Distinct Roles for Signals Relayed through the Common Cytokine Receptor \( \gamma \) Chain and Interleukin 7 Receptor \( \alpha \) Chain in Natural T Cell Development

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Summary

The commitment, differentiation, and expansion of mainstream \( \alpha/\beta \) T cells during ontogeny depend on the highly controlled interplay of signals relayed by cytokines through their receptors on progenitor cells. The role of cytokines in the development of natural killer (NK)1\( ^1 \) natural T cells is less clearly understood. In an approach to define the role of cytokines in the commitment, differentiation, and expansion of NK1\( ^1 \) T cells, their development was studied in common cytokine receptor \( \gamma \) chain (\( \gamma c \)) and interleukin (IL)-7 receptor \( \alpha \) chain (IL-7R \( \alpha \))–deficient mice. These mutations block mainstream \( \alpha/\beta \) T cell ontogeny at an early prethymocyte stage. Natural T cells do not develop in \( \gamma c \)-deficient mice; they are absent in the thymus and peripheral lymphoid organs such as the liver and the spleen. In contrast, NK1\( ^1 \) T cells develop in IL-7R \( \alpha \)–deficient mice in the thymus, and they are present in the liver and in the spleen. However, the absolute number of NK1\( ^1 \) T cells in the thymus of IL-7R \( \alpha \)-deficient mice is reduced to \( \sim 10\% \), compared to natural T cell number in the wild-type thymus. Additional data revealed that NK1\( ^1 \) T cell ontogeny is not impaired in IL-2– or IL-4–deficient mice, suggesting that neither IL-2, IL-4, nor IL-7 are required for their development. From these data, we conclude that commitment and/or differentiation to the NK1\( ^1 \) natural T cell lineage requires signal transduction through the \( \gamma c \), and once committed, their expansion requires signals relayed through the IL-7R \( \alpha \).

Natural T (NT) cells are a distinct lineage of lymphocytes whose function is thought to be immunoregulatory in nature because they secrete a wide variety of cytokines, most notably IL-4, upon activation. They express both natural killer (NKR-P1) and T (\( \alpha/\beta \) and \( \gamma/\delta \) TCR) cell markers. In mice, they are present in the liver, bone marrow, spleen, lymph node, and postnatal thymus (for review see reference 1). The development of CD4\( ^{-8} \) or CD4\( ^{4-8} \) NT cells depends on the expression of nonclassical antigen presenting molecules such as CD1d1 (2–4) and possibly H-2TL (5). They express highly conserved \( \alpha/\beta \) TCR; a large majority of them express V\( \alpha \)14J\( \alpha \)281 (85%) paired with V\( \beta \)8.2 (up to 70%) (6, 7). A similar subset of T cells also exists among the human peripheral blood CD4\( ^{4-8} \) lymphocytes (8, 9). Hence, NT cells are predicted to serve an evolutionarily conserved function. Although this function of NT cells remains elusive, their selective absence in autoimmune prone mice, such as MRL-lpr/lpr, B6-lpr/lpr, C3H-gld/gld, and BW F\( _1 \) (10, 11) as well as non-obese diabetic (NOD; 12), suggests a role in the control of the disease. Moreover, the ability to delay or prevent the onset of disease either by the adoptive transfer of NKR-P1\( ^+ \) splenocytes (10) that includes both natural killer and NT cells, or by the administration of recombinant IL-4 (13), underscores the importance of NT cells in the physiology of normal immune responses.

Here we report that: (a) commitment and/or differentiation to NT cell lineage requires signaling through the common cytokine receptor \( \gamma \) chain because \( \gamma c^0/0 \) mice do not develop NKR-P1\( ^+ \) T cells in the thymus or in the peripheral lymphoid organs, (b) the expansion of the committed NT cells requires signals relayed through the IL-7R \( \alpha \) chain because although IL-7R \( \alpha^0/0 \) mice develop NKR-P1\( ^+ \) cells, they are dramatically reduced in numbers compared to
the wild type, and (d), signal(s) transduced through γc is not mediated by IL-2, IL-4, or IL-7 because neither IL-2<sup>−/−</sup>, IL-4<sup>−/−</sup>, nor IL-7Rαγγ mutations affect NT cell development.

**Materials and Methods**

Mice. B6.IL-2<sup>−/−</sup> and IL-7Rαγγ mice were purchased from the Jackson Laboratory (Bar Harbor, ME); B6.IL-2<sup>−/−</sup> were provided by D. Serreze (The Jackson Laboratory). R. Morawetz (National Institute of Allergy and Infectious Diseases, Bethesda, MD) provided B6.IL-4<sup>−/−</sup> (14) and D. Roopenian (The Jackson Laboratory) provided B6,β2m<sup>−/−</sup> and B6.IL-4<sup>−/−</sup> mice. B6,γc<sup>−/−</sup> and B6.IL-7Rα<sup>−/−</sup> mice were bred and genotyped at the National Heart, Lung and Blood Institute (Bethesda, MD; 15) and ImmuneX (Seattle, WA; 16), respectively.

Mononuclear Cell Preparation. Mononuclear cells (MNC) from thymus and spleen were prepared by standard techniques. Intrahepatic MNC were prepared from minced liver lobes pressed through a wire mesh. The cells were suspended in 50 ml of RPMI-1640 (GIBCO BRL, Gaithersburg, MD) supplemented with 5% FCS (Hyclone Labs, Logan, UT) and allowed to settle for ~10 min on ice. Liver MNC were separated from the hematocyes by density centrifugation over lympholyte M (Cederlane Labs Ltd., Hornby, Canada). Cells at the interface were collected and washed with RPMI supplemented with 5% FCS.

Flow Cytometry. Thymocytes (1–2 × 10<sup>7</sup>) of individual animals 4 wk or older were stained for three-color flow cytometric analyses, as described previously (5), with anti–heat stable antigen (HSA)-PE (M 1/69), anti–CD8α-PE (53-6.7), anti–CD44-FITC (IM 7), and anti–NKR-P1<sup>a</sup> (NK1.1)-biotin (PK136), anti–TCR-β-biotin (H57-597), or anti–V<sub>B8.1,8.2</sub>-biotin (MR5-2). Thymocytes were also stained with anti-Ly6C-FITC (AL-21). When staining with anti-1L-2R β-PE (TM–β1), anti–HSA–FITC, and anti–CD8α–FITC were used to electronically gate in the HSA<sup>low</sup> CD8<sup>low</sup> population. The biotinylated antibody was stained with streptavidin–R–ED670 (GIBCO BRL). HSA<sup>low</sup>CD8<sup>low</sup> thymocytes were electronically gated and either CD44+NKR-P1<sup>+</sup>, CD44+TCR-αβ<sup>+</sup>, and CD44+V<sub>B8.1,8.2</sub>+NKR-P1<sup>+</sup>, IL-2R β<sup>+</sup>NKR-P1<sup>+</sup>, or IL-2R β<sup>+</sup>TCR–αβ<sup>+</sup> NT cells were analyzed by flow cytometry using a FACScan® (Becton Dickinson, Mountain View, CA). Intrathymic NT cells were stained with anti–NKR-P1<sup>+</sup>–PE and anti–TCR-β-biotin or with anti–TCR–αβ–PE and anti–NKR-P1<sup>+</sup>–b2m. Splenocytes were stained with anti–B220–FITC (RA3-6B2), anti–TCR–αβ–PE, and anti–NKR-P1<sup>+</sup>–b2m. All antibodies used in these experiments were purchased from Pharmingen (San Diego, CA). Thymic NT cell number was calculated from the percentages of the double-positive CD44<sup>+</sup> and NKR-P1<sup>+</sup>, TCR–αβ<sup>+</sup> or V<sub>B8.1,8.2</sub> thymocytes within the HSA<sup>low</sup>CD8<sup>low</sup> subset as described previously (5).

**Results**

NT Cell Ontogeny in the Thymus. γc, IL-7Rα, IL-2, and IL-4-deficient Mice. The loss of γc expression as found in X-linked severe combined immunodeficiency patients or in mice results in impaired development of mainstream αβ T cells (15, 17). To determine whether γc deficiency affects NT cell ontogeny, we examined their development in the thymus of γc<sup>−/−</sup> mice backcrossed to C57BL/6 for 4–8 generations. γc<sup>−/−</sup> mice, >6 wk old, do not develop HSA<sup>low</sup>CD8<sup>low</sup> thymocytes of B6.γc<sup>−/−</sup> (seventh generation backcross to C57BL/6) and B6.IL-2R γc<sup>−/−</sup> littersmates. HSA<sup>low</sup>CD8<sup>low</sup> thymocyte population was electronically gated and CD44<sup>+</sup>NKR-P1<sup>+</sup> T cells were analyzed with a FACScan® flow cytometer.

**Figure 1.** Common cytokine receptor γc-deficient mice do not develop thymic NTα/β cells. Dot plots displaying CD44<sup>+</sup>NKR-P1<sup>+</sup> and CD44+TCR-αβ<sup>+</sup> T cells among HSA<sup>low</sup>CD8<sup>low</sup> thymocytes of B6.γc<sup>−/−</sup> (seventh generation backcross to C57BL/6) and B6.IL-2R γc<sup>−/−</sup> littersmates. HSA<sup>low</sup>CD8<sup>low</sup> thymocyte population was electronically gated and CD44<sup>+</sup>NKR-P1<sup>+</sup> T cells were analyzed with a FACScan® flow cytometer.
ers, but not the TCR-\(\alpha/\beta\) (22). The reduced number of NT cells in the IL-7R\(^{0/0}\) mice then corresponds to the small size of its thymus (16). In contrast, the absolute number of NT cells in IL-20/0 mice is increased by 1.5–2-fold compared to the number of NKR-P1\(^1\) T cells in wild-type animals (Fig. 2E). These data suggest that signals delivered through the IL-7R\(^\alpha\) are not only important in maintaining thymic cellularity, but are also essential for the expansion of NT cells.

NT Cells in the Peripheral Lymphoid Organs of \(\gamma c\), IL-7R\(^\alpha\), and IL-2–deficient Mice. NT cells are also present in peripheral lymphoid organs such as the liver, spleen, bone marrow, and lymph nodes; they also form a subset of intraepithelial lymphocytes of the gut (23). It is at present not clear whether NT cells develop in situ in these organs or whether they home here after their genesis in the thymus (22, 24, 25). To determine whether \(\gamma c\), IL-7R\(^\alpha\), and IL-2 deficiency affect NT cell development and/or homing to the liver and spleen, the presence of NKR-P1\(^+\) TCR-\(\alpha/\beta\) cells was analyzed in these mutant animals. We find that \(\gamma c\) null mice contain dramatically reduced levels of NT cells in the liver and spleen (Fig. 3). IL-7R\(^\alpha\)0/0 mice contained reduced numbers of NT cells in the liver (about half in B6.IL-7R\(^\alpha\)0/0, or up to twofold greater in B6.IL-20/0 compared with those in the wild type). (D) Absolute numbers of HSA\(^{low}\)CD8\(^{low}\) thymocytes calculated as the thymocyte number times the fraction of this subset. (E) Thymic NT cells in wild-type, IL-20/0, IL-40/0 and IL-7R\(^\alpha\)0/0 mice. NT cell number was calculated from the percentages of the double-positive CD44\(^1\) and NKR-P1\(^1\), TCR-\(\alpha/\beta\) or V\(\beta\)8.1,8.2\(^1\) thymocytes within the electronically gated HSA\(^{low}\)CD8\(^{low}\) population in D as described previously (5).

Figure 2. IL-2–, IL-4–, and IL-7R\(^\alpha\)-deficient mice develop thymic NT \(\alpha/\beta\) T cells. (A) Dot plots of CD44\(^{hi}\)NKR-P1\(^1\), CD44\(^{hi}\)TCR-\(\alpha/\beta\)\(^{med}\), and CD44\(^{hi}\)TCR-\(\beta\)8.1,8.2\(^{med}\) T cells among HSA\(^{low}\)CD8\(^{low}\) thymocytes of B6.IL-2\(^0/0\) (n = 5), B6.IL-4\(^0/0\) (n = 6) and B6.IL-7R\(^\alpha\)0/0 mice (n = 6). (B) Dot plots of Ly6C\(^{hi}\)NKR-P1\(^1\) T cells among HSA\(^{low}\)CD8\(^{low}\) thymocytes. (C) Dot plots of IL-2 R\(^\beta\)NKR-P1\(^1\) (B6.IL-4\(^0/0\) and B6.IL-7R\(^\alpha\)0/0) and of IL-2 R\(^\beta\)TCR-\(\alpha/\beta\) (B6.IL-2\(^0/0\) and B6.IL-7R\(^\alpha\)0/0) T cells among HSA\(^{low}\)CD8\(^{low}\) thymocytes. In B and C, the percentage of NT cells was almost equal in B6.IL-4\(^0/0\), about half in B6.IL-7R\(^\alpha\)0/0, or up to twofold greater in B6.IL-20/0 compared with those in the wild type. (D) Absolute numbers of HSA\(^{low}\)CD8\(^{low}\) thymocytes calculated as the thymocyte number times the fraction of this subset. (E) Thymic NT cells in wild-type, IL-2\(^0/0\), IL-4\(^0/0\) and IL-7R\(^\alpha\)0/0 mice. NT cell number was calculated from the percentages of the double-positive CD44\(^{hi}\) and NKR-P1\(^1\), TCR-\(\alpha/\beta\) or V\(\beta\)8.1,8.2\(^1\) thymocytes within the electronically gated HSA\(^{low}\)CD8\(^{low}\) population in D as described previously (5).
cells to the liver and spleen, the signaling for this process does not require IL-2. Additionally, it is unclear whether IL-7Rα null mutation affects the development and/or homing of NT cells to the periphery, or whether it affects the expansion of this T cell subset in the liver and spleen as it does in the thymus.

Discussion

The requirement for signal transduction through γc for NT cell development that does not involve IL-2 and IL-4 as well as, by extension, IL-7 and TSLP (evidenced by their development in IL-7Rα0/0 thymocytes) as the soluble mediator is noteworthy. Thus, the lack of NT cells in γc0/Y mice might be a reflection on the requirement for IL-9, IL-15, and/or an as yet unidentified cytokine as the signal transducer for their development. NKR-P1+ cells do not develop in mice with dysregulated expression of IL-2Rβ (26) or when the IL-2Rβ function is blocked with specific antibody (27). Whereas IL-9 uses only γc as part of its receptor complex (28, 29), IL-15 function depends on both the IL-2Rβ and γc (30). This suggests that IL-15 or a hitherto-undefined cytokine that uses both IL-2Rβ and γc specifies the soluble mediator function for NT cell ontogeny. If indeed an IL-2Rβ and γc-dependent cytokine(s) serves this function, how it selectively turns on NT cell development in fetal day 9 livers (25), and later in post-natal thymus (7), remains to be determined.

Human and mouse NK cells are predicted to develop from bipotential T/NK progenitor cells that commit to either T or NK cell lineage depending on the microenvironment of the developing precursor. Recent evidence suggests that the commitment to the NK lineage is strongly influenced by IL-15 (31–33). If NT and NK cells have a common precursor, then our data are consistent with the hypothesis that commitment to NKR-P1+ T cell lineage might be influenced by signals mediated by IL-15.

Two possible mechanisms can explain the lack of NT cell development in γc0/Y mice. Signaling through the γc may be critical for the commitment of the precursor cell to the NT cell lineage. An alternative mechanism would be that further differentiation of the already committed NT cells cannot proceed in the absence of signals from the γc. Current evidence supports the latter mechanism. It was recently demonstrated that γc null mice develop Vα14 and Vβ8 positive, the conserved TCR expressed by NT cells (6, 7), thymocytes within their CD4+2− subset (34). However, these thymocytes poorly respond to in vitro cross-linking of their TCR by secreting IL-4 (34), a characteristic of mature NT cells (35). This would suggest that commitment to NT cells has occurred in the thymus of γc null mice, but the committed precursor has not completely differentiated into this lineage.

Although IL-7Rα0/0 mice develop NT cells, their absolute numbers in the thymus are dramatically lower (~10%) than those found in the wild-type mice. In vitro stimulation of unfractionated thymocytes with IL-7 results in the selective expansion of CD4+8− and CD4−8+ thymocytes that express the Vβ8.2 TCR (36). In keeping with this and consistent with our results is the finding that IL-7 cytokine-deficient mice develop NT cells, but in reduced numbers (37). In this respect, it is also noteworthy that type I diabe-

Figure 3. NT α/β cells do not develop in peripheral lymphoid organs of γc-deficient mice, but develop in IL-7Rα0/0 and IL-20/0 animals. Dot plots displaying NKR-P1+ TCR-α/β+ cells among mononuclear cells isolated from the liver (A) and spleen (B) of wild-type and mutant mice. Liver NT α/β cells were stained with anti-NKR-P1-PE and anti-TCR-β-biotin (B6.γc0/Y and B6.IL-7Rα0/0) or anti-TCR-β-PE and anti-NKR-P1-biotin (B6.IL-2−/− and B6.IL-20/0). Splenic NT α/β cells were stained with anti-B220-FITC, anti-TCR-β-PE and anti-NKR-P1-biotin, and identified among B220null splenocytes. In all cases, the biotinylated antibodies were detected by staining with streptavidin-RED670. The staining pattern of intracellular NT cells was observed in over 20 different preparations (see also reference 4).
tes-prone NOD mice do not secrete IL-4 in response to in vivo cross-linking of TCR (12) suggesting that they do not develop NT cells. Type I diabetes is a Th1 disease that can be delayed or prevented by the administration of IL-4 to prediabetic NOD mice (13). The lack of IL-4 response of B cell-prone NOD mice does not secrete IL-4 in response to in vivo TCR cross-linking is reversible by IL-7 stimulation in vitro (12). Thus, in conclusion, akin to mainstream T cells, the commitment and/or differentiation to the NT cell lineage depends on signal transduction through the γc, and once committed, their expansion requires signals relayed through the IL-7Rα.

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References

1. Vicari, A.P., and A. Zlotnik. 1996. Mouse NK1.1+ T cells: a new family of T cells. Immunity. 17:71–76.

2. Smiley, S.T., M.H. Kaplan, and M.J. Grusby. 1997. Immunoglobulin E production in the absence of interleukin-4 secreting CD1dependent cells. Science (Wash. DC). 275:977–979.

3. Chen, Y.-H., N.M. Chiu, M. Mandal, N. Wang, and C.-R. Wang. 1997. Impaired NK1.1+ T cell development and early IL-4 production in CD1deficient mice. Immunity. 6:459–467.

4. Mendiratta, S.K., W.D. Martin, S. Hong, A. Boesteanu, S. Joyce, and L. Van Kae r. 1997. CD1d1 mutant mice are deficient in natural T cells that promptly produce IL-4. Immunity. 6:469–477.

5. Joyce, S., I. Negishi, A. Boesteanu, A.D. DeSilva, P. Sharma, M.J. Chorney, D.Y. Loh, and L. Van Kae r. 1996. Expansion of natural (NK1−/−) T cells that express αβ T cell receptors in transporters associated with antigen presentation-1 null and thymus leukemia antigen positive mice. J. Exp. Med. 184:1579–1584.

6. Lantz, O., and A. Bendelac. 1994. An invariant T cell receptor α chain is used by a unique subset of major histocompatibility complex class I-specific CD4+ and CD8− T cells in mice and humans. J. Exp. Med. 180:1097–1106.

7. Bendelac, A., N. Killeen, D.R. Litman, and R.H. Schwartz. 1994. A subset of CD4+ thymocytes selected by MHC class I molecules. Science (Wash. DC). 263:1774–1778.

8. Porcelli, S.A., C.E. Yockey, M.B. Brenner, and S.P. Balk. 1993. Analysis of T cell antigen receptor (TCR) expression by human peripheral blood CD48− αβ T cells demonstrates preferential use of several Vβ genes and an invariant TCR α chain. J. Exp. Med. 178:1–16.

9. Dellabona, P., E. Padovan, G. Casaroli, M. Brockhaus, and A. Lanzeve cch. 1994. An invariant Vα24α1d Vβ11 T cell receptor is expressed in all individuals by clonally expanded CD48− T cells. J. Exp. Med. 180:1117–1176.

10. Take da, K., and G. Dennert. 1993. The development of autoimmune C57BL/6 lpr mice correlates with the disappearance of the natural killer type 1 positive cells: evidence for their suppressive action on bone marrow stem cell proliferation, B cell immunoglobulin secretion, and autoimmune symptoms. J. Exp. Med. 177:155–164.

11. Meza, M.A., T. Itoh, J.Q. Cui, Y. Makino, T. Kawano, K. Tsuchida, T. Koike, T. Shirai, H. Yagita, A. Matsuzawa, et al. 1996. Selective reduction of Vα14+ NK T cells associated with disease development in autoimmune prone mice. J. Immunol. 156:4035–4040.

12. Gombert, J.-M., E. Tancrede-Bohin, A. Hameg, M.D.C. Leite-de-Moraes, A. Vicari, J.-F. Bach, and A. Herbelin. 1996. IL-7 reverses NK1.1+ T cell defective IL-4 production in non-obese diabetic mouse. Int. Immunol. 8:1751–1758.

13. Rapoport, M.J., A. Jaramilo, D. Ziplis, A.H. Lazarus, D.V. Serreze, E.H. Leiter, P. Cyopick, J. Danska, and T.L. Dolovich. 1993. Interleukin-4 reverses T cell unresponsiveness and prevents the onset of diabetes in nonobese diabetic mice. J. Exp. Med. 178:87–99.

14. Morawetz, R.A., L. Gabriele, L.V. Rizzo, N. Noben-Trauth, R. Kuhn, K. Rajewsky, W. Muller, T.M. Doherty, F. Finkelman, R.L. Coffman, and H.C. Morse III. 1996. Interleukin (IL)-4 independent immunoglobulin class switch to immunoglobulin (Ig)E in the mouse. J. Exp. Med. 184:1654–1661.

15. Cao, X., E.W. Shores, J. Hu-Li, M.R. Anver, B.L. Kelsall, S.M. Russell, J. Drago, M. Noguchi, A. Grinberg, E.T. Bloom, et al. 1995. Defective lymphoid development in mice lacking expression of the common cytokine receptor γ chain. Immunity. 2:223–238.

16. Peschon, J.J., P.J. Morrisey, K.H. Grabstein, F.J. Ramsdell, E. Marakovsky, B.C. Gliniak, L.S. Park, S.F. Ziegler, D.E. Williams, C.B. Ware, et al. 1994. Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. J. Exp. Med. 180:1955–1960.

17. Noguchi, M., H. Yi, H.M. Rosenblatt, A.H. Filipovich, S. Adelstein, W.S. Mod i, O.W. McBride, and W.J. Leonard. 1993. Interleukin-2 receptor γ chain mutation results in X-linked severe combined immunodeficiency in humans. Cél. 73:147–157.

18. Leonard, W.J., E.W. Shores, and P.E. Love. 1995. Role of...
common cytokine receptor γ chain in cytokine signaling and lymphoid development. Immunol. Rev. 148:97–114.

19. Schorle, H., T. Holschke, T. Hunig, A. Schimpl, and I. Horak. 1991. Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting. Nature (Lond.). 352:621–624.

20. Kuhn, R., K. Rajewsky, and W. Muller. 1991. Generation and analysis of interleukin-4 deficient mice. Science (Wash. DC.). 254:707–710.

21. Yoshimoto, T., A. Bendelac, J. Hu-Li, and W.E. Paul. 1995. Defective IgE production by SJL mice is linked to the absence of CD4+ NK1.1+ T cells that promptly produce interleukin-4. Proc. Natl. Acad. Sci. USA. 92:11931–11934.

22. Bendelac, A. 1995. Mouse NK1.1+ T cells. Curr. Opin. Immunol. 7:367–374.

23. Ohteki, T., and H.R. MacDonald. 1994. Major histocompatibility complex class I related molecules control the development of CD4+8 and CD4+8 subsets of natural killer 1.1+ T cell receptor–α/β cells in the liver of mice. J. Exp. Med. 180:699–704.

24. MacDonald, H.R. 1995. NK1.1+ T cell receptor–α/β cells: new clues to their origin, specificity and function. J. Exp. Med. 182:633–638.

25. Makino, Y., R. Kanno, H. Koseki, and M. Taniguchi. 1996. Development of Vα14+ NK T cells in the early stages of embryogenesis. Proc. Natl. Acad. Sci. USA. 93:6516–6520.

26. Suwa, H., T. Tanaka, F. Kitamura, T. Shiohara, K. Kuida, and M. Miyakawa. 1995. Dysregulated expression of the IL-2 receptor β chain abrogates development of NK cells and Thy-1+ dendritic epidermal cells in transgenic mice. Int. Immunol. 7:1441–1449.

27. Takeuchi, Y., T. Tanaka, K. Hamaamurata, T. Sugimoto, M. Miyaoka, H. Yasuta, and K. Osumi. 1992. Expression and role of interleukin-2 receptor β chain on CD4+CD8+ T cell receptor ϒ8+ cells. Eur. J. Immunol. 22:2929–2935.

28. Russell, S.M., J.A. Johnson, M. Noguchi, M. Kawamura, C.M. Bacon, M. Friedmann, M. Berg, D.W. M. Vicari, B.A. Wildinu, O. Silvennoinen, et al. 1994. Interaction of IL-2Rβ and γc chains with Jak1 and Jak3: implications for XSCID and XCID. Science (Wash. D.C.). 266:1042–1045.

29. Kimura, Y., T. Takeshita, M. Kondo, N. Ishii, M. Nakamura, J. Van Snick, and K. Sugamura. 1995. Sharing of the IL-2 receptor gamma chain with the functional IL-9 receptor complex. Int. Immunol. 7:115–120.

30. Giri, J.G., M. Ahdieh, J. Eisenman, K. Shenanbeck, K. Grabein, S. Kumaki, A. N. amen, L.S. Park, D. Cosman, and D. Anderson. 1994. Utilization of the β and γ chains of the IL-2 receptor by a novel cytokine IL-15. EMBO (Eur. Mol. Biol. Organ.) J. 13:2822–2830.

31. Cavazzana-Calvo, M., S. Hachein-Bey, G. de Saint Basile, C. De Coene, F. Selz, F. Le Deist, and A. Fischer. 1996. Role of interleukin-2 (IL-2), IL-7, and IL-15 in natural killer cell differentiation from cord blood hematopoietic progenitor cells and from γc transduced severe combined immunodeficiency X1 bone marrow cells. Blood. 88:3901–3909.

32. Leclercq, G., V. Debacker, M. De Smedt, and J. Plum. 1996. Differential effects of interleukin-15 and interleukin-2 on the differentiation of bipotential T/natural killer progenitor cells. J. Exp. Med. 184:325–336.

33. Puzanav, I.J., M. Bennett, and V. Kumar. 1996. IL-15 can substitute for the marrow microenvironment in the differentiation of natural killer cells. J. Immunol. 157:4282–4285.

34. Lantz, O., L.I. Sharara, F. Tilloy, A. Anderson, and J.P. DiSanto. 1997. Lineage relationships and differentiation of natural killer (NK) T cells intrathymic selection and interleukin (IL)-4 production in the absence of NKR-P1 and Ly49 molecules. J. Exp. Med. 185:1395–1401.

35. Yoshimoto, T., and W.E. Paul. 1994. CD4+ NK1+ T cells promptly produced IL-4 in response to in vivo challenge with anti-CD3. J. Exp. Med. 179:1285–1295.

36. Vicari, A., M.D.C. Liete-de-Moraes, J.-M. Gombert, M. Dy, C. Penit, M. Papiernik, and A. Herbelin. 1994. Interleukin 7 induces preferential expansion of Vβ8.2+CD4+ and Vβ8.2+CD8+ murine thymocytes positively selected by class I molecules. J. Exp. Med. 180:653–661.

37. Vicari, A., A. Herbelin, M.D.C. Liete-de-Moraes, U. von Freeden-Jeffry, R. Murray, and A. Zlotnik. 1996. NK1.1+ T cells from IL-7 deficient mice have normal distribution and selection but exhibit impaired cytokine production. Int. Immunol. 8:1759–1766.