Interleukin-7 Receptor is Indispensable for Proliferation and Survival in Thymic γδT Cell Development

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ABSTRACT

Background: Interleukin-7 receptor (IL-7R) α-deficient mice have small numbers of B cells and αβT cells in periphery, they totally lack γδT cells. In addition, the V-J recombination and transcription of TCRγ genes is also severely impaired in IL-7Rα -deficient mice. Stat5, a signaling molecule of the IL-7R, induces germline transcription in the TCRγ locus, and promotes V-J recombination and γδT cell development. However, the roles for IL-7R signaling pathway in thymic or extrathymic γδT cell development are largely unknown. **Methods:** To clarify the role of the IL-7 receptor in proliferation and survival of γδT cells, we introduced the TCR γδ transgene, Vγ2/Vδ5, into IL-7Rα-deficient mice. and investigated the development of γδT cells. **Results:** We found that Vγ2/Vδ5 transgene restored γδT cells in the epithelium of the small intestine (IEL) but not in the thymus and the spleen. Further addition of a *bcl-2* transgene resulted in partial recovery of γδT cells in the thymus and the spleen of these mice. **Conclusion:** Taken together, this study revealed that the IL-7Rα is indispensable for proliferation and survival mainly in thymic γδT cell development. **(Immune Network 2005;5(1):23-29)**

Key Words: IL-7R, TCRγ gene, Vγ2/Vδ5 transgenic mouse, thymus

Introduction

A small number of bone marrow-derived cells give rise to the NK, intrathymic dendritic cell, and αβ and γδT cells. γδT cell development has unique features in contrast to αβT cell development (1). IL-7 is an essential cytokine for γδT cell development. IL-7 exerts its effect through interaction with the IL-7R, which is composed of a uniqueα chain (IL-7Rα) and the common cytokine receptorγ chain (γc) (2). Recently, thymic stromal lymphopoietin (TSLP) has shown to transmit signals through IL-7R α and TSLPR heterodimer (3). Injection of neutralizing antibodies to IL-7 or IL-7Rα, or genetic ablation of IL-7, IL-7Rα or γc, leads to a block of lymphocyte development (4,5). While IL-7Rα-deficient mice have small numbers of B cells and αβT cells in periphery, they totally lack γδT cells (6,7). The IL-7R transmits at least two types of signal in lymphocyte progenitors (8). One signal is for survival and proliferation. For instance, the IL-7R induces the expression of Bcl-2 in T cell precursors (9), and introduction of *bcl-2* transgene restores αβT cell development in IL-7Rα-deficient mice (10). The IL-7R supports the proliferation of lymphocyte precursors through the activation of phosphatidylinositol-3 (PI3) kinase (11). Peripheral αβT cells in IL-7Rα-deficient mice are also defective in survival and proliferation (12). The second signal from the IL-7R is to promote recombination and transcription in the IgH and TCRγ loci. For example, IL-7R signaling induces germline transcription and DNA rearrangement in D-distal V segments in pro-B cells (13). The V-J recombination and transcription of TCRγ gene is also severely impaired in IL-7Rα-deficient mice (14). Stat5, a signaling molecule of the IL-7R, induces germline transcription in

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This work was supported by Korean Research Foundation Grant (KRF-800-20040189).

the TCRγ locus, and promotes Vγ-Jγ recombination and γδT cell development (15).

In addition to IL-7, other cytokines play substantial roles in γδT cell development. IL-15 achieves its effects through interaction with the IL-15R, which is composed of a unique α chain (IL-15Rα), the common β chain (IL-2Rβ), and the γc (16). Deletion of IL-15, IL-15Rα, or IL-2Rβ results in a block of NK cell development and impaired γδT cell development in the epithelium. IL-2Rβ-deficient mice have decreased numbers of γδ IEL (17). These results suggest that IL-15 plays important roles in the development of γδ IEL and DETC. Besides IL-15, IL-2 is also implicated to be involved in thymic and extrathymic T cell development (18).

The roles for each signaling pathway in γδT cell development are largely unknown. Introduction of a *bcl-2* transgene restored αβ but not γδT cell development in IL-7Rα-deficient mice. Similarly, a *bcl-2* transgene alone did not rescue B cells, γδT cells and NK cells in γc-deficient mice (19). However, these experiments did not clarify the role of Bcl-2 in γδT cell development, because the IL-7R signaling is necessary for the recombination and transcription of TCRγ genes. Introduction of a Vγ1.1/Vδ6 TCRγδ transgene failed to restore γδT cells in IL-7Rα -deficient mice, suggesting that the IL-7R plays some role in proliferation and/or survival of γδT cells (20).

To clarify the roles of the cytokine receptors in proliferation and survival of γδT cells, we introduced a TCRγδ transgenes, Vγ2/Vδ5 into IL-7Rα-deficient mice and found that they restored γδ T cells in IEL and the skin but not in the thymus and the spleen. Further addition of a *bcl-2* transgene resulted in partial recovery of γδT cells in the thymus and the spleen of these mice. In contrast, the same Vγ3/Vδ1 TCR transgene failed to rescue γδT cells in the skin of IL-2Rβ-deficient mice (21). Thus, this study reveals that the IL-7R is indispensable for the rearrangement of TCRγ genes in all γδT precursors and promotes both proliferation and survival in thymic γδT cell development.

Materials and Methods

Antibodies. The following monoclonal antibodies were used. FITC-conjugated antibodies; 53-6.7 (anti-CD8 α), H57-597 (anti-αβ TCR), 8D6 (anti-Vγ2/Vδ5), 53-2.1 (anti-Thy-1.2), KH95 (anti-H-2D^b). Biotin-conjugated antibodies; H57-597 (anti-αβ TCR). Phycoerythrin (PE)-conjugated antibodies: GK1.5 (anti-CD4), GL3 (anti-γδ TCR), 34-2-12 (anti-H-2D^d). Other monoclonal antibodies were purchased from PharMingen (San Diego, CA).

Mice. IL-7Rα-deficient (14) and H2K-bcl-2 transgenic mice (22) were reported previously and were bred on the (129/Ola×C57BL/6) hybrid background. The *bcl-2* transgene is driven by a H-2K promoter and expressed on virtually all blood cells. Transgenic mice containing productively rearranged Vγ2/Vδ5 TCR genes were described before (23). The Vγ2/Vδ5 TCR is derived from a γδT cell line specific for a product of a gene in the TL region in the TLb haplotype (24). All mice used in Vγ2/Vδ5 TCR transgenic experiments were of the H-2$^{d/d}$ haplotype confirmed by staining spleen cells with anti-H-2D^b and anti-H-2D^d antibodies. All mice were maintained in animal facilities at Seoul National University College of Medicine.

Cell preparations and flow cytometric analysis. Thymocytes and spleen cells were harvested in PBS supplemented with 2% fetal bovine serum and 0.02% sodium azide (FACS solution). Red blood cells were lysed, and cells were washed in the FACS solution. IEL were isolated from small intestine as described previously (25). Flow cytometric analysis was performed as described (21). Debris, erythrocytes, and dead cells

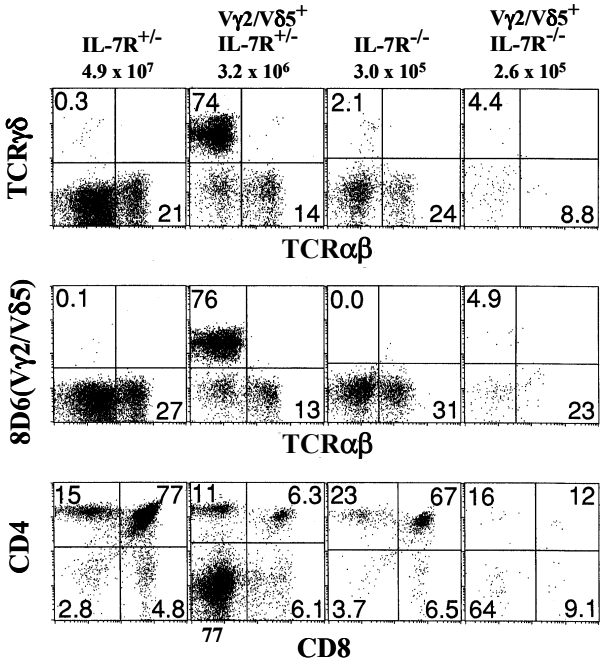

Figure 1. Introduction of a Vγ2/Vδ5 TCR transgene fails to restore γδT cells in the thymus of IL-7Rα-deficient mice. Thymocytes were isolated from IL-7Rα$^{+/-}$, TCR Tg$^+$ IL-7Rα$^{+/-}$, IL-7Rα$^{-/-}$, and TCR Tg$^+$ IL-7Rα$^{-/-}$ mice. Cells were stained with either FITC-anti-TCRαβ and PE-anti-TCRγδ, FITC-anti-Vγ2/Vδ5 TCR and biotin-anti-TCRαβ followed by PE-streptavidin, or FITC-anti-CD8 and PE-anti-CD4 antibodies. The percentages of cells for a given phenotype are shown. Representative data from 8-week-old littermates are shown. The cell numbers recovered from each mouse are shown above each panel.

were excluded from the analysis by forward and side scatters and propidium iodide gatings. Viable cells were analyzed by a FACS Calibur with CellQuest software version 3.1 (Becton Dickinson, San Jose, CA).

Results

Introduction of a Vγ2/Vδ5 TCR transgene fails to restore γδT cells in the thymus and the spleen of IL-7Rα-deficient mice. To test the role of the IL-7R on proliferation and/or survival of γδT cells, we introduced a Vγ2/Vδ5 TCR transgene into the IL-7Rα-deficient mice to bypass the defective Vγ-Jγ recombination. We backcrossed the Vγ2/Vδ5 TCR transgenic mice to IL-7Rα$^{-/-}$ mice and chose four types of mice, namely, IL-7Rα$^{+/-}$, Vγ2/Vδ5 TCR Tg^{+} IL-7Rα$^{+/-}$, IL-7Rα$^{-/-}$, and Vγ2/Vδ5 TCR Tg^{+} IL-7Rα$^{-/-}$. Thymocytes and spleen cells were isolated from the mice, and analyzed by flow cytometry (Fig. 1). While only 0.3% of thymocytes expressed γδ TCR in IL-7Rα$^{+/-}$mice, 74% of thymocytes were γδT cells expressing the Vγ2/Vδ5 TCR transgene in TCR Tg^{+} IL-7Rα$^{+/-}$ mice. In TCR Tg^{+} IL-7Rα$^{+/-}$ mice 77% of thymocytes were CD4^{-}8^{-}, suggesting that most of the transgenic γδT cells were CD4^{-}8^{-}. The number of thymocytes was reduced in Tg^{+} IL-7Rα$^{+/-}$ transgenic mice compared with IL-7Rα$^{+/-}$ mice (Fig. 2A), suggesting an adverse effect of TCR γδ transgenes on αβT cell development as proposed previously (26). In contrast, we did not detect any distinct TCRγδ^{+} cells in IL-7Rα$^{-/-}$ mice as we and others reported previously (6,7). Although we sometimes observed TCRγδ^{+} signals, we concluded that they were caused by nonspecific staining as judged by CD3 and TCRγδ staining (data not shown). In TCR Tg^{+} IL-7Rα$^{-/-}$ mice, however, we found few, if any, γδT cells. Spleen cells gave similar results to thymocytes: in TCR Tg IL-7Rα$^{+/-}$ mice a prominent γδT cell population developed in spleen, while no distinct γδT cells were detected in IL-7Rα$^{-/-}$ and TCR Tg^{+} IL-7Rα$^{-/-}$ mice (data not shown).

Next we compared the overall numbers of total and γδT cells (Fig. 2A, B, D and E). The numbers of γδT cells dramatically increased in the thymus and the spleen of TCR Tg^{+} IL-7Rα$^{+/-}$ mice compared with IL-7Rα$^{+/-}$ mice. The introduction of the TCRγδ transgene, however, resulted in a slight increase of γδT cells in the thymus and no increase in the spleen of IL-7Rα$^{-/-}$ mice. These results showed that the introduction of the Vγ2/Vδ5 TCR transgene alone failed to rescue γδT cell development in the thymus and the spleen of IL-7Rα$^{-/-}$ mice and that the IL-7R may play an important role in proliferation and/or survival of γδT cells in these organs.

The Vγ2/Vδ5 TCR transgene partially recovers γδ IEL

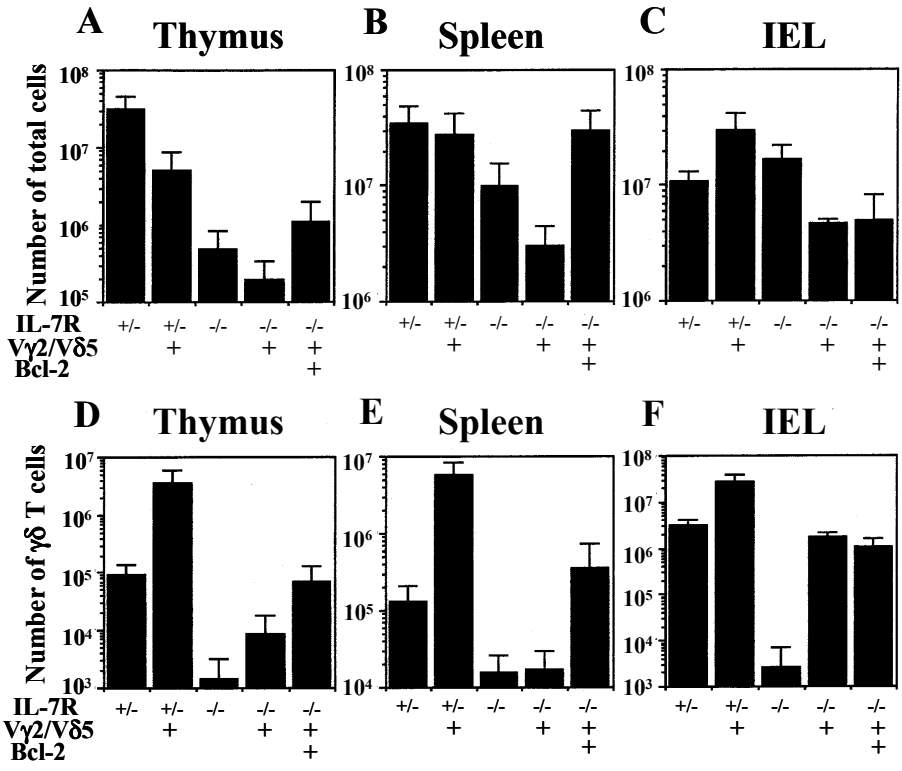

Figure 2. Numbers of total and γδT cells of IL-7Rα-deficient mice with Vγ2/Vδ5 TCR and *bcl-2* transgenes. Numbers of total (A, B, and C) and gd T (D, E, and F) cells were counted in the thymus (A and D), the spleen (B and E), and IEL (C and F) from IL-7Rα$^{+/-}$, TCR Tg^{+} IL-7Rα$^{+/-}$, IL-7Rα$^{-/-}$, and TCR Tg^{+} IL-7Rα$^{-/-}$, and *bcl-2* Tg^{+} TCR Tg^{+} IL-7Rα$^{-/-}$ mice of 8-week-old. The mean±S.E. is calculated from four mice. The numbers of γδT cells were calculated from the total cell numbers and the percentage of γδT cells in each mice.

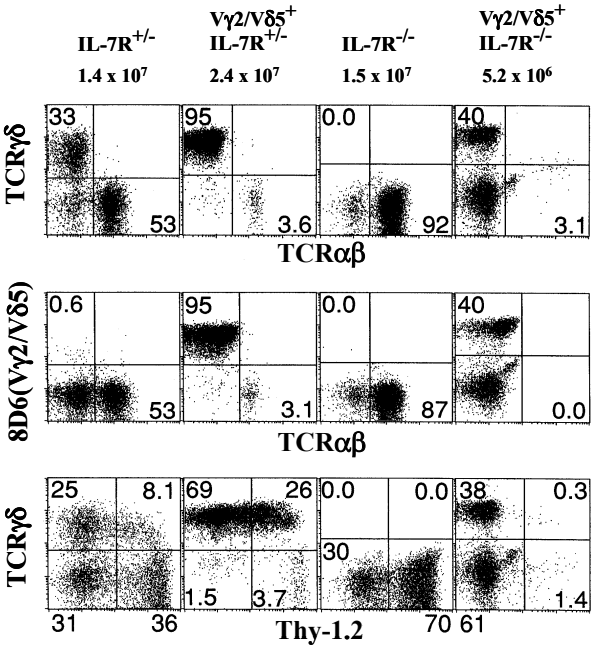

Figure 3. The $V_{\gamma 2}/V\delta_5$ TCR transgene partially restores γδ IEL in IL-7Rα-deficient mice. IEL were isolated from IL-7Rα$^{+/-}$, TCR Tg$^+$ IL-7Rα$^{+/-}$, IL-7Rα$^{-/-}$, and TCR Tg$^+$ IL-7Rα$^{-/-}$ mice. Cells were stained with either FITC-anti-TCR αβ and PE-anti-TCRγδ, FITC-anti-$V_{\gamma 2}/V\delta_5$ TCR and biotin-anti-TCRαβ followed by PE-streptavidin, or FITC-anti- Thy-1.2 and PE-anti-TCRγδ antibodies. The percentages of cells for a given phenotype are shown. Representative data from 8-week-old littermates are shown. The cell numbers recovered from each mouse are shown above each panel.

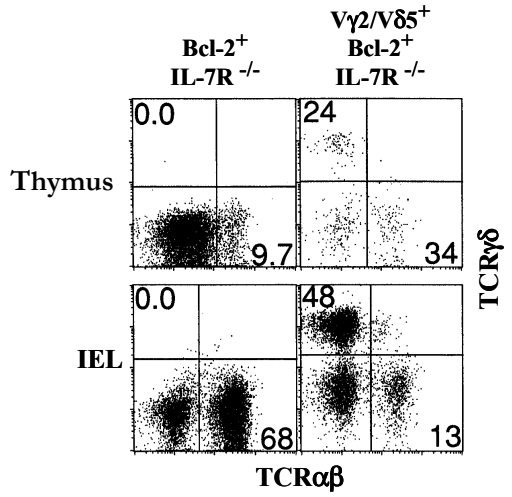

Figure 4. Introduction of a *bcl-2* transgene partially restores transgenic γδT cells in the thymus of IL-7Rα-deficient mice. Thymocytes and IEL were isolated from *bcl-2* Tg$^+$ IL-7Rα$^{-/-}$ and $V_{\gamma 2}/V\delta_5$ TCR Tg$^+$ *bcl-2* Tg$^+$ IL-7Rα$^{-/-}$ mice. Cells were stained with FITC-anti-TCRαβ and PE-anti-TCR γδ antibodies. The percentages of cells for a given phenotype are shown.

in IL-7Rα-deficient Mice. To assess the role of the IL-7R in extrathymic γδT cell development, we next analyzed IEL of the IL-7Rα-deficient mice with the $V_{\gamma 2}/V\delta_5$ TCR transgene (Fig. 3). IL-7Rα$^{+/-}$ mice showed a clear γδT cell population in IEL. The majority of IEL in TCR Tg$^+$ IL-7Rα$^{+/-}$ mice were γδT cells expressing the $V_{\gamma 2}/V\delta_5$ TCR transgene. As reported before (14), IL-7Rα$^{-/-}$ mice completely lacked γδ IEL. In contrast to the thymus and the spleen, TCR Tg$^+$ IL-7Rα$^{-/-}$ mice contained distinct transgenic γδT cells in IEL. αβ IEL development in these mice was blocked probably because of the adverse effect of the transgene (26). The numbers of γδ IEL in TCR Tg$^+$ IL-7Rα$^{-/-}$ mice were recovered almost to the levels of IL-7Rα$^{+/-}$ mice, but never reached to the levels of TCR Tg$^+$ IL-7Rα$^{+/-}$ mice (Fig. 2F). Theses results demonstrated that introduction of the $V_{\gamma 2}/V\delta_5$ TCR transgene partially restored γδ IEL in the IL-7Rα-deficient mice. They also suggested that, although IL-7 plays a substantial role in expansion and survival of IEL, other cytokine(s) like IL-15 probably supports this process in concert with IL-7. In IL-7Rα$^{+/-}$and TCR Tg$^+$ IL-7Rα$^{+/-}$ mice, we observed both Thy-1$^+$ and Thy-1$^-$ γδ IEL populations (Fig. 3). In TCR Tg$^+$ IL-7Rα$^{-/-}$ mice, however, Thy-1$^+$ γδ IEL were very few. This result suggested that the expression of Thy-1 antigen on γδ IEL is induced by IL-7R signaling.

Introduction of a bcl-2 transgene partially rescues transgenic γδT cells in the thymus and the spleen of IL-7Rα-deficient mice. Bcl-2 transgenes significantly restored αβT cells in the thymus of IL-7Rα-deficient mice (9,10). This result suggested that the IL-7R mainly transmits a survival signal in αβT cell development. In contrast, B cells and γδT cells were not restored in *bcl-2* Tg$^+$ IL-7Rα$^{-/-}$ mice (15). This was partly because of impaired V-J recombination in the TCRγ locus. To test the role of the IL-7R on cell survival of γδT cells, we introduced an H-2K-*bcl-2* transgene into the $V_{\gamma 2}/V\delta_5$ TCR Tg$^+$ IL-7Rα$^{-/-}$ mice. Thymocytes and IEL were isolated from *bcl-2* Tg$^+$ IL-7Rα$^{-/-}$ and *bcl-2* Tg$^+$ TCR Tg$^+$ IL-7Rα$^{-/-}$ ice, and analyzed by flow cytometry (Fig. 4). No distinct γδT cells were detected in the thymus and IEL of *bcl-2* Tg$^+$ IL-Rα$^{-/-}$ mice as reported before. In *bcl-2* Tg$^+$ TCR Tg$^+$ IL-7Rα$^{-/-}$ thymus, however, we observed more obvious transgenic γδT cells than in TCR Tg$^+$ IL-7Rα$^{-/-}$ thymus (Fig. 1A). The levels of the transgene expression in TCR Tg$^+$ IL-7Rα$^{-/-}$ mice were as high as those in TCR Tg$^+$ IL-7Rα$^{+/-}$mice, suggesting that the defective development of γδT cells in TCR Tg$^+$ IL-7Rα$^{-/-}$ mice was not necessarily due to impaired transcription of the transgene

(14). As an effect of the *bcl-2* transgene, αβT cell development was also partially recovered. We obtained similar results with spleen cells (data not shown). In contrast, after the introduction of the *bcl-2* transgene γδ IEL did not change much in TCR Tg^{+} IL-7Rα$^{-/-}$ mice, except that αβ IEL were partially restored.

Next we compared the overall numbers of total and γδT cells (Fig. 2). The numbers of γδT cells in the thymus and the spleen of *bcl-2* Tg^{+} TCR Tg^{+} IL-7Rα$^{-/-}$ mice were rescued almost to the levels of IL-7Rα$^{+/-}$ mice, but never reached to the levels of TCR Tg^{+} IL-7Rα$^{+/-}$ mice. In contrast, the *bcl-2* transgene did not affect the numbers of γδ IEL in TCR TCR Tg^{+} IL-7Rα$^{-/-}$ mice. These results showed that the introduction of the *bcl-2* transgene partially restored γδT cell development in the thymus and the spleen of IL-7Rα-deficient mice. These results supported the idea that the IL-7R plays a substantial role in survival of γδT cells in the thymus and the spleen by inducing Bcl-2. However, they also implied that the IL-7R transmits a proliferation signal in γδ thymocyte development. In contrast, the IL-7R is dispensable for Bcl-2 induction in γδ IEL development, probably because the IL-2Rβ can compensate for the IL-7R.

Discussion

In this study, we first showed that introduction of the Vγ2/Vδ5 TCR transgene alone failed to rescue γδT cell development in the thymus and the spleen of IL-7Rα$^{-/-}$ mice, suggesting that the IL-7R may play an important role in proliferation and/or survival of γδT cells in these organs (Fig. 1 and 2). The same transgene, however, partially restored γδ IEL in IL-7Rα$^{-/-}$ mice, showing that both IL-7 and other cytokine(s) such as IL-15 play a substantial role in expansion of γδ IEL (Fig. 2 and 3). Further introduction of the *bcl-2* transgene in these mice partially restored γδT cells in the thymus and the spleen (Fig. 2 and 4), demonstrating that the IL-7R transmits both proliferation and survival signals for γδT cells in these organs. The results also showed that the defective development of γδT cells in these mice was not due to impaired expression of the transgene (14). In contrast to Vγ2/Vδ5, the introduction of a Vγ3/Vδ1 TCR transgene into IL-7Rα$^{-/-}$ mice completely restored $Vγ3^{+}$ T cells in the fetal thymus and DETC in the adult skin (21). On the other hand, the same Vγ3/Vδ1 transgene alone, or together with the *bcl-2* transgene, failed to rescue DETC in IL-2R β$^{-/-}$ mice (21). These results demonstrated that the IL-2Rβ, rather than the IL-7R, plays an essential role in proliferation and survival of dendritic epidermal T cells (DETC) in the fetal thymus and the skin. Thus, this study proved that IL-7Rα and IL-2R β serve differential functions in proliferation and survival of γδT cells.

The IL-7R transmits at least two signals during γδ T cell development. One is for proliferation and survival, and the other is for recombination and transcription of the TCRγ locus. As we and others previously showed, the V-J recombination of TCRγ genes was severely impaired in IL-7Rα-deficient mice (14). In addition, Stat5, a signaling molecule of the IL-7R, induced germline transcription in the TCR γ locus, and promoted Vγ-Jγ recombination and γδT cell development (15). In this study two TCRγδ transgenes were shown to restore γδT cells in IL-7Rα-deficient mice: the Vγ2/Vδ5 transgene partially recovered γδ IEL. On the other hand, the Vγ3/Vδ1 transgene completely rescued DETC in the fetal thymus and the skin (21). These results suggested that IL-7R signaling is indispensable for rearrangement of TCRγ genes even in the tissues where IL-15 is available. This is either because the IL-15Rα or the IL-2Rβ is not expressed at very early stages where the rearrangement of TCRγ genes take place, or there is an IL-7R-specific signal for inducing recombination.

Thymic γδT cell development depends on IL-7R signaling for both proliferation and survival. In previous reports, the IL-7R induced the expression of *Bcl-2* in T cell precursors (9), and introduction of a *bcl-2* transgene alone restored αβT cell development in IL-7Rα-deficient mice (10). This is probably because αβT cell precursors receive proliferation and survival signals from pre TCR after they manage to express TCRβ chain (27). In contrast, γδT cell precursors seem to depend entirely on the IL-7R for their proliferation and survival in the thymus and the spleen. Bcl-2 is probably induced in γδT cell precursors by IL-7R signaling and plays an essential role in their survival, as suggested by the result that the *bcl-2* transgene partially rescued γδT cells in the thymus and the spleen of Vγ2/Vδ5 TCR Tg^{+} IL-7Rα$^{-/-}$ mice. The same result also implied that besides the survival signal γδT cell precursors receive a proliferation signal from the IL-7R. This is mediated probably by the MAP kinase cascade and PI3 kinase. It is also conceivable that the IL-7R supports the survival of γδT cells by keeping the transcription of the TCRγ genes (15). Because the *bcl-2* transgene partially rescued γδT cells in TCR Tg^{+} IL-7Rα$^{-/-}$ mice and the transgene expression on recovered γδT cells was not lowered, our results, however, suggested that the defective development of γδT cells in these mice was not due to impaired expression of the transgene.

Extrathymic γδT cell development depends on

not only the IL-7R but also the IL-2/IL-15R. While IL-7Rα-deficient mice completely lack γδ IEL (14), IL-15-, IL-15R-, and IL-2Rβ-deficient mice show only decreased numbers of γδ IEL (17). Because the $V_{\gamma 2}/V_{\delta 5}$ TCR transgene did not completely rescue γδ IEL in IL-7Rα-deficient mice, it is implied that the IL-7R induces proliferation and/or survival of γδ IEL besides rearrangement of TCRγ genes. Furthermore, introduction of the *bcl-2* transgene did not recover γδ IEL further in $V_{\gamma 2}/V_{\delta 5}$ TCR Tg^{+} IL-$7R\alpha^{-/-}$ mice, suggesting that the IL-7R transmits at least a proliferation signal in γδ IEL. In addition, γδ IEL probably receive proliferation and survival signals from the IL-2/IL-15R in response to IL-15 produced by intestinal epithelial cells. Thus, the IL-7R and the IL-2/IL-15R play roles at early and late stages of γδ IEL development, respectively. Thy-1^{+} γδ IEL were very few in $V_{\gamma 2}/V_{\delta 5}$ TCR Tg^{+} IL-$7R\alpha^{-/-}$ mice (Fig. 3). In contrast, IL-15-, IL-15Rα-, and IL-2Rβ-deficient mice have mostly Thy-1^{+} γδ IEL (17). These results suggested that only IL-7R signaling can induce Thy-1 expression on γδ IEL although the IL-2/IL-15R mobilizes a similar set of signaling molecules to the IL-7R. Thus, the Thy-1^{+} and Thy-1^{-} IEL populations in normal mice may correspond to the early and late stages of their development, respectively.

In conclusion, these data suggest that the IL-7Rα is indispensable for proliferation and survival mainly in thymic γδT cell development.

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