Nfil3 is required for the development of all innate lymphoid cell subsets

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Innate lymphoid cell (ILC) populations protect against infection and are essential for lymphoid tissue formation and tissue remodeling after damage. Nfil3 is implicated in the function of adaptive immune lineages and NK cell development, but it is not yet known if Nfil3 regulates other innate lymphoid lineages. Here, we identify that Nfil3 is essential for the development of Peyer’s patches and ILC2 and ILC3 subsets. Loss of Nfil3 selectively reduced Peyer’s patch formation and was accompanied by impaired recruitment and distribution of lymphocytes within the patches. ILC subsets exhibited high Nfil3 expression and genetic deletion of Nfil3 severely compromised the development of all subsets. Subsequently, Nfil3−/− mice were highly susceptible to disease when challenged with inflammatory or infectious agents. Thus, we demonstrate that Nfil3 is a key regulator of the development of ILC subsets essential for immune protection in the lung and gut.

Protection of mucosal surfaces depends on the delicate balance between rapid induction of innate immune responses and priming of adaptive immune responses. This early immune response has largely been thought to be orchestrated by NK cells, but recent studies have uncovered that the innate lymphocyte family is more complex and diverse than previously appreciated. It comprises not only the prototypic innate lymphoid cell type 1 (ILC1), NK cells, and lymphoid tissue-inducer (LTi) cells but also nuocytes or natural helper cells and Rorγt+ ILCs. Recently, these lineages were classified into three ILC subsets: ILC1 (NK cell and IFN-γ–producing ILCs), ILC2 (nuocytes and natural helper cells), and ILC3 (Rorγt+LTi cells and natural cytotoxicity receptor [NCR] Nkp46+ ILC3; Spits et al., 2013). ILCs exhibit many similarities to CD4+ T cell subsets in the array of cytokines they produce and their dependence on the same transcription factors for lineage commitment. A core set of transcription factors corresponding to those used in both CD4+ T cell and NK cell differentiation also significantly influence ILC subset differentiation. It is therefore likely that each cell type adopts a lineage-specific transcriptional program dictating the fate of ILC progenitors into the different subsets. As yet, however, the transcriptional networks that govern the development and effector function of the different ILC subsets are not well understood.

The transcription factor nuclear factor, IL-3 (Nfil3, also known as E4BP4) was originally described as necessary for the development of bone marrow–derived NK cells (Gascoyne et al., 2009) but is now known to also be involved in the development and the functions of other immune cells. Nfil3/E4BP4 is a key transcription factor for CD8α+ dendritic cell development (Kashiwada et al., 2011) in B cells, IgE class switching (Kashiwada et al., 2010), and regulation of CD4+ T cell lineages (Motonoura et al., 2011). Nfil3 has been proposed to regulate NK cell development by activating the transcription factor inhibitor of DNA binding 2 (Id2; Gascoyne et al., 2009); however, this is controversial as it is not required for hepatic NK cells, and Nfil3-deficient NK cells express normal levels of Id2 (Seillet et al., 2014). Id2 is essential for the development of all ILC subsets, including NK cells. Whether Nfil3 is involved in ILC subset differentiation is...
not yet known. In this report, we demonstrate that the absence of Nfil3 resulted in intrinsic defects in the development of all ILC subsets and altered Peyer's patch formation, culminating in diminished protective immune responses during lung and intestinal inflammation. These results suggest that Nfil3, like Id2, plays a broad and essential role in regulating the gene network required for ILC development.

RESULTS AND DISCUSSION
Nfil3 has been shown to regulate multiple aspects of the development and function of adaptive immune cells and is likely to also impact the development of the innate arm of the immune system given its broad expression (Ikushima et al., 1997; Kashiwada et al., 2010; Kobayashi et al., 2011; Motomura et al., 2011; Seillet et al., 2013).

We first analyzed secondary lymphatic organs in Nfil3-deficient mice and detected clear defects in the formation of Peyer's patches. These mice exhibited a significant reduction in the number, size, and cellularity of Peyer's patches (∼3-fold reduction), although the frequency of T and B cell subsets and activation status was not altered (Fig. 1, A–J). Histological analyses also revealed that Nfil3-deficient mice failed to form...
Figure 2. Nfil3 is essential for the development of innate lymphocytes. (A) Quantitative PCR analysis of Nfil3, Id2 (Id2), Gata3, and Rorγt in the indicated populations purified from the indicated tissues of Rorγt GFP/− mice. The fold change relative to conventional NK cells is shown for each ILC subset. Data show the mean ± SEM of samples analyzed in triplicate, pooled from two independent experiments. (B) Flow cytometric analysis of total hematopoietic cells (top) and Lin− (CD3− CD19−) CD45+ cells (bottom) isolated from the small intestine of WT or Nfil3-deficient mice and stained for intracellular expression of Rorγt. (C) Frequency of CD4+ (top) and KLRG1+ (bottom) cells within the NKp46− Rorγt+ ILC3 and NKp46− Rorγt− cells, respectively.
multiple, clearly defined B cell follicles and associated lymphoepithelium that form domes over follicles in the Peyer’s patch. Instead, typically one or two B cell follicles were observed in each Peyer’s patch and T cell and B cell zones were less clearly defined in these dysregulated Peyer’s patches in the absence of \textit{Nfil3} (Fig. 1, B–E). In contrast, these alterations were not evident in \textit{Nfil3}^{-/-} peripheral LNs that appeared similar to WT LNs (Fig. 1 G). These data suggest that Nfil3 is a key regulator of Peyer’s patch formation and plays an important role in the organization of cells within the patches.

Due to the requirement of LTI cells, especially CD4^+ LTi cells, for the proper generation of Peyer’s patches (Finke et al., 2002) and the high level of Nfil3 expression observed in all ILC populations (Fig. 2 A), including the ILC3-committed progenitor (Possot et al., 2011), we investigated whether Nfil3 was required for the development of the ILC subsets by measuring the prevalence of each subset in \textit{Nfil3}^{-/-} mice. We observed an overall reduction in the number of Rorγ^+ ILCs in the small intestine (Fig. 2, B–D), colon (Fig. 2, E and F), and cryptopatches (Fig. 2 G) and in the absence of Nfil3 when compared with WT (C57BL/6, WT) mice although the number and frequency of Rorγ^+ CD4^+ T cells was increased in the intestine of \textit{Nfi3}-deficient mice. The size and number of lymphoid cells in the intestinal cryptopatches appeared unchanged between WT and \textit{Nfil3}^{-/-} mice, suggesting that \textit{Nfi3}-deficient ILC have a similar capacity to form cryptopatches.

Interestingly, within the ILC3 populations, the CD4^+ subset was the most severely affected, exhibiting a >5–10-fold reduction compared with ~2- and 3-fold difference in CD4^- and NCR^+ ILC subsets, respectively. This population is pivotal to Peyer's patch development and its loss may significantly contribute to the altered development of the patches. In addition to the previously known defect in ILC1 development (Fuchs et al., 2013), the ILC2 population was the most dramatically affected by \textit{Nfil3} deficiency. We also observed a dramatic reduction in ILC2 (~5-fold loss) in the small intestinal lamina propria (Fig. 2, C and D), as well as in the lung (Fig. 2 H) and visceral adipose tissue (Fig. 2 I). In summary, our data indicate that Nfil3 is required for the development of all ILC populations.

The fact that all ILC subsets are affected by the loss of \textit{Nfil3} expression suggested that the development of a common precursor might be impaired in \textit{Nfil3}-deficient mice. To date, the proposed common innate lymphoid progenitor (CILP) has not been identified, thus precluding the definitive analysis of the role of Nfil3 in the development of this elusive ILC precursor. However, the precursor of the ILC2 (ILC2P) has recently been defined as a Lin^- CD25^- CD127^- Sca-1^+ Gata-3^+ Id2^+ subset in the bone marrow (Hoyler et al., 2012). Analysis of lineage negative bone marrow of Id2^+/+\textit{Nfil3}^{+/+} and Id2^+/+\textit{Nfil3}^{-/-} mice showed that ILC2Ps were severely reduced in the absence of \textit{Nfil3} (Fig. 2 J). We speculated that this early loss of the ILC2P would likely impair the capacity to generate the peripheral ILC2 pool, although a very small number of residual ILC2P were detected in \textit{Nfil3}^{-/-} mice, and these cells maintained their expression of Id2-GFP. Thus, loss of \textit{Nfil3} results in impaired development of multiple ILC populations including the early precursor population required for the development of all ILC2.

\textbf{Cell-intrinsic \textit{Nfil3} is required for ILC development}

To determine whether the phenotype we observed in \textit{Nfil3}^{-/-} mice was a direct result of a cell-intrinsic role for Nfil3, we generated mixed bone marrow chimeras in which we transplanted lethally irradiated Ly5.1^+ recipient mice with a 1:1 ratio of WT (Ly5.1^+/Ly5.2^+) and \textit{Nfil3}^{-/-} (Ly5.2^+) bone marrow (Fig. 3 A and B). After 8 wk, WT cells effectively reconstituted the different ILC subsets in gut and lung, but \textit{Nfil3}-deficient cells failed to do so and showed more than a 10-fold reduction in the competitive setting (Fig. 3 A–E). Other hematopoietic lineages such as mature splenic B cells that do not rely on Nfil3 for development, however, reconstituted at the expected ratio of 1:1 (unpublished data) indicating that the developmental defect was specific to ILCs.

We recently showed that Nfil3 is already expressed in the common lymphoid progenitor (CLP) but that their development was not affected in \textit{Nfil3}-deficient mice (Seillet et al., 2014). In addition to total bone marrow chimeras, CLP were purified from bone marrow of Id2^+/+\textit{Nfil3}^{+/+} or Id2^+/+\textit{Nfil3}^{-/-} mice and adoptively transferred into \textit{Rag2}^{-/-} \textit{γc}^{-/-} recipient
mice that lack T and B cells, as well as all ILC populations (Fig. 3, F and G). We observed that Nfil3-deficient Id2+/gfpNfil3−/− CLPs failed to efficiently give rise to ILC subsets after adoptive transfer. Thus, loss of ILC in mucosal tissues in the absence of Nfil3 arose from a failure in differentiation after the CLP stage and is not due to a defect in the hematopoietic stem cell and/or multipotent progenitor compartment.

Nfil3-regulated ILC populations play important roles at mucosal surfaces

ILCs are localized in mucosal tissues and are thought to play important roles in immune protection. Therefore, we sought to determine whether loss of ILC subsets that accompanies Nfil3-deficiency influences the capacity to mount protection in the lung and gut. First, we examined whether the absence of Nfil3 altered the inflammation induced by intranasal challenge with papain. At steady state, the total number and frequency of eosinophils was similar in both Nfil3−/− and WT mice (Nfil3−/− 3.1 ± 0.3 × 10^6, 1.5 ± 0.3%; C57BL/6 3.3 ± 0.6 × 10^6, 1.3 ± 0.1%) and the number of Nfil3−/− eosinophils was similar to WT eosinophils in papain-treated mixed bone marrow chimeras (unpublished data). We first measured eosinophil recruitment which was reduced by ~2-fold in Nfil3−/− mice, indicating a defect in ILC2 activity (Fig. 4 A). In treated mice, ILC2 in the lungs of both WT and Nfil3-deficient mice were analyzed and, as anticipated, ILC2 were barely detectable in Nfil3-deficient mice (Fig. 4 B). This coincided with ablation of IL-5– and IL-13–producing ILC2 in the absence of Nfil3, explaining the reduced eosinophil recruitment (Fig. 4 B, right). Next, we investigated the mucosal response to C. rodentium infection in the gut of WT and Nfil3−/− mice (Fig. 4, C–G). In the absence of Nfil3, the total number of IL-22–producing ILC3 was significantly reduced (Fig. 4, D and E), indicating that although most ILC3 were lost in the absence of Nfil3, the remaining Rorγt+ ILC3 retained a capacity to produce IL-22 but this was not sufficient to prevent enhanced bacterial translocation (Fig. 4 F), shortening of the colon (Fig. 4 G), and weight loss (Fig. 4 H) in the Nfil3-deficient mice. These effects were accompanied by erosion of the intestines in Nfil3−/− mice but not in WT mice (Fig. 4 I). Collectively, these findings indicate that loss of Nfil3 results in the failure to mount a protective mucosal immune response due to significant reduction in ILC development.

Figure 3. Nfil3 regulation of ILC development is cell intrinsic.

Lethally irradiated WT (Ly5.1+) recipient mice were reconstituted with an equal mix of WT (Ly5.1+Ly5.2) and Nfil3−/− (Ly5.2+) bone marrow cells. After 8 wk, the proportion of ILC1, ILC2, and ILC3 were determined in the small intestinal lamina propria (A–C) and the lung (D and E). IA and C) Dot plots show representative profiles of ILC3 (A) and ILC2 (C, left) in Nfil3−/− and WT mice (Ly5.1+Ly5.2) and Nfil3−/− (Ly5.2+) bone marrow compartments gated on Lin− (CD3−CD19−) CD45+ hematopoietic cells. (B) Frequency of ILC subsets within the WT (Ly5.1+Ly5.2) and Nfil3−/− (Ly5.2+) populations in mixed chimeric mice. Data show the mean ± SEM (n = 3 mice/genotype) of one representative of two experiments. Statistical differences were tested using an unpaired Student’s t test. (C) Expression of ST-2 within the KLRG1+Gata-3+ ILC2 subset (right). (D) Expression of NK1.1 and Gata-3 in Lin− (CD3−CD19−Gr1−) CD45+ cells isolated from the lungs and KLRG1 and ST2 expression on ILC2 (bottom). (E) Frequency of the different ILC1 and ILC2 in lung in each WT (Nfil3+/+) and Nfil3−/− compartment in mixed chimeras. (A–E) Analyses show representative profiles of two experiments with
Interestingly, a very small but distinct population of ILCs remained in Nfil3−/− mice, suggesting that if ILCs can pass early checkpoints during development, they do not require Nfil3 for maintenance in the periphery, as has recently been showed in mature NK cells (Firth et al., 2013). Thus, we speculated that IL-2–IL-2mAb complex treatment, which can expand NK cells and ILC2 (Boymann et al., 2006; Nussbaum et al., 2013), would allow us to test their requirement for Nfil3 in mature ILC2. The frequency and the total number of ILC2 in the lung and mesenteric LNs (mLN) were analyzed (Fig. 5, A–D). Strikingly, ILC2 and ILC2P expanded ∼10-fold compared with untreated controls in both WT and Nfil3-deficient mice. IL-2/IL-2mAb treatment was not sufficient to return ILC2 cell numbers to the levels observed in WT mice, but a comparable fold expansion was observed in both Nfil3−/− and WT ILC2, indicating that these mature ILC2 had a similar ability to expand. Thus, residual Nfil3−/− ILC2 responded effectively to normal cytokine cues suggesting that they do not further require Nfil3 after activation or expansion in the periphery.

Several transcription factors have emerged as critical for the development of the ILC family, pointing to the complex regulation required for the generation of individual specialized subsets. Our findings identify Nfil3 as an essential factor for the development of innate immunity by impacting on all ILC subsets. Unlike loss of Id2 and Rorγt, in which secondary lymphoid tissues such as LNs and Peyer’s patch do not form, rudimentary Peyer’s patch were found in the absence of Nfil3, albeit smaller and less prevalent, than in WT mice. Interestingly, LNs appeared relatively unaffected by the loss of Nfil3, suggesting that Nfil3 acts specifically in Peyer’s patch organogenesis.
Mixed bone marrow chimeras. Mixed bone marrow chimeras were established by reconstituting lethally irradiated (2 × 0.55 Gy) Ly5.1+ 2-week recipient mice with a 1:1 mixture of Nfil3−/− (2.5 × 10^6) and WT (Ly5.1/Ly5.2, 2.5 × 10^6) bone marrow cells and allowed to reconstitute for 8 wk.

For experiments in which the CLP were adoptively transferred into recipient mice, Lin−/IL-7Rα−/Flk3−/Flk2−/Scal−/−CD117+ bone marrow cell were purified by flow cytometric sorting from IL2Rα−/Nfil3−/− or IL2Rα−/Nfil3−/− mice after lineage depletion, as previously described (Carotta et al., 2011). 3 × 10^6 CLPs were injected in Rag2−/− mice and ILC populations were analyzed 2 wk after transfer.

Tissue preparation. Mononuclear cells from intestinal lamina propria were isolated as previously described (Mielenz et al., 2013; Rankin et al., 2013). Lungs were cut into small fragments and digested for 30 min at 37°C with Collagenase III (1 mg/ml; Worthington) and DNase I (200 µg/ml; Roche). Cells were filtered by using a cell strainer after red blood cell lysis. Peritoneal adipose tissue was used as representative visceral adipose tissue. Adipose tissue was finely dissected with a scalpel blade and digested with 3 ml of PBS containing 0.2 mg/ml Collagenase IV and 4% BSA at 37°C for 45 min with gentle agitation. Digests were filtered through 70-µm cell strainers and centrifuged at 800 g for 15 min to enrich for immune cells in stromal vascular fractions. Single-cell suspensions were blocked with PBS containing 5 µg/ml anti-CD16/CD32 (2.4G2) and stained for 30 min on ice with fluorophore-conjugated antibodies. The following antibodies were used for the identification and purification of ILC2 cells: CD19 (ID3), B220 (RA3-6B2), CD3 (145-2C110), CD4 (GK1.4), CD11b (M1/70), Gr-1 (RB6-8C5), TCRβ (H57-597), NKp46 (29A1.4), NK1.1 (PK136), CD45.1 (A20), CD45.2 (104), CD117 (2B8), CD127 (A7R34), Sca1 (E13-161.7), KLRG1 (2F1), Thy1.2 (30H12), and ST2 (DJ8 or RMST2-2). Intracellular staining was performed using the Transcription Factor Staining Buffer Set (eBioscience) and antibodies to Gata-3, Rorγt (AFKJS-9), IL-13 (eBio13A), and IL-5 (TRFK5). Intracellular cytochrome staining for IL-13 and IL-5 was performed after stimulation for 4 h with PMA (50 ng/ml) and ionomycin (100 ng/ml) in the presence of Brefeldin A (1 mg). Cells were analyzed using a FACSCanto II (BD) and FlowJo software (Tree Star) was used for analysis. Flow cytometric profiles were based on full-color analyses performed with a FACSCanto II (BD).

In vivo treatment with IL-2/–anti–IL-2 complexes. For expansion of ILC populations, mice were treated with IL-2/JES6-1 complexes as previously described (Boyman et al., 2006). For each injection, IL-2 (1 µg; Peprotech) was complexed with 5 µg JES-1 mAb (WEHI) at a molar ratio of 2:1 (Tech) was complexed with 5 µg JES-1 mAb (WEHI) at a molar ratio of 2:1. Mice were inoculated with 2 × 10^6 colony forming units of C. rodentium by oral gavage. Mice were analyzed 8 d after infection and bacterial dissemination was determined by culture of livers and spleens from infected mice on agar plates containing nalidixic acid as previously described (Rankin et al., 2013).

Papain-induced lung inflammation. Mice were treated intranasally with PBS or 20 µl of papain (5 mg/ml diluted in PBS) on three consecutive days. 24 h after the final treatment, lung cells were isolated and stained for analysis by flow cytometry with antibodies to CD45, CD11c, and Siglec F to identify infiltrating eosinophils.

In vivo treatment with IL-2/–anti–IL-2 complexes. For expansion of ILC populations, mice were treated with IL-2/JES6-1 complexes as previously described (Boyman et al., 2006). For each injection, IL-2 (1 µg Peprotech) was complexed with 5 µg JES-1 mAb (WEHI) at a molar ratio of 2:1 and incubated for 30 min at 37°C. Aliquots were stored at −70°C and resuspended in PBS immediately before use.

Quantitative RT-PCR. Total RNA was prepared from purified ILC populations using the RNeasy mini kit (Qiagen), and then cDNA was synthesized with oligo(dT) and Thermoscript reverse transcription (Invitrogen). Real-time PCR was done using SensMix SYBR no-Rox kit (BioLine) and the following primer pairs: Nfil3 forward, 5′-GAACCTCGCTGATGCTGGT-3′, Nfil3 reverse 5′-ATTCCCGTTTCTCCGACACG-3′; Id2 forward, 5′-ACCCAGGACCTTGAGACAG-3′; Id2 reverse, 5′-AAGCTGAAAGGAATTCCAG-3′; Gata-3 forward, 5′-CTACCGGTTGCGGAATGTAAG-3′, Gata-3 reverse, 5′-TGCTAGACATCTCCGGTTCTC-3′; Hprt forward,
hpt reverse, 5'-TCCAAACTTT- GAGAGTCC-3'.

Analyses were done in triplicate and normalized mean expression was calculated using the Q-Gene application with hpt as the reference gene (Simon, 2003).

Statistical analysis. GraphPad Prism software was used for statistical analysis. The two-tailed Mann-Whitney U-test or unpaired Student's t test were used for comparisons. All results are expressed as mean ± SEM.

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