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# Brief Report

## IMMUNOBIOLOGY

### Interleukin-5–producing group 2 innate lymphoid cells control eosinophilia induced by interleukin-2 therapy

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#### Key Points

- Tissue resident group 2 innate lymphoid cells are the main cells producing IL-5 and driving eosinophilia in response to low-dose IL-2 therapy.
- We described a novel cellular network activated during IL-2 treatment that may lead to a more efficient use of IL-2 in immunotherapy.

Interleukin (IL)-2 promotes regulatory T-cell development and function, and treatment with IL-2 is being tested as therapy for some autoimmune diseases. However, patients receiving IL-2 treatment also experience eosinophilia due to an unknown mechanism. Here, we show that patients receiving low-dose IL-2 have elevated levels of serum IL-5, and this correlates with their degree of eosinophilia. In mice, low-dose IL-2–anti-IL-2 antibody complexes drove group 2 innate lymphoid cells (ILC2) to produce IL-5 and proliferate. Using genetic approaches in mice, we demonstrate that activation of ILC2 was responsible for the eosinophilia observed with IL-2 therapy. These observations reveal a novel cellular network that is activated during IL-2 treatment. A better understanding of the cross talk between these cell populations may lead to more effective targeting of IL-2 to treat autoimmune disease. (*Blood*. 2014;124(24):3572-3576)

#### Introduction

Treatment with interleukin (IL)-2 has been used for more than 2 decades to enhance antitumor immunity in patients with advanced kidney cancer and melanoma.<sup>1,2</sup> Unfortunately, this high-dose IL-2 treatment is associated with side effects (ie, capillary leak syndrome and hepatic and renal dysfunction) limiting its clinical utility.<sup>3</sup> IL-5 induced eosinophilia is one of the most common and unwanted effects observed in cancer patients treated with IL-2–based therapy.<sup>4</sup> Since the discovery of T-regulatory cells (Treg), studies in mice have shown that low-dose IL-2 therapy actually prevents or ameliorates autoimmune diseases by activating and expanding these cells.<sup>5,6</sup> These observations were applied in a first series of studies in humans to treat chronic graft-versus-host disease–related vasculitis and hepatitis C virus (HCV)-related vasculitis.<sup>1,7-9</sup> These studies showed that low-dose IL-2 treatment could provide clinical benefits for the patient's disease with minimal side effects.<sup>10</sup> However, in a phase I trial in autoimmune type 1 diabetes (T1D), low-dose IL-2 plus sirolimus (an analog of rapamycin) induced a transient reduction of insulin production, suggesting some residual toxicity, possibly due to toxic effects of the drug on pancreatic  $\beta$ -cells and/or to the activation of non-Treg by IL-2 in this setting.<sup>11,12</sup>

#### Study design

##### Mice and cytokine administration

Red5, YetCre13, and ROSA–diphtheria toxin fragment A (DTA) (Gt(Rosa)26<sup>DTA</sup>) mice were described previously<sup>13,14</sup> and injected with IL-2/anti-IL-2<sup>5</sup> or phosphate-buffered saline (PBS). Mice were maintained in the University of California, San Francisco pathogen-free animal facility in accordance with guidelines established by the Institutional Animal Care and Use Committee and Laboratory Animal Resource Center.

##### Tissue preparation and flow cytometry

Tissues were processed as previously described and single-cell suspensions were used for flow cytometry analysis with the indicated antibodies.<sup>13,14</sup>

##### Clinical studies design and participants

Patient characteristics and studies design for the HCV-related vasculitis and T1D trials have been reported previously.<sup>8,15</sup>

#### Results and discussion

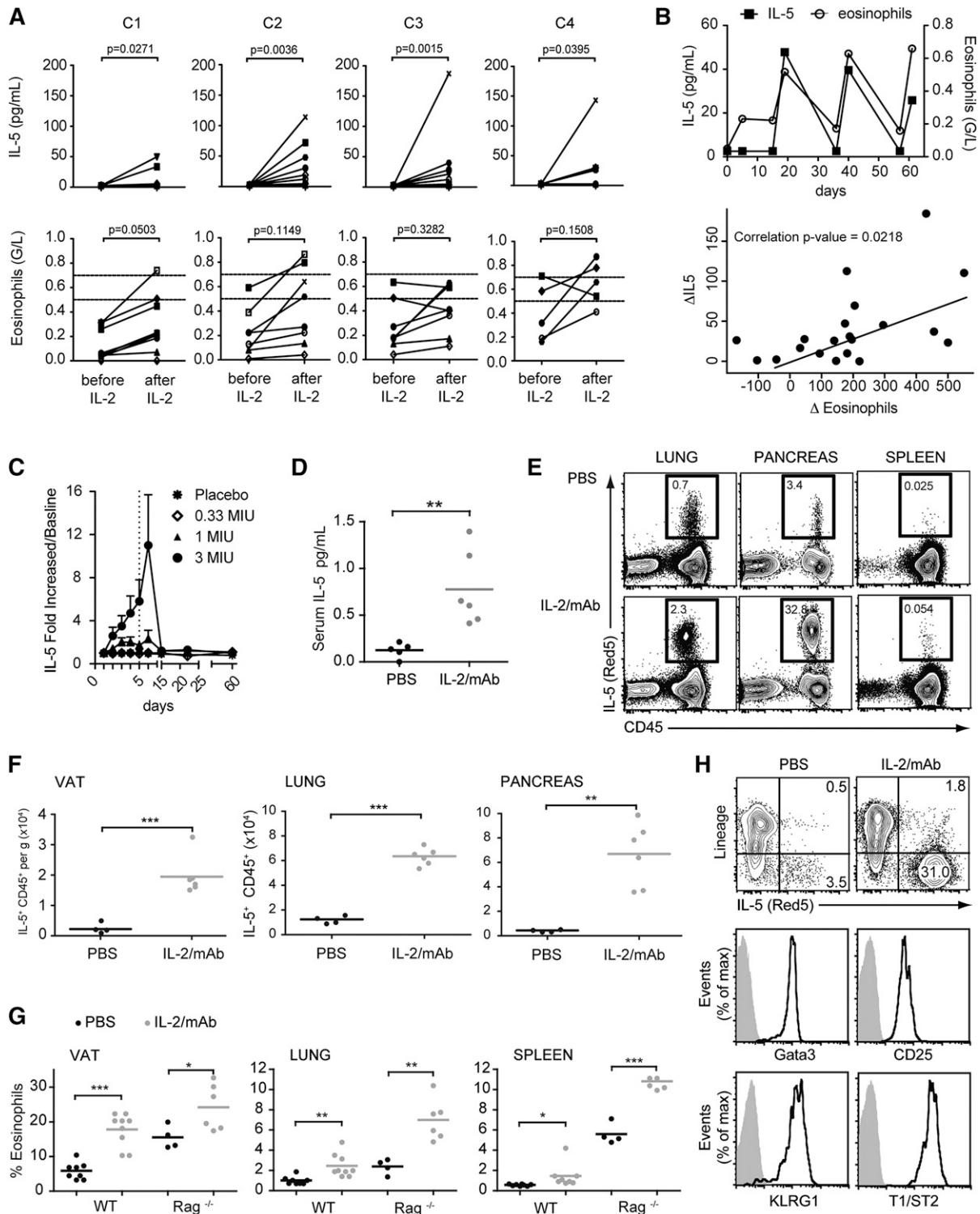
IL-5–induced eosinophilia is one of the most common unwanted side effects observed with high-dose IL-2 immunotherapy.<sup>4,16,17</sup> To

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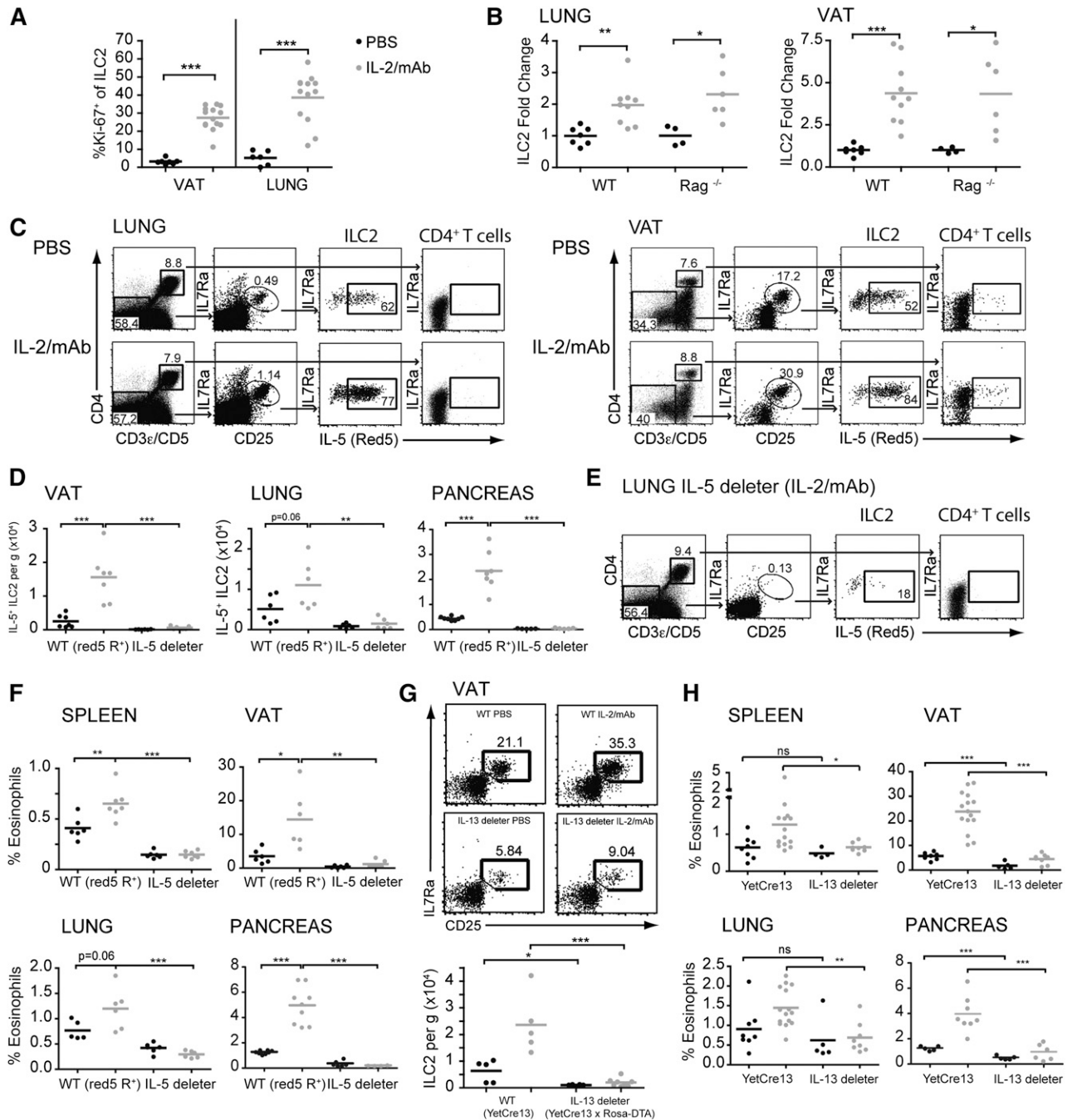
F.V.G. and A.B.M. contributed equally to this study.

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**Figure 1. IL-2 promotes IL-5-producing ILC2s and induces eosinophilia.** (A) HCV-induced vasculitis patients received IL-2 at 1.5 million international units (MIU)/day from days 1 to 5 (course 1 [C1]), then at 3 MIU/day from days 15 to 19 (course 2 [C2]), 36 to 40 (course 3 [C3]), and 57 to 61 (course 4 [C4]). IL-5-fold increase (pg/mL) and eosinophil counts in Giga/L were measured just before and after 5 days of IL-2. Normal eosinophil counts in the local laboratory are 0 to 0.7 G/L for men and 0 to 0.5 G/L for women, and are shown as dashed lines. Statistical significance of the differences between the groups was assessed using the Mann-Whitney *U* test. (B) Correlation between increase in IL-5 and eosinophils for the same patients as in (A). Correlations between eosinophils and IL-5 concentrations were determined by Spearman's correlation coefficient;  $P = .0218$ . (C) IL-5-fold increase over the time of T1D patients received a 5-day course of placebo or of IL-2 at the doses of 0.33 MIU/day, 1 MIU/day, and 3 MIU/day. (D) Serum IL-5 concentration in Red5 heterozygous mice treated with phosphate-buffered saline (PBS) or IL-2/anti-IL-2 mAb complex administered every other day for 3 doses. (E) Fluorescence-activated cell sorter plots of IL-5<sup>+</sup> (Red5 tdTomato reporter) producing cells in the indicated tissues after PBS or IL-2 treatment (VAT: perigonadal VAT). (F) Quantitation of CD45<sup>+</sup> IL-5<sup>+</sup> cells in tissues from IL-5 reporter mice after PBS or IL-2 treatment (VAT: perigonadal VAT). (G) Quantitation of eosinophils (CD45<sup>+</sup> CD11b<sup>+</sup> SiglecF<sup>+</sup>) in WT or Rag-deficient (RAG<sup>-/-</sup>) animals from the indicated tissues after PBS or IL-2/anti-IL-2-treated mice. (H) Fluorescence-activated cell sorter plots of the lineage-defining markers negative subset expressing IL-5 (Red5) in the pancreas after PBS or IL-2 complex (top panel). Characterization of the Red5-producing cells in the pancreas, pre-gated on lineage-negative, CD45<sup>+</sup> cells (bottom panels). Mean values  $\pm$  standard error of the mean. All data were analyzed by comparison of means using unpaired 2-tailed Student *t* tests. Data are representative of 3 or more experiments or were pooled from 2 to 3 experiments. \* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .001$ .



**Figure 2. IL-5/13-producing ILC2 induce eosinophilia in response to IL-2 therapy.** (A) Quantitation by flow cytometry of ILC2 Ki-67 expression with and without IL-2 treatment. (B) Quantitation of total ILC2 from the indicated strains and tissues, expressed as a fold change from phosphate-buffered saline (PBS)-treated control animals. (C) Fluorescence-activated cell sorter gating of CD4<sup>+</sup> T cells and ILC2 (lin<sup>-</sup> CD127<sup>+</sup> CD25<sup>+</sup>) and expression of IL-5 (Red5) in the strains and tissues indicated after PBS or IL-2 treatment. (D) Quantitation of IL-5<sup>+</sup> ILC2 in IL-5 reporter (red5 R<sup>+</sup>) and IL-5-deleter animals in VAT, lung, and pancreas. (E) Fluorescence-activated cell sorter gating as in (C) for the lung of IL-5-deleter mice treated with IL-2/anti-IL-2 mAb complex. (F) Quantitation of eosinophils in Red5 reporter heterozygous (Red5 R<sup>+</sup>) or IL-5-deleter animals. (G) Representative fluorescence-activated cell sorter gating (top panels) and quantitation (bottom panel) of VAT ILC2 in control IL-13 reporter animals (YetCre13) or IL-13-deleter (YetCre13 × ROSA-DTA) animals after IL-2 complexes. (H) Quantitation of eosinophils in IL-13 reporter controls (YetCre13) or IL-13-deleter animals. Black line (PBS), gray line (IL-2/mAb). Mean values ± SEM. All data were analyzed by comparison of means using unpaired 2-tailed Student t tests. Data are representative of 3 or more experiments or pooled from 2 to 3 experiments. ns, not significant. \**P* < .05; \*\**P* < .01; \*\*\**P* < .001.

evaluate if patients treated with low-dose IL-2 also develop eosinophilia, we used data from 2 clinical trials designed to increase Treg cell numbers and induce peripheral tolerance. In the first trial,<sup>8</sup> 10 individuals with HCV-induced vasculitis received 4 courses of low-dose IL-2 injections that induced a significant increase in serum IL-5 with a variable change in eosinophil counts, which moderately increased over normal values in 12 of 89 evaluations (Figure 1A). However, despite variability and a small number of patients, we observed a strong

correlation between increased levels of IL-5 and eosinophils in some patients (Figure 1B). Importantly, there was a significant correlation between eosinophil counts and IL-5 plasma levels in those patients that had detectable IL-5 at baseline (Figure 1B; *P* = .02). In the second trial,<sup>15</sup> T1D patients were treated for 5 days with 3 different doses of IL-2. The cytokine therapy induced a transient and dose-dependent increase in plasma IL-5 levels, with a cumulative effect after each injection of IL-2 (Figure 1C). Overall, these data

showed that low-dose IL-2 therapy leads to increased blood concentrations of IL-5 and moderate eosinophilia in some patients. However the mechanism(s) involved in this side effect of the IL-2 therapy was unclear.

To determine the mechanism by which IL-2 treatment induced IL-5 and subsequent eosinophilia, we used a newly generated IL-5 reporter mouse.<sup>13</sup> As in the human studies, analysis of sera showed an increase in IL-5 production after treatment of mice with low-dose IL-2/monoclonal antibody (mAb) complex (Figure 1D). The IL-5<sup>+</sup> cells were mainly present in nonlymphoid tissues such as the lung, visceral adipose tissue (VAT), and pancreas, but not in the spleen, suggesting that the major cells producing IL-5 were not typical circulating lymphocytes (Figure 1E). After IL-2/mAb treatment, IL-5<sup>+</sup> cell number strongly increased, with an average fourfold to fivefold increase in cell number (Figure 1E-F). Interestingly, in RAG<sup>-/-</sup> mice, the numbers of IL-5<sup>+</sup> cells in the somatic tissues was equivalent or higher to the numbers seen in wild-type (WT) mice (data not shown). Consistent with the IL-5 data, analysis of eosinophils in IL-2-treated mice showed a pattern with a twofold to threefold increase of eosinophils in both WT and RAG<sup>-/-</sup> animals (Figure 1G). These results suggest that T- or B-lymphocytes were not necessary for the expansion and/or survival of eosinophils in response to IL-2.

The recent identification of tissue resident group 2 innate lymphoid cells (ILC2) led us to investigate whether these cells were responsible for producing IL-5 in response to IL-2 treatment.<sup>18</sup> ILC2 lack the expression of lineage-defining markers, express high levels of Gata3, KLRG1, T1/ST2, and CD25,<sup>19,20</sup> and are known to proliferate in response to IL-2.<sup>21,22</sup> After IL-2/mAb therapy, we observed that the majority of cells expressing IL-5 have the characteristics of ILC2 (Figure 1H). At steady state, less than 5% of ILC2 were proliferating based on Ki-67 expression, compared with >30% after IL-2/mAb therapy (Figure 2A). This increased proliferation was associated with a twofold to fivefold increased number of ILC2 (Figure 2B) and an increased fluorescence intensity of the IL-5 reporter gene (Figures 1E and 2C). With these conditions, the CD4<sup>+</sup> cells constituted only a minor subset (<5%) of the IL-5<sup>+</sup> cells (Figure 2C). Interestingly, the eosinophilia induced by the IL-2 therapy was also observed in RAG<sup>-/-</sup> mice (Figure 1G), whereas the only IL-5-producing cells are ILC2. Under these conditions, we observed an accumulation of tissue ILC2 similar to WT animals treated with IL-2 (Figure 2B). These observations suggested that the eosinophilia generated during this therapy was induced by the activation of ILC2 to produce IL-5.

To confirm this hypothesis, we used a genetic approach to ablate ILC2. Mice with Cre recombinase engineered under the control of the IL-5 locus were crossed with mice carrying a ROSA-flox-stop-diphtheria toxin, thus ablating all IL-5-producing cells from the mice (termed IL-5-deleter).<sup>13,14</sup> Deletion of IL-5<sup>+</sup> cells decreased the numbers of ILC2 by > 90% without affecting the total T-cell count (Figure 2D-E and data not shown). More importantly, treatment with IL-2/mAb did not increase the number of eosinophils in the IL-5-deleter mice (Figure 2F). These results suggested that ILC2, which were the major producers of IL-5 in naïve mice, were needed for the eosinophilia induced by IL-2 therapy. However, deletion of IL-5-producing cells also significantly decreased the basal level of the eosinophils; therefore, we decided to use mice with Cre under the control of the IL-13 locus (termed IL-13-deleter). Indeed, fate-mapping techniques have shown that IL-13 is expressed only in a subset of ILC2,<sup>14,23</sup> and that IL-13 expression in ILC2 is induced upon activation.<sup>13</sup> Under steady-state conditions, most ILC2 expressed low levels of IL-13, leading to a reduction in ILC2 deletion as compared with IL-5-deleter mice (Figure 2D-G). Furthermore, the frequency

of eosinophils was not significantly affected in IL-13-deleter mice, except for minor reductions in pancreatic and VAT ILC2<sup>14</sup> (Figure 2H). During IL-2/mAb treatment, ILC2 expansion was abrogated and the percentage of eosinophils was not significantly increased in the IL-13-deleter mice (Figure 2G-H). These observations confirm the hypothesis that activated ILC2 were the main cell population involved in the development of eosinophilia with IL-2 therapy.

The clinical use of low-dose IL-2 therapy is a promising approach to improve peripheral immune tolerance. However, the early results of IL-2 treatment and clinical outcome has been complex.<sup>10</sup> Although clinical improvements have been observed in patients with HCV-induced vasculitis<sup>8</sup> and graft-versus-host disease,<sup>7,9</sup> T1D patients treated with low-dose IL-2 in conjunction with sirolimus showed a transient  $\beta$ -cell dysfunction, despite an increase in Treg.<sup>11</sup> The absence of clinical benefit was associated with an increase in activated non-Tregs (such as natural killer cells and eosinophils) that might have adversely impacted islet function.<sup>10</sup> These observations suggest that a better understanding of the targets of IL-2 therapy would be important in designing and evaluating future clinical studies. By using the reporter and deleter mouse model, we provide the first direct evidence that eosinophilia induced by IL-2/anti-IL-2 mAb treatment is due to the activation of tissue resident ILC2 resulting in the release of IL-5. Interestingly, under the same condition, blood ILC2s did not accumulate (data not shown). Since peripheral blood mononuclear cells were the only clinical samples available from patients treated with low-dose IL-2, we monitored serum IL-5 concentration and eosinophils counts as a surrogate readout to evaluate the activation of ILC2. The IL-2 therapy led to increased IL-5 levels in sera and eosinophils numbers among the peripheral blood mononuclear cells, suggesting that in addition to targeting Treg, low-dose IL-2 therapy also induces the activation of ILC2 that release IL-5 and drive eosinophilia. However, to directly assess the role of ILC2 in the immunologic outcome and clinical efficacy of IL-2 immunotherapy in humans, more experiments must be conducted where access to tissues is feasible. In conclusion, these observations reveal a novel cellular network activated during IL-2 treatment and provide new information that may lead to a more efficient use of IL-2 in immunotherapy and contribute to a better understanding of the side effect induced by this cytokine in the clinic.

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## Authorship

Contribution: A.B.M. and F.V.G. designed experiments; A.B.M., F.V.G., M.M.M., and M.R. performed research; A.B.M., F.V.G.,

M.M.M., M.R., D.K., R.M.L., and J.A.B. analyzed data; H.E.L. provided reagent; and A.B.M., F.V.G., D.K., R.M.L., and J.A.B. wrote the manuscript.

Conflict-of-interest disclosure: M.R. and D.K. are inventors of a patent application claiming the use of low-dose IL-2 for treating autoimmune disease, which is owned by their academic institutions and is licensed to ILTOO Pharma in which they hold

shares. The remaining authors declare no competing financial interests.

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