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Preferential expression of IL-2 receptor subunits on memory populations within CD4$^+$ and CD8$^+$ T cells

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SUMMARY

Using anti-Tac and anti-Mik-β1 monoclonal antibodies to α and β subunits of the interleukin-2 receptor (IL-2R), respectively, a marked difference in expression of IL-2R subunits on blood CD4$^+$ and CD8$^+$ T cells was demonstrated between adults and newborns. In the adult blood, reciprocal expression of IL-2Rα and IL-2Rβ was observed in CD4$^+$ and CD8$^+$ T cells. Some CD4$^+$ T cells expressing IL-2Rα were often detected, but IL-2Rβ^+ CD4$^+$ cells were very few. On the other hand, CD8$^+$ T cells expressed significant IL-2Rβ but little IL-2Rα. In marked contrast to adult individuals, both CD4$^+$ and CD8$^+$ T cells from the newborns, which seemed to consist mainly of naive populations, showed only negligible expression of IL-2R subunits. It was found that IL-2R subunits appeared to be preferentially expressed on CD4$^+$ and CD8$^+$ T cells with memory phenotypes in the adult blood. Isolated memory (CD45RO$^+$) CD4$^+$ and CD8$^+$ T cells, unlike naive (CD45RO$^-$) ones, were able to proliferate in response to exogenous IL-2 as well as the recall antigen. The present results suggest that IL-2R subunits expressed on circulating T-cell subsets may play an important role in memory T-cell function.

INTRODUCTION

Resting T cells can be activated by antigens or mitogens to proliferate, largely depending on their own production of interleukin-2 (IL-2).[1] T-cell growth induced by IL-2 is transmitted via the interaction of IL-2 with its specific receptors expressed on activated T cells.[2] High-affinity functional IL-2 receptors (IL-2R) have been demonstrated to be composed of at least two distinct subunits, the α-chain of molecular weight (MW) 55,000 (p55 or IL-2Rα) and the β-chain of MW 75,000 (p75 or IL-2Rβ).[3–5] The development of monoclonal antibodies (mAb) against these IL-2R molecules has allowed the functional and structural characterization of IL-2R,[6–8] and cDNA encoding each subunit of the human IL-2R has now been isolated.[9,10] The predicted structure of IL-2Rβ reveals a large cytoplasmic domain of 286 amino acids, suggesting that it may function in a IL-2-mediated signal transduction.

Radiolabelled IL-2 cross-linking studies have shown that a proportion of seemingly resting T cells, as well as most natural killer (NK) cells from the peripheral blood, express the IL-2Rβ but little or very faint IL-2Rα.[11,12] Although some circulating T cells are responsive to IL-2 *in vitro*, corresponding to their expression of IL-2Rβ, the nature of IL-2R-expressing T cells in the blood has not been defined. In order to elucidate the roles of IL-2R expressed on circulating T cells, in the present work we comparatively examined the expression profiles of IL-2R subunits on T-cell subsets from adult blood and neonatal blood. From immunofluorescence analysis using mAb against two IL-2R subunits, it was found that some CD4$^+$ and CD8$^+$ T cells from the blood of adult individuals obviously expressed the IL-2Rα or IL-2Rβ, respectively, whereas such an expression of IL-2R subunits by T-cell subsets was not seen in the neonatal blood. We show here that the memory or previously activated populations within circulating T-cell subsets preferentially express the IL-2Rα or IL-2Rβ to exert their functional roles in *in vivo* conditions.

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MATERIALS AND METHODS

Monoclonal antibodies

The mAb Mik-β1 (IgG2a), which identifies the human IL-2Rβ,[7] was generously provided by Dr M. Tsudo (Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan). Anti-Tac mAb (IgG2a) against the human IL-2Rα[6] was the kind gift of Dr T. A. Waldmann (NIH, Bethesda, MD). The mAb UCHL1 (IgG2a) against CD45RO[13] was purchased from Dakopatts A/S (Copenhagen, Denmark). Phycoerythrin (PE)-conjugated anti-CD45RA (2H4, IgG1) mAb[14] was obtained from Coulter Immunology (Hialeah, FL). Fluorescein isothiocyanate (FITC)-conjugated anti-CD4 (anti-Leu-3a, IgG1) and anti-CD8 (anti-Leu-2a, IgG1) mAb were from Becton-Dickinson Immunocytometry Systems (Mountain View, CA). FITC-

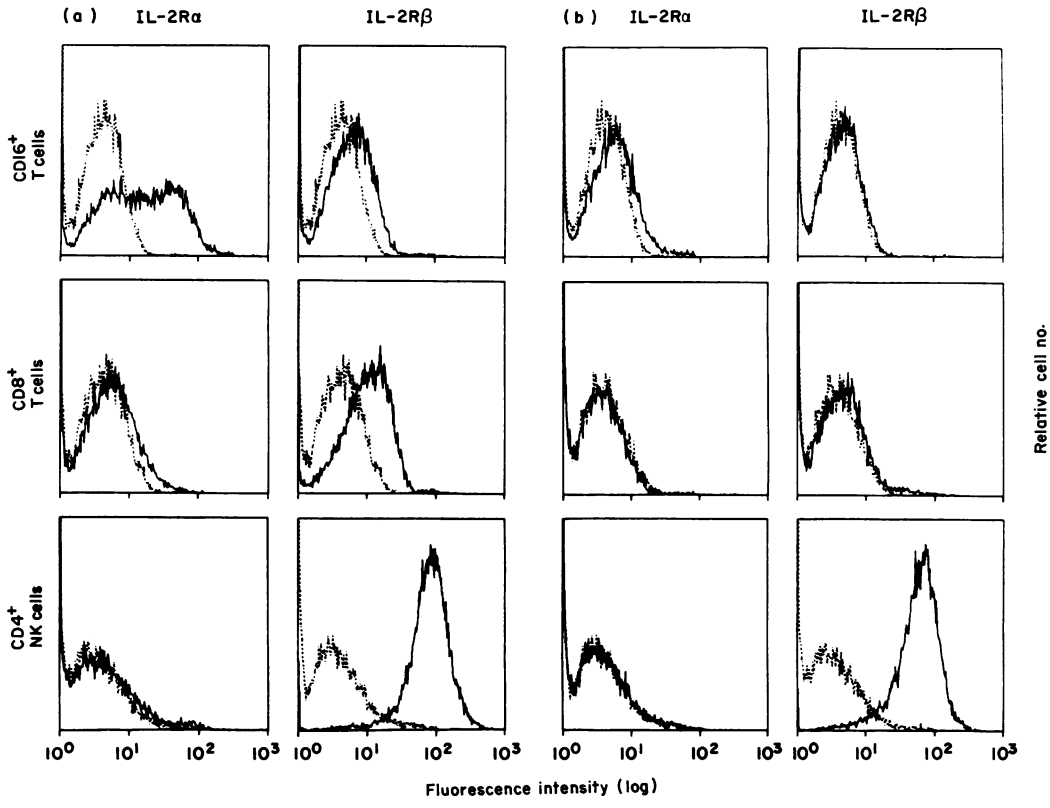

Figure 1. Two-colour immunofluorescence analysis for IL-2Rα and IL-2Rβ expression on T-cell subsets and NK cells from the adult blood (a) and neonatal blood (b). MNC were first treated with anti-Tac (anti-IL-2Rα) or Mik-β1 (anti-IL-2Rβ) mAb, and further counterstained with biotin-conjugated anti-mouse IgG2a antibody and PE-conjugated streptavidin. Next, the cells were stained with FITC-conjugated anti-CD4, anti-CD8 or anti-CD16 mAb. A gate was set to $CD4^+$, $CD8^+$ or $CD16^+$ lymphocytes (green fluorescence) and histograms were generated with red fluorescence of 10,000 cells (solid lines) on an EPICS-C flow cytometer. Dotted lines indicate background staining with control IgG2a mAb.

conjugated anti-CD16 (OKNK, IgM) mAb was supplied by Ortho Diagnostic Systems, K. K. (Tokyo, Japan).

Immunofluorescence analysis

Two-colour immunofluorescence staining was performed to evaluate the cellular expression of the IL-2Rα and IL-2Rβ, as described elsewhere.[15] The cells were first treated with anti-Tac (anti-IL-2Rα) mAb, Mik-β1 (anti-IL-2Rβ) mAb or isotype-matched control, and counterstained with biotinylated rabbit anti-mouse IgG2a antibody (Zymed Laboratories, San Francisco, CA), followed by incubation with PE-conjugated streptavidin (Becton-Dickinson Immunocytometry Systems). Next, the cells were stained for the identification of $CD4^+$ T cells, $CD8^+$ T cells, or $CD16^+$ NK cells with the corresponding mAb labelled with FITC. The stained cells were analysed using an Epics-C flow cytometer (Coulter Electronics Inc., Hialeah, FL).

Cell preparation

Cord blood samples were collected from the umbilical vein immediately after the uneventful delivery of full-term newborns. Adult subjects were healthy volunteers between the ages of 25 and 35 years. Mononuclear cells (MNC) were isolated from heparinized whole blood by Ficoll–Hypaque density gradient centrifugation. E-rosetting T cells were separated from MNC by rosetting with 2-aminoethylisothiouronium bromide-treated sheep erythrocytes, followed by Ficoll–Hypaque density gradient centrifugation.[16] Total T cells were stained for CD45RO (UCHL1) and CD4 or CD8 by the two-colour immunofluorescence method as above, and separated into $CD45RO^-$ (naive) and $CD45RO^+$ (memory) populations of $CD4^+$ or $CD8^+$ T cells by using an Epics-C flow cytometer, as described elsewhere.[15] In some experiments, the naive and memory cell populations were prepared by negative selection to deplete $CD45RO^+$ and $CD45RA^+$ cells, respectively. Adherent cells as the source of monocytes were obtained from MNC on plastic flasks and irradiated with 3000 rads.

Cell cultures

The culture medium consisted of RPMI-1640 (Gibco Laboratories, Grand Island, NY) containing 10% heat-inactivated pooled human serum, 25 mM HEPES, 5×10^{-5} M 2-ME, 0·3 mg/ml L-glutamine, 200 U/ml penicillin G and 10 μg/ml gentamicin. The cells were seeded at 5×10^4/well in 96-well flat-bottomed plates (Corning Glass Works, Corning, NY) in a final volume of 200 μl of culture medium and cultured for 5 days at 37° in 5% CO_2 and 95% air. For IL-2 responsiveness, various concentrations of human recombinant IL-2 ($1{\cdot}56 \times 10^7$ U/mg of protein; Shionogi & Co., Osaka, Japan) were added to the cell cultures. The cells were also stimulated with 1 μg/ml of purified protein derivative (PPD ; Japan BCG Co. Ltd, Tokyo, Japan) with the

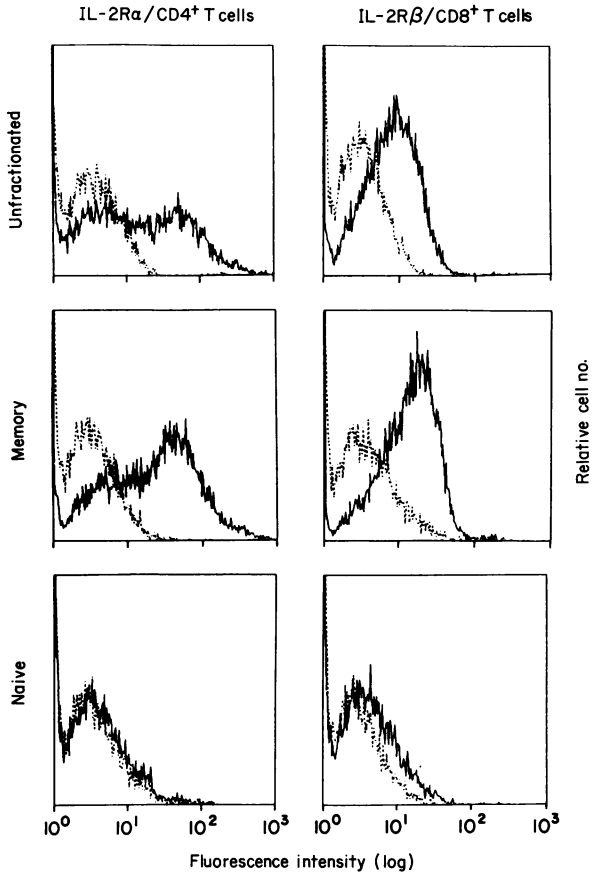

Figure 2. Preferential expression of IL-2R subunits on memory populations of CD4+ T and CD8+ T cells. Unfractionated, memory (CD45RA−) and naive (CD45RO−) cell populations of T-cell subsets were isolated using an EPICS-C flow cytometer. Subsequently, each population was stained and analysed for IL-2R subunits as described in the legend of Fig. 1. Solid and dotted lines indicate the immunostaining with anti-IL-2Rα or anti-IL-2Rβ mAb and control antibody, respectively.

supplement of irradiated monocytes. DNA synthesis was determined by [^{3}H]thymidine (TdR) incorporation (0·2 μCi/well, 6·7 Ci/mmol; New England Nuclear, Boston, MA) during the last 12 hr of culture.

RESULTS

Expression of IL-2R (α and β) subunits on CD4+ and CD8+ T cells from adult blood but not from neonatal blood

When analysed by two-colour immunofluorescence analysis, it was consistently demonstrated that the vast majority of CD16+ NK cells from newborns as well as adult donors were strongly stained by anti-IL-2Rβ (Mik-β1) but not by anti-IL-2Rα (anti-Tac) mAb (Fig. 1a), consistent with the results of radiolabelled IL-2 cross-linking studies[11,12] and of similar examinations using anti-IL-2Rβ mAb.[17,18] In adult subjects, appreciable expression of IL-2Rβ on CD8+ T cells, though less than that expressed on NK cells, was demonstrable, but only few, if any, IL-2Rβ were expressed on CD4+ T cells. With respect to IL-2Rα expression, CD4+ T cells but not CD8+ T cells from the adult blood

Table 1. Proliferative responses of naive and memory populations of CD4+ and CD8+ T cells to IL-2 or PPD

	[^{3}H]TdR incorporation			
	CD4+ T cells		CD8+ T cells	
Stimuli	Naive	Memory	Naive	Memory
	(c.p.m. × 10^{-3})			
None	0·12 (0·07)	0·11 (0·07)	0·03 (0·02)	0·04 (0·02)
IL-2 (10 U/ml)	0·39 (0·20)	2·74 (0·80)	0·43 (0·13)	2·99 (0·95)
IL-2 (100 U/ml)	0·72 (0·43)	5·61 (1·28)	2·56 (0·91)	10·90 (4·19)
IL-2 (1000 U/ml)	1·14 (0·60)	11·18 (2·08)	8·62 (2·30)	22·64 (6·17)
PPD	0·20 (0·07)	21·93 (6·48)	0·04 (0·01)	4·88 (1·60)

Memory (CD45RO+) and naive (CD45RO−) populations of CD4+ and CD8+ T cells were obtained from PPD-reactive adult donors. Each isolated cell population (5 × 10^4/well) was stimulated by various concentrations of IL-2 for 5 days. For antigenic responses, PPD (1 μg/ml) was added together with irradiated monocytes. [^{3}H]TdR incorporation was measured during the last 12 hr of culture and is expressed as the mean, with SEM in parentheses, from four donors.

significantly expressed IL-2Rα. Unlike IL-2Rβ expression of adult CD8+ T cells, adult CD4+ T cells were seen to exhibit a somewhat bimodal distribution of IL-2Rα expression. In addition, it should be noted that the degree of expression of IL-2R subunits on CD8+ and CD4+ T cells varied from donor to donor. In contrast to the adult blood, only few CD4+ and CD8+ T cells obtained from the newborn blood could be stained by mAb against IL-2Rα as well IL-2Rβ (Fig. 1b). These observations suggested that a defined population of CD4+ and CD8+ T cells in the adult blood might express either chain of IL-2R.

Expression of IL-2R (α and β) subunits by memory and naive cells of adult CD4+ and CD8+ T cells

On the basis of various isoforms of CD45, human peripheral CD4+ and CD8+ T cells can be divided further into two populations, namely the memory cells, which are able to respond to soluble antigens, and the naive cells, which have not yet been stimulated by antigens.[19,20] While naive T cells are confined to the CD45RA+ subset, memory T cells are identifiable by CD45RO expression. Reasonably, it has been reported that the frequency of CD4+ and CD8+ T cells expressing CD45RO is scarce at birth and increases with advancing age.[21] Based on our observations above, a possibility was raised that T cells expressing IL-2R subunits might mainly reside in the circulating memory cell pool.

We next examined the different expression of two IL-2R subunits between the memory and naive populations of CD4+ or CD8+ T cells in adult blood. CD4+ and CD8+ T cells were enriched for memory and naive cells by depletion of CD45RA+ and CD45RO+ cells, respectively, in order to subsequently evaluate their expression of IL-2Rα and IL-2Rβ by two-colour immunofluorescence staining. As can be seen in Fig. 2, the enrichment of memory cells in CD4+ T cells and CD8+ T cells resulted in markedly enhanced expression of IL-2Rα and IL-2Rβ, respectively. In contrast, separated naive CD4+ and CD8+ T cells showed less IL-2Rα or IL-2Rβ just as if they were neonatal T cells.

Proliferative responses of memory CD4+ and CD8+ T cells to exogenous IL-2

As shown in Table 1, the appreciable proliferation in response to IL-2, in addition to the PPD-induced response, was exclusively induced in the memory populations of CD4+ and CD8+ T cells in PPD-reactive adult donors. It should be noticed that memory CD4+ T cells required relatively higher doses of IL-2 for induction of IL-2-mediated responsiveness than CD8+ ones, apparently reflecting their expression of IL-2Rα with less IL-2 binding. However, based on the current concept that signal transduction via IL-2 receptors is a function of IL-2Rβ but not IL-2Rα,[3-5] it would not be expected that memory CD4+ T cells with restricted IL-2Rα expression actually proliferate in response to exogenous IL-2. It has been reported that IL-2 could up-regulate its own receptors.[22] So, it is plausible to suppose that relatively high doses of IL-2 might induce IL-2Rβ to be expressed on memory CD4+ T cells, resulting in the formation of functional high-affinity receptors. In fact, we observed that memory CD4+ T cells cultured with IL-2 expressed IL-2Rβ with enhanced levels of IL-2Rα as well (data not shown).

DISCUSSION

Two subunits of the receptors for IL-2 have been identified, a 55,000 MW glycoprotein (α-chain) with low affinity binding to IL-2 and a 75,000 MW glycoprotein (β-chain) with an intermediate affinity binding to IL-2.[3-5] The high affinity IL-2R is composed of both α and β subunits. Although both IL-2R subunits appear simultaneously on activated T and B cells, it has been demonstrated that IL-2Rβ is constitutively expressed on NK cells in the peripheral blood.[11,12,17,18] Radiolabelled IL-2 cross-linking experiments have indicated that low numbers of freshly isolated T cells express IL-2Rβ on their surfaces.[12,33] Consistent with results of other studies,[17] we have demonstrated, by two-colour immunofluorescence using anti-IL-2Rβ mAb, that IL-2Rβ is weakly expressed on CD8+ but not CD4+ T cells freshly isolated from adult blood. Although prior studies have suggested that substantial numbers of IL-2Rα-bearing T cells are not present in the circulation,[24] it was found that some CD4+ T cells unequivocally expressing IL-2Rα circulate in the adult blood. Similar observations have recently been reported by Jackson *et al.*[25]

In the present work, we have demonstrated that both CD4+ and CD8+ T cells from the neonatal blood express only a few IL-2R subunits. While a proportion of CD4+ and CD8+ T cells in the adult blood, which carry T-cell receptor (TcR) α/β heterodimers, express α or β subunits of the IL-2R, most T cells bearing TcR γ/δ heterodimers appear to express IL-2Rβ.[26] In unpublished observations, we found that most TcR γ/δ T cells expressed IL-2 Rβ, even at around 1 month of age, although it was hard to evaluate IL-2R expression on TcR γ/δ T cells in the neonatal blood, due to the paucity of these cells at birth. These observations imply that, while TcR γ/δ T cells as well as NK cells constitutively express IL-2Rβ, TcR α/β (CD4+ and CD8+) T cells come to express IL-2R subunits, seemingly with increasing exposure to external antigenic stimuli.

Memory and naive T-cell populations can be discriminated by differential expression of isoforms of CD45 (CD45RO or CD45RA).[19,20] Memory T cells are also characterized by enhanced levels of expression of various accessory molecules (such as CD2, CD29, CD54 and CD58), all of which may serve to activate T cells.[27] Wallace and Beverley[28] have recently demonstrated that unfractionated memory (CD45RO+) T cells show variable levels of CD25 (IL-2Rα). However, it remains to be determined whether CD25 might be expressed preferentially on CD4+ or CD8+ T cells. Our microscopic examinations disclosed that memory cells were slightly larger in size than naive cells (unpublished observations), indicating that memory cells may not be actually resting or rather be maintained in some activated states. In the present work, we asked whether IL-2R subunits might be predominantly expressed on *in vivo* antigen-primed or memory populations of CD4+ and CD8+ T cells. Memory (CD45RA−, CD45RO+) and naive (CD45RA+, CD45RO−) T cells from the adult blood were enriched by depletion of CD45RA+ and CD45RO+ cells, respectively, and subsequently evaluated for expression of IL-2R subunits on CD4+ and CD8+ T cells. The results presented in the present study clearly support the assumption that expression of IL-2R subunits might be restricted to memory populations of CD4+ and CD8+ T cells.

Why blood CD4+ and CD8+ T cells favoured expression of IL-2Rα and IL-2Rβ, respectively, is unknown. In this regard, malignant CD4+ cells in adult T-cell leukaemia have been shown to express the IL-2Rα but not IL-2Rβ.[29] Antigenic boosting induces an increase in IL-2Rα+ CD4+ T cells in the blood of immunized persons.[30] Expansion of IL-2Rβ+ CD8+ T cells was seen in Epstein–Barr virus-induced infectious mononucleosis.[31] We have shown that isolated memory CD4+ and CD8+ T cells, unlike naive ones, are able to proliferate in response to exogenous IL-2, corresponding to their expressed IL-2R subunits. According to the significance of IL-2 for T-cell growth, it is plausible to suppose that memory T cells could readily respond to recall antigens, their expressed IL-2R subunits being largely involved in antigen-induced proliferation. It seems that reciprocal expression of IL-2 subunits on T-cell subsets might be related to their inherent biological roles.

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