Peripheral T Cell Survival Requires Continual Ligation of the T Cell Receptor to Major Histocompatibility Complex–Encoded Molecules

By Jörg Kirberg,* ‡ Anton Berns,* and Harald von Boehmer§

From the *Netherlands Cancer Institute, Division of Molecular Genetics, 1066 CX Amsterdam, The Netherlands; ‡Basel Institute for Immunology, 4005 Basel, Switzerland; and §Institute Necker, INSERM 373, F-75730 Paris Cedex 15, France

Summary

In the thymus, T cells are selected according to their T cell receptor (TCR) specificity. After positive selection, mature cells are exported from primary lymphoid organs to seed the secondary lymphoid tissue. An important question is whether survival of mature T cells is an intrinsic property or requires continuous survival signals, i.e., engagement of the TCR by major histocompatibility complex (MHC) molecules in the periphery, perhaps in a similar way as occurring during thymic positive selection. To address this issue we used recombination-activating gene (Rag)-deficient H-2b mice expressing a transgenic TCR restricted by I-E\textsuperscript{d} class II MHC molecules. After engraftment with Rag\textsuperscript{-/-} H-2d fetal thymi, CD4\textsuperscript{+}8\textsuperscript{-} peripheral T cells emerged. These cells were isolated and transferred into immunodeficient hosts of H-2b or H-2d haplotype, some of the latter being common cytokine receptor \(\gamma\) chain deficient to exclude rejection of H-2b donor cells by host natural killer cells. Our results show that in the absence, but not in the presence, of selecting MHC molecules, peripheral mature T cells are short lived and disappear within 7 wk, indicating that continuous contact of the TCR with selecting MHC molecules is required for survival of T cells.

Materials and Methods

Mice. BALB/c and BALB/c nu/nu mice were from IFFA-Credo (Orléans, France), BLACK nu/nu mice were from Bomholtgard (Ry, Denmark) and screened for H-2b homozygosity. Rag-2– (18) and Rag-1– (19) deficient mice were H-2b homozygous.

1Abbreviations used in this paper: dGuo, 2'-deoxyguanosine; Rag, recombination activating gene; sIg, surface Ig; HSA, heat stable antigen.
Large numbers of cells recovered from lymph nodes each multiplied by the percentage of cells within the region of interest as determined by FACS® analysis. In case of staining before and after depletion of sIg+ cells, the average of both determinations, taking into account sIg+ cell depletion, was used for calculation. Note that from the experience of others, the recovery of lymphocytes immediately after transfer is estimated to be ~20% after intravenous transfer (14, 24).

Lymphocyte Proliferation Assay. Cell sorter purified responder cells were cultured with 5 \times 10^5 X-irradiated (2,200 rad) stimulator cells in 200 µl Iscove’s modified Dulbecco’s medium supplemented with FCS (10%), β-mercaptoethanol (5 \times 10^{-5} M), penicillin (100 IU/ml), and streptomycin (100 mg/ml). To some cultures, peptide 107-119 of influenza hemagglutinin (SVSSFERFEIFPK) was added at a final concentration of 5 µM. Cultures were kept in a water-saturated atmosphere of 6% CO_2 in air at 37°C. After 48–60 h, 1 µCi [3H]thymidine (Amersham Corp., Arlington Heights, IL) was added and cells were cultured for a further 12–24 h when they were harvested. Incorporation radioactivity was measured by standard liquid scintillation counting.

Fetal T evening H-2b ABII TCR Rag-2\textsuperscript{d} thymi were isolated at days 14–16 of gestation (plug day = day 0). For some experiments (Fig. 1), thymus lobes were isolated from BALB/c mice and cultured 5 d in medium containing 1:35 mM 2-deoxyglucose (dGlu; Sigma Chemical Co., St. Louis, MO). 1–2 lobes were transplanted under the kidney capsule of H-2b ABII TCR Rag-2\textsuperscript{d} mice. 6–16 wk later, cells were isolated from lymph nodes and spleen, stained with CD4, CD8, and I-A\textsuperscript{d}-specific mAbs, and cell sorter purified. CD4\textsuperscript{+}8\textsuperscript{+}I-A\textsuperscript{d} and CD4\textsuperscript{+}8\textsuperscript{-}I-A\textsuperscript{d} cells were injected intravenously into various 4–6-wk-old recipient mice.

Results

H-2b-restricted CD4\textsuperscript{+}8\textsuperscript{-} T cells in T hymus Grafted ABII TCR Rag-2\textsuperscript{d} H-2\textsuperscript{d} Mice. In our studies, we used ABII TCR transgenic mice that express a transgenic TCR specific for peptide 111-119 of influenza hemagglutinin presented by

![Figure 1. Thymic development of CD4\textsuperscript{+}8\textsuperscript{-} T cells in H-2b fetal thymus-grafted H-2b ABII TCR Rag-2\textsuperscript{d} H-2\textsuperscript{d} Mice. In our studies, we used ABII TCR transgenic mice that express a transgenic TCR specific for peptide 111-119 of influenza hemagglutinin presented by...](image-url)
I-E<sup>d</sup> class II MHC molecules. These mice were crossed onto the Rag<sup>−/−</sup> background to exclude the interference of TCRs with unknown specificity due to lack of allelic exclusion of the TCR-<i>α</i> locus (25, 26). To obtain T cells that are selected in the thymus but not able to encounter the selecting MHC molecules in peripheral lymphoid tissue, we transplanted H-2<sup>d</sup> ABII TCR Rag<sup>−/−</sup> mice with fetal thymus lobes from H-2<sup>d</sup> Rag<sup>−/−</sup> mice that had previously been transplanted with fetal thymus lobes from H-2<sup>d</sup> Rag<sup>−/−</sup> mice. Cells were analyzed by four-color flow cytometry as shown.

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Figure 2. CD4<sup>+</sup>8<sup>+</sup> lymphocytes are present in H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice grafted with an H-2<sup>d</sup> fetal thymus. Lymphocytes were recovered from H-2<sup>d</sup> ABII TCR Rag<sup>−/−</sup> and H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice at the time of the experiment. (Image not shown.) Under such conditions, the thymus graft is seeded by T cell precursors of the host such that mature CD4<sup>+</sup>8<sup>+</sup> T cells with the transgenic TCR develop in the grafted H-2<sup>d</sup> thymus, but not the host H-2<sup>b</sup> thymus (Fig. 1). Subsequently, CD4<sup>+</sup>8<sup>+</sup> T cells from the grafted thymus are exported to the periphery (Fig. 2). Such CD4<sup>+</sup>8<sup>+</sup> peripheral T cells are not present in H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice, since cells with the I-E<sup>d</sup>-restricted ABII TCR cannot develop in a H-2<sup>b</sup> thymus (8). There are also CD4<sup>+</sup>8<sup>+</sup> low T cells in these mice that will be discussed below.

To confirm that the CD4<sup>+</sup>8<sup>+</sup> T cells in grafted mice were functionally mature, cells from such mice as well as from H-2<sup>d</sup> ABII TCR Rag<sup>−/−</sup> mice were isolated and stimulated with antigen presented by H-2<sup>d</sup> APCs. As shown in Table 1, both populations of cells gave proliferative responses that were in the same order of magnitude, indicating that they had acquired functional competence.

The data, however, present a clear difference in the absolute number of CD4<sup>+</sup>8<sup>+</sup> T cells in the thymus-grafted H-2<sup>d</sup> ABII TCR Rag<sup>−/−</sup> mice and the H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice in that the former contained far fewer cells than the latter (2.9 × 10<sup>6</sup>; n = 3); and ranging between 10<sup>6</sup> to 10<sup>8</sup>, respectively). This difference could be due to the fact that fewer CD4<sup>+</sup>8<sup>+</sup> T cells are produced/exported from the grafted thymus and/or the fact that the lack of I-E<sup>d</sup> class II MHC molecules in the peripheral lymphoid organs of grafted H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice resulted in a shorter life span of these cells. Further, the few CD4<sup>+</sup>8<sup>+</sup> T cells might be continuously renewed and/or depend on few I-E<sup>d</sup>-expressing cells originating from the fetal thymus graft. To address the issue of whether expression of MHC molecules the CD4<sup>+</sup>8<sup>+</sup> T cells were selected on in the thymus was required for their peripheral survival, we performed transfer experiments into immunodeficient hosts expressing different MHC molecules.

CD4<sup>+</sup>8<sup>+</sup> Peripheral T cells from H-2<sup>b</sup> T thymus-grafted H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice were transferred into either H-2<sup>b</sup> or H-2<sup>d</sup> immunodeficient recipient mice. As shown in Fig. 3, no 6.5 × 10<sup>6</sup> CD4<sup>+</sup>8<sup>+</sup> cells could be detected in either H-2<sup>b</sup> nu/nu or H-2<sup>d</sup> nu/nu recipient mice 7 wk after transfer, whereas 6.5 × 10<sup>5</sup> CD4<sup>+</sup>8<sup>+</sup> cells were found in the H-2<sup>b</sup> but not H-2<sup>d</sup> recipients. (Similar results were obtained after transfer into H-2<sup>d</sup> Rag<sup>−/−</sup>/ Rag<sup>−/−</sup> recipient mice, data not shown.) In terms of engraftment, this result would be compatible with the notion that the transferred cells expressing H-2<sup>b</sup> MHC molecules only, could engraft in H-2<sup>b</sup> hosts, but not in H-2<sup>d</sup> hosts because of rejection by host NK cells (28-30). To circumvent this problem, a similar transfer of cells from thymus-grafted H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice was performed into H-2<sup>b</sup> Rag<sup>−/−</sup> and H-2<sup>d</sup> Rag<sup>−/−</sup>-IL-2R<sup>γ</sup>−/− mice, devoid of NK cells.

Table 1. Proliferation of CD4<sup>+</sup>8<sup>+</sup> ABII TCR Lymphocytes Positively Selected in Endogenous or Transplanted H-2<sup>b</sup> T thymi

<table>
<thead>
<tr>
<th>Stimulators (2,200 rad)</th>
<th>BALB/c nu/nu</th>
<th>BALB/c nu/nu + peptide</th>
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<tr>
<td>ABII RAG-2&lt;sup&gt;−/−&lt;/sup&gt;-H-2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>600</td>
<td>15,000</td>
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<tr>
<td>ABII RAG-2&lt;sup&gt;−/−&lt;/sup&gt;-H-2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>260</td>
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<td>FThy RAG-2&lt;sup&gt;−/−&lt;/sup&gt;-H-2&lt;sup&gt;d&lt;/sup&gt;</td>
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CD4<sup>+</sup>8<sup>+</sup> lymphocytes were cell sorter purified from H-2<sup>d</sup> ABII TCR Rag<sup>−/−</sup> and H-2<sup>b</sup> ABII TCR Rag<sup>−/−</sup> mice that had previously been transplanted with an H-2<sup>d</sup>Rag<sup>−/−</sup> fetal thymus. 5 × 10<sup>6</sup> responder cells were cultured with irradiated BALB/c nu/nu stimulators. To some cultures, peptide had been added as source of antigen.
As shown in Fig. 4, 6.5\(^{+}\) CD4\(^{+}\)8\(^{+}\) cells survived only in H-2d recipients, whereas 6.5\(^{+}\)CD4\(^{2-}\)8\(^{low}\) cells survived both in H-2b and H-2d recipients when analyzed 7 wk after transfer. Taken together, these results show that in H-2b recipients, NK cells do not reject the transferred cells as 6.5\(^{+}\)CD4\(^{2-}\)8\(^{low}\) cells survive, but 6.5\(^{+}\)CD4\(^{+}\)8\(^{+}\) cells vanish due to the lack of H-2d MHC molecules. In contrast, 6.5\(^{+}\)CD4\(^{+}\)8\(^{+}\) cells survive long term in the presence of H-2d MHC molecules once not rejected by NK cells.

In other experiments, we have followed the fate of CD4\(^{+}\)8\(^{+}\) and CD4\(^{2-}\)8\(^{low}\) cells from thymus-grafted H-2b/d ABII TCR Rag\(^{-/-}\)mice upon transfer into either H-2b or H-2d immunodeficient recipient mice. (The H-2b/d ABII TCR Rag\(^{-/-}\) mice themselves cannot select the ABII TCR in the thymus due to preferential pairing of E\(\alpha\) with E\(\beta\)b chains, references 8, 31, 32.) 3 d after transfer, both populations were present in H-2b nu/nu and H-2d nu/nu recipients. 7 wk later, both subsets were present in H-2d nu/nu recipients but could no longer be found in H-2b nu/nu recipients (data not shown, made available to reviewers). This might indicate that the shared class I MHC molecule expression between H-2b/d hybrid donor and homozygous host protected the donor cells from NK cell-mediated lysis in H-2d homozygous hosts. In both of these cases, T cells could have been stimulated by antigen. The high proportion of proliferating CD4\(^{+}\)8\(^{+}\) T cells at various points in time after thymus transfer could indicate that this was indeed the case, and some CD4\(^{+}\)8\(^{+}\) T cells might have rather disappeared because of exhaustion (39, 40). These possibil-

**Discussion**

Our data show that appropriate MHC molecules are required to support the survival of mature \(\alpha/\beta\) T cells in peripheral lymphoid tissue; a conclusion in line with previously published experiments (15). In the latter study, however, polyclonal CD4\(^{+}\)8\(^{-}\) T cells in thymus-grafted Rag class II MHC double deficient mice appeared to survive much longer since significant numbers of cells could still be found 16 wk after export from the thymus ceased. This may be due to the fact that in these experiments CD4\(^{+}\)8\(^{-}\) T cells with class I MHC–restricted TCRs (36–38) could interact with class I MHC molecules expressed in the peripheral lymphoid tissue or due to the fact that some class II MHC–positive cells had migrated from the transplanted thymus into the periphery. In both of these cases, T cells could have been stimulated by antigen. The high proportion of proliferating CD4\(^{+}\)8\(^{-}\) T cells at various points in time after thymus transfer could indicate that this was indeed the case, and some CD4\(^{+}\)8\(^{-}\) T cells might have rather disappeared because of exhaustion (39, 40). These possibil-

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**Figure 3.** CD4\(^{+}\)8\(^{+}\) lymphocytes from H-2d thymus-grafted H-2b ABII TCR Rag\(^{-/-}\)mice die in H-2b adoptive hosts. 7.5 \(\times\) 10\(^{5}\) CD4\(^{+}\)8\(^{+}\) and 5 \(\times\) 10\(^{5}\) CD4\(^{+}\)8\(^{low}\) lymphocytes from H-2b Rag\(^{-/-}\)fetal thymus-transplanted H-2b ABII TCR Rag\(^{-/-}\) mice were adoptively transferred into H-2b and H-2b nu/nu mice. 7 wk later, cells from lymph nodes and spleen (RBCs lysed) were isolated, depleted of sIg\(^{+}\) cells, and analyzed by four-color flow cytometry. Data from lymph nodes and spleen gave similar results. Calculated numbers of 6.5\(^{+}\)HSA\(^{2-}\) cells were 5,600, 6,500, and 1,800 for CD4\(^{+}\)8\(^{+}\) and 1,800, 463,600, and 400 for CD4\(^{+}\)8\(^{low}\) cells in unmanipulated H-2b (one mouse), injected H-2b (average of two mice), and injected H-2d (average of two mice) nu/nu mice, respectively. (Note that numbers also contain the calculated background values of mice not injected.) Another experiment and two experiments using H-2b Rag\(^{-/-}\) and H-2b Rag\(^{-/-}\) recipients gave similar results.
Figure 4. CD4+8− lymphocytes from H-2d thymus-grafted H-2b ABII TCR Rgag−/− mice survive in H-2d Nk cell-deficient adoptive hosts. 10^6 CD4+8− and 10^5 CD4+8^low lymphocytes from H-2b Rgag−/− fetal thymus-transplanted H-2b ABII TCR Rgag−/− mice were adoptively transferred into H-2b Rgag−/− and H-2d Rgag−/− IL-2R γ−/− mice. 7 wk after transfer, cells from lymph nodes and spleen were analyzed as in Fig. 3. Calculated numbers of 6.5^HSA− cells were 900, 13,500, 5,900, and 3 × 10^6 for CD4+8− and 600, 6,100, 7.6 × 10^5, and 1.5 × 10^6 for CD4+8^low cells in unmanipulated H-2b Rgag−/− IL-2R γ−/−, unmanipulated H-2d Rgag−/− (not shown), injected H-2b Rgag−/−, and injected H-2d Rgag−/− IL-2R γ−/− mice, respectively. Expansion in Rgag-deficient H-2d mice was consistent with previous data (41). We also performed this type of experiment with two thymectomized H-2d Rgag−/− IL-2R γ−/− mice and obtained similar results.

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In line with our previous observations, we noticed expansion of CD4+8− ABII TCR-expressing cells in H-2d mice (reference 41 and this report). Currently, it is not clear whether T cell survival in the absence (13, 14) or the presence (41) of proliferation (or both possibilities) reflects the normal physiologic situation. Interestingly, normal mice that had been thymectomized have some cells of naive phenotype that label with BrdU (42).

Irrespective of the MHC environment, CD4+8^low cells that are not dependent on positive selection in the thymus, did expand after transfer. Presently, the biology of these cells is not well understood and it has been speculated that these cells represent γ/δ lineage T cells expressing the transgenic α/β TCR (27).

While it becomes established that T cells require the interaction of their TCRs with selecting MHC molecules for survival in the peripheral lymphoid tissue, the mechanism behind this requirement is unknown. In the thymus, immature CD4+8− cells express low levels of the cell death-repressing bcl-2 protein. They have a half life of 3 d (43) unless their TCR binds with sufficient affinity to self-MHC molecules resulting in maturation that is accompanied by bcl-2 upregulation (44–47). One might then speculate that the level of bcl-2 expression and, hence, survival is (indirectly) regulated by TCR ligation with selecting MHC molecules in the absence of antigen. In that respect, peripheral survival could be similar to thymic positive selection. The data reported on T cells from bcl-2-deficient mice are compatible with such a hypothesis (48–51). We have investigated bcl-2 expression by intracellular staining of CD4+8− cells from thymus-grafted H-2d ABII TCR Rgag−/− and H-2d ABII TCR Rgag−/− mice. However, the differences we observed were far less dramatic than during thymic positive selection (mean fluorescence reduced to 74 compared to 98 in controls, whereas in the thymus, a threefold difference was detectable: 44 versus 120 in an independent experiment). This could be due to the fact that cells with low bcl-2 expression are rapidly dying and eliminated and escape detection.

Further, it will be of interest to determine whether TCR contact with selecting MHC molecules on any type of cell is sufficient for T cell survival or whether the selecting MHC molecules have to be encountered on a specific cell type. The latter would be analogous to the requirement of TCR–MHC molecule interaction on thymic epithelial cells for thymic positive selection (3). Interestingly, RelB-deficient mice that lack dendritic cells have an increased proportion of activated T cells, whereas absolute numbers of T cells are reduced (52, 53). The former might be due to limited self-censorship in the thymus followed by peripheral activation by self-antigens the T cells were not tolerized for in the thymus (52–55). The latter, however, could indicate that (naive) peripheral T cell survival requires TCR interaction with selecting MHC molecules on dendritic cells. The data of DeKoning et al. on transfer of naive TCR transgenic T cells into RelB−/− mice support this theory (53).
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Address correspondence to Jörg Kirberg, Division of Molecular Genetics, The Netherlands Cancer Institute, Pienemanlaan 121, N L-1066 CX Amsterdam, The Netherlands. Phone: 0031-20-512 19 98; FAX: 0031-20-512 20 11; E-mail: kirberg@nki.nl

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