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CUTTING EDGE

Cutting Edge: Opposite Effects of IL-1 and IL-2 on the Regulation of IL-17$^+$ T Cell Pool IL-1 Subverts IL-2-Mediated Suppression[1]

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In this report, we show that IL-17$^+$CD4$^+$ and IL-17$^+$CD8$^+$ T cells are largely found in lung and digestive mucosa compartments in normal mice. Endogenous and exogenous IL-1 dramatically contribute to IL-17$^+$ T cell differentiation mediated by TGFβ and IL-6. IL-1 is capable of stimulating IL-17$^+$ T cell differentiation in the absence of IL-6. Furthermore, although IL-2 reduces IL-17$^+$ T cell differentiation, IL-1 completely disables this effect. Mechanistically, IL-1 and IL-2 play opposite roles in regulating the expression of several molecules regulating Th17 cell differentiation, including the orphan nuclear receptor RORγt, the IL-1 receptor, and the IL-23 receptor. IL-1 subverts the effects of IL-2 on the expression of these gene transcripts. Altogether, our work demonstrates that IL-6 is important but not indispensable for IL-17$^+$ T cell differentiation and that IL-1plays a predominant role in promoting IL-17$^+$ T cell induction. Thus, the IL-17$^+$ T cell pool may be controlled by the local cytokine profile in the microenvironment. The Journal of Immunology,* 2006, 179: 1423–1426.

Interleukin 17-positive/CD4-positive (Th17) T cells and IL-17 play an active role in the inflammation and autoimmune diseases in murine systems (1–8). TGFβ and IL-6 induce Th17 cell differentiation in mice (9–11). IL-23 (3–5, 12–15) and IL-1 (6, 16, 17) may be important for amplifying and stabilizing the production of IL-17 in chronic inflammation. We recently showed that TGFβ and IL-6 also induced IL-17$^+$CD8$^+$ T cell differentiation (18). Active inflammation is often accompanied by local immune infiltration, activation, and IL-2 production in multiple autoimmune diseases. However, we and others have recently reported that IL-2 strongly suppresses Th17 cell differentiation (18, 19). Why, then have we often observed an accumulation of Th17 cells in multiple disease models? The reason may lie in the fact that the IL-17$^+$ T cell pool may be controlled by the local environmental cytokine profile and the suppressive effects of IL-2 on Th17 cells may be subverted by other cytokines. In this study, we tested this possibility and systemically examined the effects of IL-1, IL-2, IL-6, TGFβ, and their combinations on Th17 and IL-17$^+$CD8$^+$ T cell differentiation and the underlying molecular mechanisms.

Materials and Methods

Mice

All mouse procedures were performed in accordance with institutional protocol guidelines at the University of Michigan (Ann Arbor, MI) under an approved protocol. C57BL/6 wild-type and B6.129S2-*Il6*^{tm1Kopf}/J (IL-6$^{-/-}$) mice (males, 8–10-wk old) were obtained from The Jackson Laboratory. Different organs were collected for the analysis of T cells and their cytokine profile as we described previously (18, 20, 21).

In vitro culture system

T cells were isolated with a commercial kit to high purity (>95%) (Stem Cell Technology) or electronically sorted with a FACSAria cytometer (99% purity) and stimulated with 2.5 μg/ml anti-CD3 and 1.2 μg/ml anti-CD28 (BD Biosciences) in the presence of anti-IL-4 (1 μg/ml), anti-IFN-γ (2 μg/ml; R&D Systems), and IL-23 (5 ng/ml; R&D Systems). Different cytokines, including TGF-β1 (10 ng/ml), IL-6 (10 ng/ml), IL-2 (0.1 μg/ml), IL-1α (1 ng/ml), IL-1β (5 ng/ml), or anti-IL-1 type I receptor (100 ng/ml) (R &D Systems), were added as described. Primary or cultured T cells were subjected to T cell phenotyping. Supernatants were collected for detecting IL-17A by an ELISA kit (R&D Systems).

T cell phenotype and cytokine profile

T cell phenotype and cytokine profile were described in our previous report (18).

Real-time PCR

Total RNA was extracted with the RNeasy mini kit (Qiagen). cDNA was generated using a first-strand cloned avian myeloblastosis virus kit (Invitrogen Life Technologies). Expressions of the genes were quantified with the SYBER Green PCR master mix kit on a Mastercycler ep *realplex* apparatus (Eppendorf). All gene-expression results were expressed as arbitrary units relative to the expression of the gene encoding GAPDH. Sequences for specific primers were available upon request.

Statistical calculations

Differences in cell surface and intracellular molecule expression were determined by a χ^2 test, with $p < 0.05$ considered significant.

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Results

Distribution and differentiation susceptibility of IL-17$^+$ T cells

The prevalence and organ distribution of IL-17$^+$CD4$^+$ T cells (Th17) are not described in the literature. We observed two IL-17$^+$ T cell populations, IL-17$^+$CD4$^+$ and IL-17$^+$CD8$^+$ T cells (<0.8%) in the blood, bone marrow, kidney, liver, lymph nodes, spleen, and thymus in normal mice (Fig. 1*A*). Interestingly, the percentages of IL-17$^+$CD4$^+$ and IL-17$^+$CD8$^+$ T cells were relatively higher in the intestinal and lung tissues than in other compartments (Fig. 1*A*). The data suggest that IL-17$^+$ T cells may play a role in mucosa compartments in immune homeostasis.

Consistent with previous reports, TGFβ and IL-6 promoted spleen CD4$^+$ (9–11) and CD8$^+$ T cells (18) differentiated into IL-17$^+$ T cells. Strikingly, spleen CD4$^+$ and CD8$^+$ T cells differentiated into IL-17$^+$ T cells with significantly more efficiency than lymph node cells from the same mice (Fig. 1, *B* and *C*). Our data demonstrate variable susceptibilities of IL-17$^+$ T cell differentiation in different organs in the same individual animals.

IL-1 promotes IL-17$^+$CD4$^+$ and IL-17$^+$CD8$^+$ T cell differentiation

IL-1 enhances T cell IL-17 production induced by IL-23 (6). We examined the effects of IL-1, IL-6, TGFβ, and their combinations on IL-17$^+$ T cell differentiation. TGFβ or IL-6 alone induced little IL-17 production and few IL-17$^+$ T cells (Fig. 2, *A–C*). Consistent with the reports, TGFβ and IL-6 induced IL-17$^+$CD4$^+$ (9–11) and IL-17$^+$CD8$^+$ T cell (18) differentiation and IL-17A production (Fig. 2, *A–C*). Strikingly, IL-1 dramatically increased IL-17$^+$CD4$^+$ T cells, IL-17$^+$CD8$^+$ T cells, and IL-17A production in the presence of TGFβ and IL-6 (Fig. 2, *A–C*). To determine the role of endogenous IL-1 in IL-17$^+$ T cell differentiation, we blocked the IL-1/IL-1 receptor pathway by using an anti-IL-1 type I receptor Ab in a T cell cultured with TGFβ and IL-6. We observed that blocking IL-1 significantly reduced IL-17$^+$ T cell differentiation, including cells from spleen and lymph nodes (Fig. 2*D*). The data demonstrate a central role of IL-1 in IL-17$^+$ T cell differentiation.

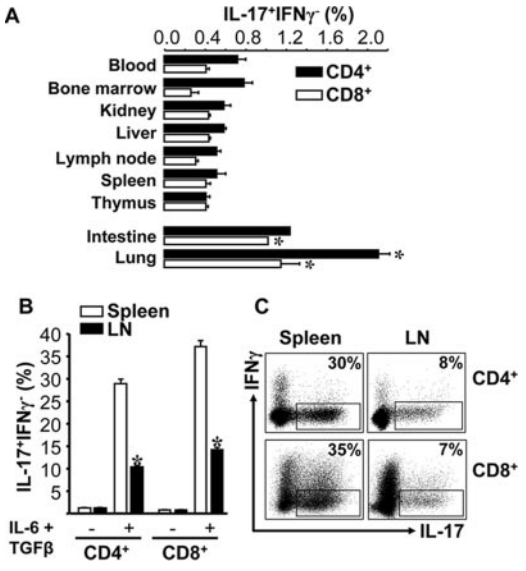

FIGURE 1. Distribution and differentiation susceptibility of IL-17$^+$ T cells. *A*, IL-17$^+$ T cell distribution in normal mice. Single cell suspension was obtained from multiple organs in normal C57BL/6 mice. The single cells were subjected to staining with the indicated Abs and analyzed with an LSR II cytometer. Results were shown as the percentage of IL-17$^+$IFN-γ^- cells in CD4$^+$ and CD8$^+$ T cells (mean $\pm$ SEM; *, $p < 0.01$; $n = 6$). *B* and *C*, Different susceptibility of IL-17$^+$ T cell differentiation. CD4$^+$ and CD8$^+$ T cells were sorted from spleen and lymph nodes (LN) in normal C57BL/6 mice and cultured for 3 days with TGFβ and IL-6. The resulting T cells were analyzed by LSR II for the expression of IL-17 and IFN-γ. Results were shown as the percentage of IL-17$^+$IFN-γ^- cells in CD4$^+$ and CD8$^+$ T cells. *B*, Mean $\pm$ SEM. *C*, One representative data set of flow cytometry dot plots; *, $p < 0.01$; $n = 10$.

IL-1 promotes IL-17$^+$ T cells in the absence of IL-6

IL-1 dramatically increased IL-17$^+$ T cells and IL-17A production in the presence of TGFβ and IL-6 (Fig. 2, *A–C*). We further investigated the role of IL-1 in the absence of exogenous and endogenous IL-6. We showed that IL-1 alone induced potent IL-17A expression and production (Fig. 2, *A* and *B*). Further, IL-1 induced IL-17$^+$ T cell differentiation and IL-17 expression and production with TGFβ in the absence of exogenous IL-6 (Fig. 2, *A–C*). The data suggest that exogenous IL-6 is not essential for inducing IL-17$^+$ T cells.

We next showed that IL-17$^+$CD4$^+$ and IL-17$^+$CD8$^+$ T cells were detectable in the blood, bone marrow, lymph nodes, spleen, and thymus in IL-6$^{-/-}$ mice (Fig. 3*A*), although less so than in wild-type mice (Fig. 1*A*). Further, IL-1 stimulated IL-17$^+$ T cell differentiation from IL-6$^{-/-}$ T cells with or without TGFβ (Fig. 3*B*). Altogether, our data suggest that IL-1 is capable of inducing IL-17$^+$ T cells in the absence of IL-6 and that IL-6 is not indispensable for IL-17$^+$ T cell differentiation.

IL-1 subverts suppressive effects of IL-2 on IL-17$^+$ T cell differentiation

We next examined the kinetic effects of IL-1 and IL-2 on IL-17$^+$ T cell differentiation. We showed that IL-1 kinetically promoted IL-17$^+$ T cell differentiation (Fig. 4*A*), IL-17A production (Fig. 4*B*), and expression (Fig. 4*C*). In contrast, IL-2 kinetically inhibited IL-17$^+$ T cell differentiation, IL-17A production, and expression (Fig. 4, *A–C*). However, the addition of IL-1 largely disabled the suppressive effects of IL-2 on IL-17$^+$ T cell differentiation in the presence (Fig. 4, *A–C*) or absence of IL-23. The similar effects were observed on the expression of IL-17F (Fig. 4*C*). IL-1 and IL-2 had no significant effects on other IL-17 family members (not shown). In addition to subverting the suppressive effects of IL-2, IL-1 also subverted the suppressive effects mediated by IFN-γ or IL-4 (not shown).

We further analyzed the effects of IL-1 and IL-2 on several gene transcripts related to Th17 cell differentiation. We observed that IL-1 stimulated the expression of RORγt (Fig. 4*D*), IL-23 receptor (Fig. 4*E*), and IL-1 receptor (Fig. 4*F*). IL-2 inhibited the expression of these transcripts (Fig. 4, *D–F*). Further, IL-1 was able to recover the expression of these molecules inhibited by IL-2 (Fig. 4, *D–F*). Similar effects were observed on IL-17$^+$CD4$^+$ and IL-17$^+$CD8$^+$ T cells. The data indicate that IL-1 and IL-2 play opposite roles in regulating IL-17$^+$ T cell differentiation and that IL-1 can subvert suppressive effects of IL-2 on IL-17$^+$ T cell differentiation.

Discussion

In this study, we show the existence of IL-17$^+$ T cells in both CD4$^+$ and CD8$^+$ T cells in normal mice. IL-17$^+$ T cells are largely found in the mucosa compartment but not in the lymph nodes. This suggests that IL-17$^+$ T cells may be involved in homeostatic immune responses in the mucosa compartment.

TGFβ and IL-6 promote Th17 differentiation (9–11). Interestingly, lymph node T cells differentiate less efficiently into Th17 cells as compared with spleen T cells. The data suggest

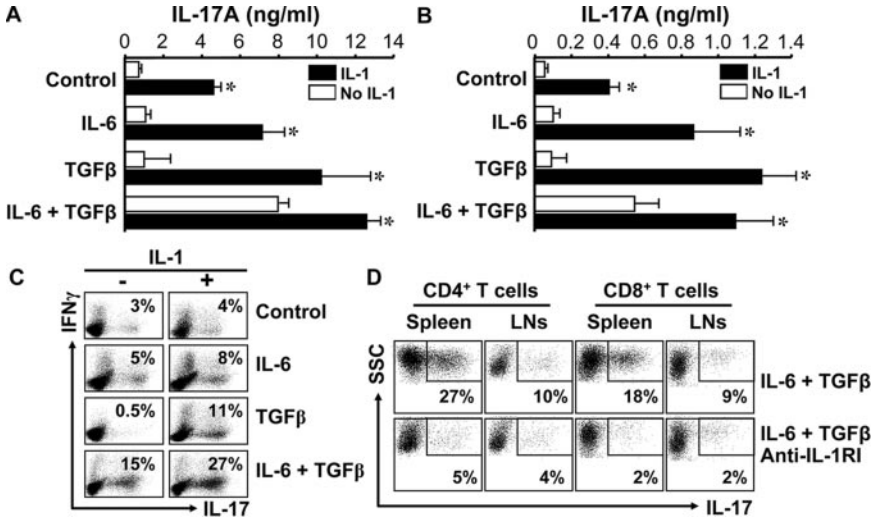

FIGURE 2. IL-1 promotes IL-17 $^{+}$CD4^{+} and IL-17 $^{+}$CD8^{+} T cell differentiation. Sorted spleen CD4^{+} and CD8^{+} T cells were cultured for 3 days with IL-1, TGFβ, IL-6, or their combinations. *A* and *B*, IL-1 increased IL-17A production. IL-17A was detected with an ELISA kit in the CD4^{+} (*A*) and CD8^{+} (*B*) T cell culture supernatants. Results were expressed as the mean values of IL-17A $\pm$ SEM (*, $p < 0.01$; $n = 8$). *C*, Exogenous IL-1 increased IL-17 $^{+}$CD4^{+} and IL-17 $^{+}$CD8^{+} T cell differentiation. The cultured T cells were analyzed with an LSR II cytometer for the expression of IL-17 and IFN-γ. Results were expressed as the percentage of IL-17 $^{+}$IFN-γ^{-} T cells in CD4^{+} T cells. Similar results were observed on CD8^{+} T cells. One of eight experiments is shown. *D*, Endogenous IL-1 contributed to IL-17 $^{+}$ T cell differentiation mediated by TGFβ and IL-6. Spleen or lymph node CD4^{+} and CD8^{+} T cells were cultured for 3 days with TGFβ and IL-6. Anti-IL-1 type IR was added. The resulting T cells were analyzed by an LSR II cytometer for the expression of IL-17 and IFN-γ. Results were expressed as the percentage of IL-17 $^{+}$IFN-γ^{-} T cells in CD4^{+} and CD8^{+} T cells. Less than 1% of IL-17 $^{+}$IFN-γ^{-} T cells were observed in T cells without stimulation. One of four experiments is shown.

that IL-17^{+} T cells may largely be differentiated in the peripheral organs (e.g., spleen) rather than in the lymph nodes. In support of this possibility, IL-17^{+} T cells are found in the mouse and human tumor tissues but not in the tumor-draining lymph nodes in tumor-bearing mice (18).

IL-1, IL-2, IL-6, and TGFβ are involved in controlling Th17 cell differentiation. We examined the effects of these cytokines and their combinations on IL-17^{+} T cell differentiation. These cytokines alone have no significant effects on IL-17^{+} T cell differentiation. Consistent with the literature (9–11, 18), TGFβ and IL-6 promote Th17 and IL-17^{+}CD8^{+} T cell differentiation. Strikingly, IL-1 can profoundly promote IL-17^{+} T cell differentiation with TGFβ in the absence of IL-6. IL-17^{+} T cells are detectable in IL-6$^{-/-}$ mice. The data indicate that IL-6 is not indispensable for IL-17^{+} T cell differentiation.

We further demonstrate that exogenous IL-1 increases IL-17^{+} T cell differentiation in the presence of TGFβ and IL-6. Interestingly, blocking IL-1 largely disables IL-17^{+} T cell differentiation mediated by TGFβ and IL-6. The data indicate that IL-1 plays a predominant role in IL-17^{+} T cell differentiation. In support of this notion, IL-1 enhances Th17 cell differentiation mediated by IL-23 in mice with autoimmune encephalomyelitis (6) and with *Bordetella* infection (17). IL-17 production is increased in IL-1 receptor antagonist knockout mice (16). Altogether, the data indicate that IL-1 may be a potent inducer of IL-17^{+} T cells in the specific local environment.

IL-2 is crucial for the production and function of regulatory T cells in mice. IL-2 is used to boost tumor immunity in patients with cancer (22) (S. I. Wei and R. P. Kryczek, manuscript in preparation). We investigated the potential effects of IL-2 on IL-17^{+} T cell differentiation. Consistent with previous reports, IL-2 reduced Th17 (18, 19) and IL-17^{+}CD8^{+} T cell (18) differentiation. Interestingly, IL-1 is able to restore IL-17^{+} T cell differentiation inhibited by IL-2, IFN-γ, and IL-4. The data demonstrate the opposite effects of IL-1 and IL-2 on IL-17^{+} cell differentiation. In further support of this conclusion, we observed that IL-2 inhibits the expression of multiple gene transcripts involved in regulating Th17 cell differentiation, including those of RORγt (23), IL-23 receptor (12, 14, 15), and IL-1 receptor (6, 16). IL-1 stimulates and restores their expression on T cells. The data may explain why Th17 cells can be found in the environment with active local immune infiltration and IL-2, IL-4, or IFN-γ production in multiple autoimmune diseases and further suggest that IL-1 is the decisive factor controlling the IL-17^{+} T cell pool.

Th17 cells may produce IL-22 (24, 25). The production of IL-22 and IL-17 from Th17 cells may be differentially

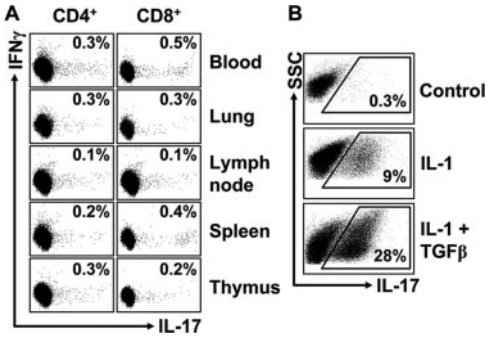

FIGURE 3. IL-6 is not indispensable for IL-17 $^{+}$ T cell differentiation. *A*, IL-17 $^{+}$ T cells were detectable in IL-6$^{-/-}$ mice. Single cell suspension was obtained from multiple organs in C57BL/6 IL-6$^{-/-}$ mice. The single cells were subjected to staining with the indicated Abs and analyzed with an LSR II cytometer. Results were shown as the percentage of IL-17 $^{+}$IFN-γ^{-} cells in CD4^{+} and CD8^{+} T cells. One of three experiments is shown. *B*, IL-1 induced Th17 T cell differentiation with TGFβ in the absence of IL-6. CD4^{+} T cells were isolated from IL-6$^{-/-}$ C57BL/6 mice and cultured for 5 days with TGFβ and IL-1. T cells were analyzed with LSR II for the expression of IL-17 and IFN-γ. Results were expressed as the percentage of IL-17 $^{+}$ cells in CD4^{+} T cells. One of three experiments is shown.

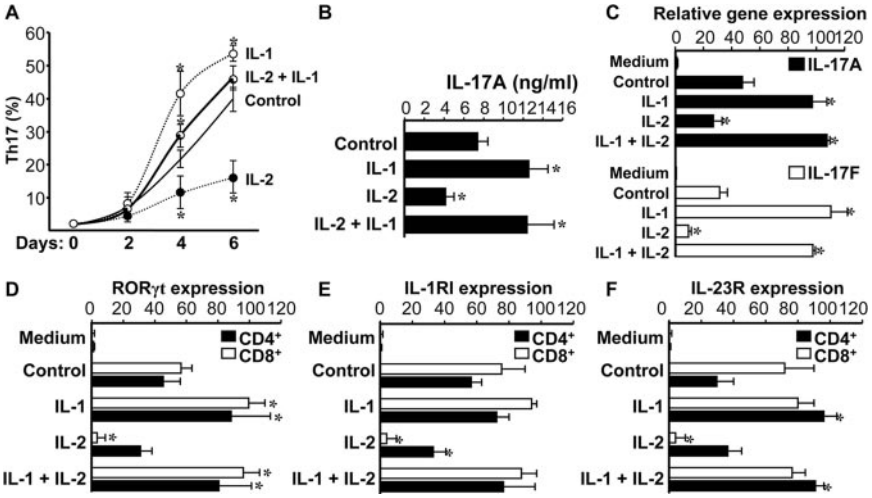

FIGURE 4. IL-1 subverts suppressive effects of IL-2 on IL-17$^+$ T cell differentiation. Spleen CD4$^+$ and CD8$^+$ T cells were cultured for 0–6 days with TGFβ and IL-6. IL-1α and IL-2 or their combinations were added into the culture. *A–C*, IL-1 and IL-2 played opposite roles in regulating IL-17$^+$ T cell differentiation. *A*, The cultured CD4$^+$ T cells were analyzed with an LSR II cytometer for the expression of IL-17 and IFN-γ. Results were expressed as the percentage of IL-17$^+$IFN-γ^- T cells in CD4$^+$ T cells (mean $\pm$ SEM; *, $p < 0.01$; $n = 6$). *B*, IL-17A was detected with ELISA kit in the CD4$^+$ T cell culture supernatants. Results were expressed as the mean values of IL-17A $\pm$ SEM (*, $p < 0.01$; $n = 6$). *C*, IL-17A and IL-17F transcripts were quantified by real-time PCR in the cultured CD4$^+$ T cells. Results were expressed as the mean units $\pm$ SEM (*, $p < 0.01$; $n = 6$). *D–F*, IL-1 and IL-2 oppositely regulated gene transcripts controlling Th17 differentiation. The expression of RORγt (*D*), IL-1 receptor (*E*), and IL-23 receptor (*F*) were quantified by real-time PCR. Results were expressed as the mean units $\pm$ SEM of targeted molecules in CD4$^+$ and CD8$^+$ T cells (*, $p < 0.01$; $n = 6$).

regulated. For example, TGFβ, although crucial for IL-17 production, actually inhibits IL-22 production (26). It will be interesting to investigate whether IL-1 and IL-2 can regulate IL-22 production by Th17 cells.

In summary, we show that IL-1 plays a central role in IL-17$^+$ T cell differentiation and that IL-6 is not indispensable for it. Our data further reveal a novel regulatory mechanism for IL-17$^+$ T cell differentiation: IL-1 and IL-2 play opposite roles in controlling IL-17$^+$ T cells. The levels of IL-1 in the local environment may determine IL-17$^+$ T cell pool in multiple disease models.

Disclosures

The authors have no financial conflict of interest.

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