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Citation for published version:

Digital Object Identifier (DOI):
10.1128/IAI.00436-12

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Infection and Immunity

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Type 2 Innate Immunity in Helminth Infection Is Induced Redundantly and Acts Autonomously following CD11c⁺ Cell Depletion

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Infection with gastrointestinal helminths generates a dominant type 2 response among both adaptive (Th2) and innate (macrophage, eosinophil, and innate lymphoid) immune cell types. Two additional innate cell types, CD11c-high dendritic cells (DCs) and basophils, have been implicated in the genesis of type 2 immunity. Investigating the type 2 response to intestinal nematode parasites, including *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis*, we first confirmed the requirement for DCs in stimulating Th2 adaptive immunity against these helminths through depletion of CD11c-high cells by administration of diphtheria toxin to CD11c.DOG mice. In contrast, responsiveness was intact in mice depleted of basophils by antibody treatment. Th2 responses can be induced by adoptive transfer of DCs, but not basophils, exposed to soluble excretory-secretory products from these helminths. However, innate type 2 responses arose equally strongly in the presence or absence of CD11c-high cells or basophils; thus, in CD11c.DOG mice, the alternative activation of macrophages, as measured by expression of arginase-1, RELM-α, and Ym-1 (Chi3L3) in the intestine following *H. polygyrus* infection or in the lung following *N. brasiliensis* infection, was unaltered by depletion of CD11c-expressing DCs and alveolar macrophages or by antibody-mediated basophil depletion. Similarly, goblet cell-associated RELM-β in lung and intestinal tissues, lung eosinophilia, and expansion of innate lymphoid (“nuocytes”) populations all proceeded irrespective of depletion of CD11c-high cells or basophils. Thus, while CD11c-high DCs initiate helminth-specific adaptive immunity, innate type 2 cells are able to mount an autonomous response to the challenge of parasite infection.

Type 2 immunity encompasses a suite of cellular and cytokine-dependent immune responses associated with the Th2 phenotype of interleukin-4 (IL-4), IL-5, and IL-13 production (42, 68). The downstream effector mechanisms mobilized by these cytokines include B cell class switching to IgG1, IgG4, and IgE, eosinophilia, goblet cell hyperplasia, and alternative activation of macrophages, as well as activity on many other target cells (2). The recent recognition of a non-B, non-T (NBNT) “natural helper” lymphoid population that can parallel the Th2 phenotype in production of the same canonical cytokines (25, 35, 37, 46, 51) emphasizes that a broader type 2 compartment embraces both innate and adaptive immunity.

Helminth parasites provide highly polarizing stimuli for the mammalian immune response, generating a Th2-dominated profile in nearly every infection setting (14, 43), in part by releasing potent Th2-driving molecular products (11, 21, 59). Helminths and their antigens have thus provided powerful tools to dissect how the immune system discriminates between pathogenic challenges and selects type 2 immunity. A key focus has been to identify innate immune cells, which stimulate naïve Th0 precursors, with the dendritic cell (DC) being the principal player in this process. Thus, helminth antigen-pulsed DCs induce strong Th2 responses (5, 29), and mice depleted of CD11c-high DCs through a diphtheria toxin (DTx) receptor (DTR)-linked construct fail to mount Th2 responses to *Schistosoma mansoni* or *Heligmosomoides polygyrus* helminth infection (45, 56). Moreover, the response to schistosome egg antigen (SEA) is also abolished in the absence of DCs (45), consistent with identification of molecular constituents of SEA acting via DCs to induce the Th2 phenotype (11, 59).

Basophils have also been identified as participants in Th2 immunity, in general as amplifiers through production of IL-4 (22, 33, 65), and are indeed the main source of IL-4 in primary infection with the gastrointestinal nematode *Nippostrongylus brasiliensis* (65). In some models, including *Trichuris muris* infection, basophils have also been reported to be essential for initiation of Th2 responses (44, 58). In other systems, however, basophils appear to be less critical for inducing primary Th2 differentiation. Thus, IL-3 or IL-3 receptor (IL-3R)-deficient mice show intact Th2 responses to *N. brasiliensis* in the absence of basophil recruitment (24), and antibody-mediated basophil depletion does not diminish Th2 induction in infection (24, 45, 65). Likewise, in transgenic constructs of basophil-specific lineage ablation, normal Th2 responsiveness to *N. brasiliensis* is observed (39, 60). Nonetheless, basophils can significantly enhance Th2 immunity in settings such as infected tissue (64) and can promote rapid primary (60) and secondary (41) Th2 immunity to *N. brasiliensis*.

Additional innate immune populations are implicated in amplifying Th2 responses and/or conducting important functions in protecting against disease. Among these, alternatively activated macrophages (AAMs) are prominent in the pulmonary response to *N. brasiliensis* (36, 50) and mediate intestinal immunity to both...
N. brasiliensis and H. polygyrus infection (4, 70). AAM induction takes place even in RAG-deficient (27) and SCID mice (50), although T cell-derived IL-4 and IL-13 are required for alternative activation to be sustained (27). Eosinophils also contribute significant IL-4 production (68), which can directly induce AAMs (69), and act as effector cells in immunity against many tissue-migrating helminth larvae (3). In addition, an important new cell type is the nuocyte or innate lymphoid type 2 cell, which lacks B or T cell receptors and markers yet produces significant levels of IL-4, IL-5, and IL-13 (25, 35, 37, 46, 51).

In this study, we therefore set out to establish the relative importance of DCs and basophils in the generation of these diverse innate and adaptive type 2 responder populations. Studying both infection and immunization with nematode-secreted Th2-disposing antigens, we showed that DCs are indeed essential for the Th2 response, while basophils are not required for this activity, in either setting. Critically, however, the depletion of DCs or basophils did not compromise expansion of AAMs, eosinophils, or innate type 2 lymphoid cells. These data suggest that multiple populations of innate cells act autonomously by adopting a type 2 program under the conditions of helminth infection, perhaps reflecting the imperative to evolve redundant immune mechanisms to protect against parasite invasion (2).

**MATERIALS AND METHODS**

Mice, parasites, and antigens. Wild-type BALB/c and C57BL/6 mice and CD11c.DOG mice on the C57BL/6 background, which express human diphtheria toxin receptor and ovalbumin amino acids (aa) 140 to 386 under the control of the CD11c promoter (19, 20), were bred and maintained in a specific-pathogen-free facility at the University of Edinburgh. Mice were injected subcutaneously (s.c.) with 250 N. brasiliensis infective third-stage larvae (L3) or with 200 H. polygyrus bakeri (7, 30) L3 using a gavage tube, or with 50 μg N. brasiliensis or H. polygyrus (HES) and N. brasiliensis (NES) were prepared as previously described (18, 21).

In vivo depletion of dendritic cells and basophils. CD11c.DOG mice were depleted of CD11c+hi dendritic cells by intraperitoneal i.p.) injection of 8 ng/g diphtheria toxin daily from day −1 to 6 after infection (19, 20, 45). Efficacy of depletion was assessed by flow cytometry of splenocytes and Liberase-digested mesenteric LN cells (MLNC) (see Fig. 1A and B). BALB/c mice were depleted of basophils by i.p. injection of 10 μg MAR-1 antibody or Armenian hamster IgG isotype control (eBioscience) on days 0, 1, and 2 postinfection. Check blood was taken on day 4 postinfection to assess basophil depletion by flow cytometry.

Bone marrow-derived DCs and basophils. DCs and basophils were generated in vitro from femoral bone marrow cells in the presence of 20 ng/ml granulocyte-macrophage colony-stimulating factor (GM-CSF) and 5 ng/ml IL-3, respectively, replenishing the medium at days 6, 8 for DCs and days 3 and 8 for basophils, before harvesting on day 10. Basophils were purified by flow sorting as DX-5+ c-kit− Gr−1−. Cells were incubated for 18 h in medium containing 20 μg/ml antigen and 5 ng/ml GM-CSF or 5 ng/ml IL-3. DCs were >85% CD11c+ major histocompatibility complex (MHC) class II+, whereas basophils were >95% CD49b+c-kit− and expressed high levels of FcεRI but no detectable MHC class II following culture. Cells were then washed in phosphate-buffered saline (PBS) and transferred into the hind foot at 2.5 × 106 cells per foot. Popliteal LNs (PLNs) were harvested at day 5 posttransfer and antigen-specific restimulations performed in Ex-Vivo medium containing penicillin-streptomycin and 1-glutamine.

Flow cytometry and LN cytokine assays. MLNs were removed into Hanks balanced salt solution (HBSS) before being digested in 250 μg/ml Liberase TL (Roche) for 30 min at 37°C in a shaking incubator with the addition of 0.02 M EDTA (pH 7.3) for the final 5 min. MLNs were then washed and homogenized in HBSS and centrifuged at 400 × g for 5 min before being resuspended in fluorescence-activated cell sorter (FACS) buffer (0.5% bovine serum albumin [BSA], 0.05% sodium azide, 1× PBS). The left lobe of the lung was prepared similarly by dissection into small pieces in PBS containing 250 μg/ml Liberase and 80 U/ml DNase I (Sigma). Following digestion and homogenization, the cell suspension was treated with red cell lysis buffer, and cells were washed, counted, and stained for flow cytometry. Cells were stained with surface and lineage markers as follows: phycoerythrin (PE)-conjugated Siglec F (clone E50-2440; BD Pharmingen), PE-Cy7-conjugated F4/80 (clone BM8; eBioscience), alloparycoccus (APC)-conjugated CD11c (clone N418; eBioscience), fluorescein isothiocyanate (FITC)-conjugated MHC class II (clone M5/114.15.2; BioLegend), and Pacific Blue-conjugated CD11b (clone M1/70; Biolegend) antibodies. Lung samples were then fixed with 1× Foxp3 fixation buffer (eBioscience) before intracellular staining was performed with antibodies to murine Resistin (RELM-α) at 2 μg/ml (Peprotech) and 0.72 μg/ml biotinylated antibody to mouse chitinase 3-like (3/ECF-L. Ym-1; R&D) in Foxp3 permeabilization buffer before a secondary stain with 0.67 μg/ml Zenon rabbit IgG Alexa-Fluor 488 (Invitrogen) and 1/200 streptavidin-peridinin chlorophyll protein (PerCP) (Biolegend). Staining was compared to that for isotype controls of pooled naive and infected samples.

Check blood cells were sensitized with 12 μg/ml recombinant murine IgE (Pharmingen) and then stained using a combination of 1/250 biotin anti-mouse IgE (Pharmingen) and 1/200 streptavidin-APC (Biolegend) with FITC-conjugated CD1 (clone 17A2; Biolegend), PE-Cy7-conjugated CD49b (clone DX5; eBioscience), PerCP-conjugated B220 (clone RA3-68B; Biolegend), and PE-conjugated CD117 (c-kit) (clone ACK2; Biolegend) antibodies. Red blood cells were lysed using 1× BD FACS red cell lysing solution before acquisition.

For intracellular staining, 6 × 106 cells/well were plated in a 24-well plate with 0.5 μg/ml phorbol myristate acetate (PMA) and 1 μg/ml ionomycin for 1 h before addition of 10 μg/ml brefeldin A, which was left for a further 3 h. Cells were then washed and blocked by resuspension in FACS buffer containing Fix/Perm buffer for 15 min. After washing, cells were incubated with 1/200 anti-CD8–FITC and anti-CD4–PerCP for 20 min, washed again, and then fixed for 20 min with 200 μl Fix/Perm buffer (BD Pharmingen). Fixation buffer was removed with two washes with permeabilization buffer (BD Pharmingen), and samples were split and subsequently stained for intracellular cytokines using 1/200 anti-gamma interferon (IFN-γ)–APC, anti-IL-4–PE, anti-IL-10–APC, anti-IL-13–APC, or the relevant isotype control for 20 min in Perm buffer. After another wash in Perm buffer, samples were resuspended in FACS buffer and analyzed by flow cytometry using a Becton Dickinson Canto or LSR-II flow cytometer.

For antigen-specific restimulation, 106 mesenteric or popliteal lymph node cells per well were plated in the presence of medium, 5 μg/ml NES, or 1 μg/ml HES for 72 h at 37°C with 5% CO2 before centrifuging at 400 × g for 5 min and freezing the supernatants at −20°C, which were then analyzed for IFN-γ, IL-4, IL-5, IL-10, IL-13, and IL-17 by commercially available enzyme-linked immunosorbent assay (ELISA) (BD Pharmingen).

RT-PCR. Lung and intestinal tissues were prepared for reverse transcription PCR (RT-PCR) by immersion in TRizol (Invitrogen), and RNA extraction was performed following the manufacturer’s protocol, transcribing 1 μg RNA using Moloney murine leukemia virus (MMLV) RT (Stratagene). Ym-1, RELM-α, RELM-β, arginase-1, and IL-13 mRNA levels were measured by real-time PCR using a Roche Light Cycler real-time PCR machine (47). The hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene was used as the reference gene. Light Cycler PCR amplifications were carried out in 10-μl mixtures containing 4 μl cDNA, 0.3 μM primers, and 2× Light Cycler-DNA SYBR green I mix (Roche). PCR was performed using the following conditions: 5 min of denaturation at 95°C, 10 s of annealing of primers at 60°C, and 20 s of elongation at 72°C, for 50 cycles. The fluorescent DNA binding dye SYBR green
(Roche) was monitored after each cycle. Expression levels were estimated using the absolute quantitation method by comparison to a standard curve generated from a pool of all samples appropriately diluted. Relative expression of the gene of interest was then calculated as the ratio to expression of a housekeeping gene that remained unaltered after treatment.

Statistical analysis. Data were assessed for equal variance and log transformed if they did not fit this criterion. Statistical analyses used paired t tests or nonparametric Mann-Whitney U tests if the data were not normally distributed.

RESULTS

We have previously reported that depletion of CD11c-expressing cells in helminth-infected mice severely disrupts an adaptive Th2 response, as measured by IL-4 and IL-13 production by CD4$^+$ T cells, to infection with S. mansoni (45) or H. polygyrus (56). Because recent studies have identified a strong type 2 innate cell response (including for subsets such as AAMs, eosinophils, and innate lymphoid cells) in infections with N. brasiliensis, we first tested whether innate and adaptive type 2 responses were intact in DC-depleted mice infected with this parasite. Depletion, measured the day following final DTx administration, was >85% of total CD11c$^+$ cells (Fig. 1A and B).

As expected from our previous data using S. mansoni and H. polygyrus infections, CD11c$^{bgh}$ cell depletion significantly ablated the Th2 response to N. brasiliensis, as measured by polyclonal CD4$^+$ IL-4$^+$ and IL-13$^+$ cell percentages (Fig. 1C) as well as the antigen-specific IL-4 and IL-10 cytokine response from MLNC cultured in vitro with N. brasiliensis excretory-secretory antigen (NES) (Fig. 1D and E). IL-5 secretion by MLNC from infected mice in vitro could be observed at two levels: a constitutive response, which did not require the presence of NES antigen, and an antigen-dependent element. The latter was more severely diminished in mice following DC depletion (Fig. 1F). Interestingly, there was a trend, but not a significant one, for reduced production of antigen-specific IL-13 following depletion of CD11c$^+$ cells in N. brasiliensis-infected mice (Fig. 1G), while a sharp increase in the Th1 (IFN-$\gamma$) profile was observed following DC depletion (Fig. 1H), perhaps reflecting the loss of antigen-specific IL-10 production in the CD11c$^{bgh}$ DC-depleted mice. While no significant change in Foxp3$^+$ Treg numbers is observed in N. brasiliensis infection (data not shown), we also found that the IL-17 recall response of MLNC to NES was significantly depressed in CD11c$^{bgh}$ DC-depleted mice (Fig. 1I).

The ability of helminths to stimulate Th2 responses can be reproduced by certain helminth-derived products given in soluble form to naïve mice (11, 21, 59). Th2 responses can also be induced by adoptive transfer into naïve hosts of CD11c$^+$ bone marrow-derived DCs exposed to helminth molecules (5, 29), including NES (21). In view of recent reports that Th2 responses can be induced by basophils, even in the absence of DCs, we reevaluated the ability of NES-pulsed cells to drive Th2 differentiation in vivo. DCs and basophils were generated from murine bone marrow with GM-CSF or IL-3, respectively; basophils were flow sorted for CD49b$^+$ c-kit$^+$ Gr-1$^-$, and then both cell types were cultured overnight with medium or NES and adoptively transferred into

FIG 1 CD11c$^+$ cell depletion ablates adaptive Th2 responsiveness. CD11c.DOG mice were given 8 ng/g DTx (or PBS as a control) daily from day 1 to 6 of mouse-adapted N. brasiliensis (Nb) infection, and MLNC were harvested at day 7 postinfection. (A and B) DC depletion in the mesenteric lymph node (MLN) as staining for CD11c and MHC class II, shown as a representative bivariant plot scaled to 210,000 events (A) and a graphical summary of all data (B). (C) Intracellular IL-4 expression by MLN CD4$^+$ T cells in PBS- and DTx-treated uninfected and infected (Nb) mice. (D to I) Cytokine release by cultured MLNC stimulated with NES (black bars) or medium (open bars), in PBS- and DTx-treated uninfected and infected (Nb) mice, assayed for IL-4 (D), IL-10 (E), IL-5 (F), IL-13 (G), IFN-$\gamma$ (H), and IL-17 (I). Data presented are means ± standard errors (SE) for LNC from 3 to 5 individual mice per group and are representative of two similar experiments. Statistically significant differences are shown as * (P < 0.05), ** (P < 0.01), or *** (P < 0.001).
the hind feet of naïve mice. Five days following transfer, popliteal lymph node (PLN) cells were recovered and stimulated with NES antigen or anti-CD3 in vitro. While DC transfer induced strong antigen-specific and polyclonal Th2 responses in terms of IL-4 production, only low levels were observed following basophil transfer (Fig. 2A and B). Moreover, DCs induced strong antigen-specific release of IL-10 (Fig. 2C), which we have shown to be instrumental in establishing dominant Th2 responses in N. brasiliensis infection (6). NES-pulsed DCs also elicited low levels of antigen-specific IL-17 production (Fig. 2D), reflecting the underlying Th17 response evident during infection with this parasite. Hence, insofar as in vitro-differentiated DCs and basophils replicate the functions of their in vivo counterparts, transfer of antigen to the draining lymph node and induction of Th2 responses are accomplished primarily by DCs.

Following initiation, multiple cell types are involved in expanding and sustaining the type 2 response (2, 42). In particular, basophils can become sensitized by NES and release large quantities of IL-4 and IL-13 (40). Given the amounts of IL-4 released by polyclonal stimulation of recipient lymph node cells following transfer of NES-pulsed DCs (Fig. 2B), it is possible that host basophil activity could contribute to a similar function in response to primary helminth infection. We therefore assessed whether basophils promoted type 2 immunity later in the course of live infection in the contrasting model systems of N. brasiliensis (in which worm expulsion occurs within 6 to 10 days) and H. polygyrus (which establishes a long-lived chronic infection in susceptible mouse strains).

Following N. brasiliensis infection, basophilia is known to develop rapidly from day 3 following infection (33, 38, 54, 60, 65). Rather than use genetic models of basophil deficiency (39, 60), which may affect the baseline levels of innate populations, we chose to treat mice with the monoclonal antibody MAR-1, as described by other authors (10, 15, 24, 45, 57, 63), which eliminated >90% of circulating.
Basophil depletion does not diminish adaptive or innate type 2-associated parameters following *H. polygyrus* infection. (A and B) HES-specific IL-4 and IL-10 production in response to medium (open bars) or HES (black bars) by MLNC from naïve, isotype-treated, and MAR-1-treated *H. polygyrus*-infected (Hp) mice. (C and D) RT-PCR for arginase-1 and RELM-β expression in intestinal tissue from naïve, isotype-treated, and MAR-1-treated *H. polygyrus*-infected (Hp) mice. (E) Eosinophil populations in the mesenteric lymph nodes of isotype- and MAR-1-treated *H. polygyrus*-infected (Hp) mice. Mesenteric LNC and lungs were harvested at 7 days following infection. Data presented are means from 4 or 5 individual mice and are representative of two similar experiments. Statistically significant differences are shown as ** (P < 0.01) or *** (P < 0.001).
cell-depleted mice (Fig. 5D and E). Surface phenotyping revealed that the CD3$^-$ CD19$^-$ IL-13$^+$ cells were CD8$^+$, TCRβ$^+$, c-kit$^{int}$, CD90$^+$, T1/ST2$^+$, Sca-1$^+$ and CD4$^+$, similar to the case for innate helper cells or nuocytes (Fig. 5G).

**DISCUSSION**

Type 2 immunity integrates multiple components of both innate and adaptive natures, embracing both antigen-specific Th2 lymphocytes and a range of innate inducer and effector cell types (2, 42, 53, 68). Although a prominent question in recent years has been the nature of the innate cell type that drives Th2 differentiation (28, 42), a broader issue is how innate type 2 populations are generated irrespective of CD11c$^+$ cell depletion. Likewise, although AAMs are activated through the IL-4R, they are unaffected by removal of IL-4-producing basophils from infected mice. Previously, it had been reported that alveolar macrophages express AAM markers within 48 h of *N. brasiliensis* infection (50) and that AAMs maintain their phenotype in a CD4$^+$ T cell-replete environment (27, 50). Interestingly, we show that the generation of lung AAMs occurs even when resident alveolar macrophages are efficiently deleted and that their numbers are undiminished even after 7 days in a DC- and Th2-depleted environment.

It is well established that AAMs can arise in lymphopenic environments such as RAG$^{-/-}$ and SCID mice, which have no adaptive immunity, and that they are prominent in the innate response to injury (27, 50). In general, adaptive Th2-derived IL-4/IL-13 is necessary to maintain the AAM population (27, 50), although eosinophil-derived IL-4 is sufficient for AAM induction in adi- pose tissue (69). Our studies indicate that innate IL-4, and particularly IL-13, is sufficiently robust in the absence of DCs to stimulate AAM development during helminth infection. One source of DC-independent IL-13 in infection may be the innate helper cell or nuocyte, which, interestingly, displays a CD4$^+$ phenotype in *N. brasiliensis* infection, implying that not all CD4$^+$ sources of type 2 cytokines are conventional T cells.

Our data indicate that tissue and lymph node eosinophilia is
also independent of basophils, supporting previous studies (39, 40, 60). As CD4+ IL-5 responses were reduced by DC depletion, production of this cytokine by non-T cells may be sufficient to drive eosinophil development, as observed in earlier studies of T cell-deficient nude rodents infected with nematodes such as *Ascaris suum* (48) and *Toxocara canis* (62). Eosinophils are not required for Th2 generation (as shown in both *N. brasiliensis* [67] and *S. mansoni* [61]), although, as with basophils, their production of IL-4 can make a significant contribution to the pace and intensity of the Th2 response.

Despite the accumulating data showing that basophils are not necessary to raise the first alarm, and indeed are not well-equipped to do so due to their short life span (40) and absence of antigen presentation machinery (38), there are many examples in acute settings. Our results conclusively show that the adaptive Th2 response in MAR-1-treated mice is counterbalanced by a strong regulatory response and additional changes to DC function. Moreover, the DC subset which dominates in draining lymph nodes recovered from chronically infected mice can induce Foxp3+ Tregs (56) and inhibit antibacterial immunity (9), while *H. polygyrus* ES (HES) treatment of DCs renders them less immunogenic when transferred into naïve hosts (55). Thus, while diverse helminth species show similar initiation of type 2 immunity, there are sharp contrasts in the subsequent course of infection as well as the functional phenotype of DC populations.

We have analyzed in this report the relative importance of two major innate immune populations in the initiation of type 2 immunity against helminth infection within both innate and adaptive settings. Our results conclusively show that the adaptive Th2 response in these systems is dependent upon CD11c+ high DCs and that basophils are not required for this outcome. Our data also clearly highlight DC-independent pathways to mobilize innate type 2 immunity which operate autonomously during helminth infection. Such redundancy within the innate type 2 compartment may serve to safeguard the host from the range of helminth pathogens now known to interfere with normal DC function (12, 17, 56) and provide an alternative means to mobilize essential effector functions for protective immunity.
ACKNOWLEDGMENTS

The studies presented here were funded by the Wellcome Trust through a Programme Grant.

We thank Martin Waterfall for FACS sorting and Alex Phythian-Adams for management of CD11c.DOG mice.

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