL28RA−/−) type II collagen was emulsified in complete Freund’s adjuvant and injected subcutaneously at the base of the tail and in a second site on the flank. Mice were assessed daily, with paw swelling measurements and a clinical score given to each paw as follows: 0, no swelling; 1, mild swelling; 2, significant swelling; 3, ankylosis. Day 1 of onset was classed as the first day a single paw scored 1 or more and this was the day treatment began. Pegylated recombinant mouse IL-28A (a gift from Zymogenetics/Bristol-Myers Squibb, Seattle, WA) was administered daily by intraperitoneal injection at the indicated dose. Control mice were injected with phosphate buffered saline. Mice were allocated sequentially to treatment groups at first sign of arthritis, i.e., the first arthritic mouse was treated with PBS, the next with IL-28, the next with PBS, and so on. To
minimize stress on the animals, scoring and paw measurement were performed at the same time as injections, and thus the investigator was not blinded in respect to treatment groups. One mouse developed an infection and was excluded from the study. Lymphocytes from arthritic mice were cultured for 48 h with anti-CD3 monoclonal antibody (145-2C11), bovine collagen type II or media alone before addition of EdU (Life Technologies) for 3 h. Cells were processed for flow cytometry after manufacturer’s instructions to determine the percentage of cells in S phase. Collagen-specific IgG1 and IgG2a antibodies in mouse serum were detected using an ELISA method as previously described (Inglis et al., 2008).

Air pouch model. WT C57BL/6j male mice (Charles River) were purchased at 8 wk of age and allowed to acclimate for 1 wk. Mice were anesthetized with isoflurane and 3 ml of air injected subcutaneously to create a dorsal air pouch with a top-up of air 3 d later. Concurrent with the top-up of air, mice were treated with an intraperitoneal injection of IL-28A or PBS and with a second injection at day 5. At 6 d after the creation of the air pouch, mice were challenged with 100 µg zymosan injected directly into the pouch.

Histology. For histological analysis, mice were sacrificed on day 10 after onset of arthritis. Arthritic paws were severed above the ankle and fixed in 10% buffered formalin. Paws were decalcified in 20% formal-formic acid and dehydrated before embedding in paraffin wax. Sagittal sections were stained with hematoxylin and eosin. Joints were scored in a blinded manner for degree of joint space infiltrate, bone erosion, and synovial thickening. For immunohistochemical analysis, paraffin-embedded sections were stained with Ly6G Biotin (clone 1A8; BioLegend) or isotype control, using an avidin/biotin staining.

Cell and tissue isolation. Inguinal and popliteal lymph nodes were removed and passed through a 70-µm cell strainer. Blood was collected together with heparin followed by two rounds of red blood cell lysis or immunomagnetic separation to determine the percentage of cells in S phase. Collagen-specific EdU staining.

mRNA analysis. Cells were washed and pelleted before lysis in RLT Buffer (QIAGEN). RNA was extracted using the RNeasy kit following the manufacturer’s protocol (QIAGEN). RNA was transcribed into cDNA using a High Capacity cDNA RT kit (Life Technologies) and mRNA detected with TaqMan Gene Expression Assays on an Applied Biosystems 7900HT Instrument (Life Technologies). Relative mRNA values were quantified using the ΔΔCt method with normalization to HPRT gene expression.

Cytokine detection. Serum cytokines were quantified using a multiplex assay (Meso Scale Discovery) following the manufacturer’s instructions. IL-1β levels in air pouch lavage were detected by ELISA (BD) following the manufacturer’s instructions.

Western blot. Percoll-purified neutrophils from bone marrow were stimulated with 100 ng/ml IL-28A or 100 ng/ml IFN-β for 15 or 30 min. Cells were harvested and lysed directly in Laemmli buffer. Protein lysates were resolved by Novex Tris-glycine gel (Life Technologies), transferred onto a PVDF membrane (GE Healthcare) by wet Western blotting, and subjected to incubation with rabbit anti-pSTAT1 (Cell Signaling Technology) or rabbit anti-STAT1 (Cell Signaling Technology) antibodies, followed by detection with horseradish peroxidase–conjugated secondary antibodies and chemiluminescent substrate solution ECL2 (GE Healthcare).

Neutrophil migration. For real time analysis of migrating neutrophils, a 12-channel TAXIScan was used (Nitta et al., 2007) and used with a 5-µm chip according to the manufacturer’s protocol (Effector Cell Institute). Sequential image data were generated from individual jpegs processed with ImageJ (National Institutes of Health), equipped with the manual tracking and chemotaxis tool plugins (Ibidi). Euclidean distances refer to the total Euclidean distance traveled by individual cells in a particular experiment.

Online supplemental material. Fig S1 shows flow cytometry gating of neutrophils isolated from bone marrow, arthritic joints, and air pouch. Video 1 shows migration of cells from air pouch infiltrates of PBS-treated animals toward PBS. Video 2 shows migration of cells from air pouch infiltrates of PBS-treated animals toward LTB4. Video 3 shows migration of cells from air pouch infiltrates of IL-28A–treated animals toward PBS. Video 4 shows migration of cells from air pouch infiltrates of IL-28A–treated animals toward LTB4. Online supplemental material is available at http://www.jem.org/cgi/content/full/jem.20140995/DC1.

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Author contributions: K. Blazek, A.J. Byrne, M. Weiss, H.L. Eeames, J.E. Pease, and R.O. Williams and D. Perocheau conducted the experiments and analyzed the data; I.A. Udalova designed the study, supervised the project, and wrote the manuscript. R.O. Williams and F. McCann advised on the experimental procedures, supervised some experimental work, and edited the manuscript. S. Doyle provided recombinant IL-28A and discussed the data.

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