The CD43 130-kD Peripheral T-Cell Activation Antigen Is Downregulated in Thymic Positive Selection

By Losley G. Ellies, Wen Tao, Waltraud Fellinger, Hung-Sia Teh, and Herrmann J. Ziltener

Specific glycoforms of CD43, the major O-glycosylated cell-surface protein on T lymphocytes, can affect cell adhesion according to the types of carbohydrate side chains carried. In the peripheral immune system, CD43 130 kD, which carries core 2 O-glycan structures on its surface, is an activation antigen expressed on both CD4 and CD8 single-positive (SP) T cells. We have previously shown that the 115-kD resting and 130-kD activation glycoforms of murine CD43 are differentially regulated on peripheral SP T cells. In this study, we used transgenic mice expressing T-cell receptors (TCRs) specific for antigens presented by class I and class II major histocompatibility complex (MHC) molecules to determine whether CD43 glycoforms are involved in thymocyte differ-

entiation. Positive selection in these mice results in an increase in the production of CD8 and CD4 SP T cells, respectively, which express the transgenic TCR. Positive selection is also accompanied by the upregulation of TCR, CD69, and CD5. Using these markers to define stages of thymocyte maturation, we found that CD43 130 kD was downregulated in the positive selection of CD4 CD8 double-positive thymocytes expressing a class I but not class II MHC-restricted TCR. These data suggest that core 2 glycosyltransferase (C2GnT) modulated expression of CD43 glycoforms may be involved in thymic selection events.

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Materials and Methods

Mice. The αβ TCR transgenic mice with specificity for the male (H-Y) antigen were bred on an H-2d (nonselecting) or H-2b (selecting) background in the animal facility in the Department of Microbiology at the University of British Columbia as previously described. The H-Y TCR transgenic mice with the β2-microglobulin null mutation were produced as previously described. Breeders for the 2C transgenic mice expressing the αβ antigen receptor from the cytotoxic T-clone 2C on an H-2d background were produced.

From The Biomedical Research Centre, and the Departments of Clinical Dental Sciences, Microbiology and Immunology, and Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada.

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vided by Dr Dennis Loh (Howard Hughes Medical Institute, Washington University, St Louis, MO). Breeders for the AND TCR transgenic mice with TCR specificity for pigeon cytochrome c in the context of I-E^d were obtained from Dr Steve Hedrick (Department of Biology and Cancer Center, University of California, San Diego, La Jolla, CA). C57BL/6 (B6) mice were obtained from The Jackson Laboratories (West Grove, PA). Mice used in all experiments were 4 to 8 weeks old.

In vitro panning of thymocytes. Petri dishes were coated with 20 μg/mL rabbit-antirat IgG for 1.5 hours and washed with phosphate-buffered saline. Twenty micrograms per milliliter of either monoclonal antibody (MoAb) GK1.5 (anti-CD4), HO2.2 (anti-CD8.2), or 83-12-5 (anti-CD8.1) was added for 1.5 hours. The plates were rinsed with 0.2 mol/L Na2B4O7 buffer, pH 9, and 31 mg dimethyl pimelimidate in 6 mL 0.2 mol/L Na2B4O7 buffer was added at room temperature for 30 minutes with gentle shaking to crosslink the MoAbs. The plates were rinsed in 0.2 mol/L ethanolamine, pH 8.0. Single-cell suspensions of thymocytes were isolated from C57BL/6, H-2^d, and H-2^k age-matched female mice and panned at 4°C over plates coated with anti-CD8 and then anti-CD4 MoAbs to obtain DP thymocytes of greater than 95% purity.

Isolation of peripheral T lymphocytes.Peripheral lymph nodes were dissected from age-matched C57BL/6 and H-2^k mice. Single-cell suspensions were double stained with either anti-CD4-phycocerythrin (PE) and S7-flourescein isothiocyanate (FITC) or 1B11-FITC, or with anti-CD8-PE and S7-FITC or 1B11-HTC.

Antibodies and flow cytometry. 1B11 (anti-CD4 130 kD) and 1F10 (control IgG2a) were biotinylated and FITC labeled according to the methods of Goding. Anti-CD44 and T3.70 (anti-Va H-Y TCR) were affinity purified from ascites and spent culture medium, respectively, and FITC labeled according to the same method. S7-FITC (anti-CD4 115 kD), S7-biotin, S7-PE, 1B11-PE, anti-CD69-biotin, anti-CD5-biotin, anti-CD8-FITC, anti-CD8-PE, anti-CD4-PE, and streptavidin Cy-chrome were all obtained from PharMingen (San Diego, CA).

Cells for flow cytometry were suspended in fluorescence-activated cell sorting (FACS) buffer and incubated with appropriate MoAbs for 30 minutes at 4°C in 96-well round-bottom plates (Nunclon; InterMed, Roskilde, Denmark). Cells were washed twice and streptavidin Cy-chrome added if necessary for a further 30 minutes of incubation. The cells were washed twice and resuspended in FACS buffer for analysis on a FACScan IV flow cytometer using Lysis II software (Becton Dickinson, Mountain View, CA). Data were collected on 5,000 to 10,000 viable cells as determined by forward and side light scatter.

In vitro thymocyte stimulation. Thymocytes (5 × 10^3) from female H-2^d H-Y TCR transgenic mice with the β2-microglobulin null mutation were cultured in a volume of 0.2 mL in Iscove’s Modified Dulbecco’s Medium supplemented with 10% fetal calf serum and 5 × 10^-5 mol/L β-mercaptoethanol in flat-bottomed microtiter wells precoated with or without 10 μg/mL of 2C11 (anti-CD3). After a culture period of 16 hours the thymocytes were obtained and subjected to flow cytometric analysis for expression of indicated cell-surface markers.

RESULTS

Downregulation of CD43 130 kD is associated with positive selection of the H-Y TCR. We used TCR transgenic mice to evaluate the potential participation of CD43 in T-cell development. The first series of experiments involved the use of transgenic mice expressing the H-Y TCR specific for the male antigen presented by the D^b class I MHC molecule. Previous studies have shown that in mice expressing D^b and this transgenic TCR, negative selection of DP thymocytes occurs in male mice, resulting in the deletion of these thymocytes. Positive selection occurs in female mice, resulting in an increased production of CD8 SP thymocytes expressing the transgenic TCR. To ensure that we were not observing an effect unique to the presence of the transgenic TCR, normal B6 mice were included as additional controls, CD43 115-kD and 130-kD expression was examined on the DP population of thymocytes using MoAbs S7 and 1B11, which recognize these glycoforms specifically. This was done by triple staining thymocytes using MoAbs specific for CD4, CD8, and either S7 or 1B11 and gating on DP cells. As we have described previously, the profile of CD43 130 kD in normal murine thymic T-cell subsets showed that DN, DP, and CD8 SP T cells were all positive for CD43 130 kD (MoAb 1B11) whereas CD4 SP T cells were mostly negative for CD43 130 kD. All Tm cells were strongly positive for CD43 115 kD (MoAb S7).

As shown in Fig 1A, positive selection of the H-Y TCR in female H-2^d mice results in the overproduction of CD8 SP thymocytes as previously described. There was no overproduction of CD8 SP thymocytes in H-2^k mice. Determination of the expression level of CD43 130 kD showed that in contrast to the marked upregulation of CD43 130 kD observed in the periphery during T-cell activation, a moderate downregulation of this antigen occurred in DP thymocytes in female H-2^d, but not H-2^k H-Y mice or in B6 mice (Fig 1C). This downregulation of the CD43 130-kD glycoform was specific because there were no significant changes in the expression levels of CD43 115 kD (S7) or CD44 on DP thymocytes. These data suggest that the downregulation of CD43 130 kD in DP thymocytes is associated with positive selection of the H-Y TCR.

The positive selection process is associated with the upregulation of TCR, CD5, and CD69 on DP thymocytes. Therefore, it was important to determine whether the downregulation of CD43 130 kD was concomitant with the upregulation of these markers during positive selection. DP thymocytes of greater than 95% purity from female H-2^d or H-2^k H-Y TCR transgenic mice were obtained by panning with anti-CD4 and anti-CD8 MoAbs. Figure 2A provides the controls indicating that the expression levels of CD5, CD69, and T3.70 (detects the transgenic TCR α chain) on DP thymocytes from H-2^d transgenic mice were upregulated in comparison to H-2^k transgenic mice. The expression level of CD43 130 kD in relation to these markers was determined by double-staining DP thymocytes with 1B11 and CD5, CD69, or TCR. The 1B11 expression levels on DP thymocytes gated on CD5, CD69, or T3.70 positive cells are shown in Fig 2B. It is clear from this analysis that DP thymocytes from H-2^d transgenic mice expressed a lower level of the 1B11 epitope when compared with their H-2^k counterparts. These results provide additional evidence that the positive selection of DP thymocytes expressing the H-Y TCR is associated with the specific downregulation of the CD43 130-kD glycoform.

TCR signaling of DP thymocytes is insufficient to downregulate CD43 130 kD. To determine whether in vitro stimulation of DP thymocytes can directly mediate the down-
Fig 1. Downregulation of CD43 130 kD is associated with positive selection of thymocytes in H-2b H-Y transgenic mice. (A) Thymocytes from control and nonselecting (H-2d) and selecting (H-2b) backgrounds for the H-Y TCR transgenic mice were stained with anti-CD4 and anti-CD8 and quadrant statistics performed. (B) Thymocytes from B6 (thin line), H-2d H-Y (dotted line), or H-2b H-Y (bold line) mice were gated on DP cells (top right corner of contour plots in [A]) and in overlay histograms were examined for expression of 1F10, an isotype control MoAb; MoAb S7, recognizing CD43 115 kD; or anti-CD44. IC11 expression on DP thymocytes from B6, H-2d H-Y, or H-2b H-Y mice. The 1B11 gate was chosen arbitrarily as the mid-point of 1B11 fluorescence of DP thymocytes from B6 mice.

Regulation of CD43 130 kD, we stimulated thymocytes from H-2b H-Y TCR transgenic mice with the β2-microglobulin null mutation with immobilized anti-CD3ε for 16 hours and stained the cells for various cell surface markers after this incubation period (Fig 3). Thymocytes from these mice were used as they provide a source of thymocytes that have a large population of DP thymocytes which have been subjected to minimal selection. After the 16-hour culture period, the thymocytes were triple-stained with antibodies to CD4, CD8, and the indicated marker. The triple-stained thymocytes were gated for DP thymocytes and the expression level of the indicated marker in unstimulated or anti-CD3 stimulated thymocytes is shown. This analysis indicated that whereas the expression level of CD5 and CD69 were dramatically upregulated in anti-CD3 stimulated DP thymocytes, the expression level of 1B11, S7, and F23.1 were not significantly affected by anti-CD3 stimulation. Similarly, expression of the late activation marker of positive selection, CD44, was unaffected by anti-CD3 stimulation. These results indicated that the downregulation of CD43 130 kD during positive selection is dependent on interactions in addition to the TCR.

Downregulation of CD43 130 kD is associated with positive selection of class I but not class II MHC–restricted TCRs. To determine whether downregulation of CD43 130 kD is associated with positive selection of TCRs with different antigen specificity, we extended these analyses to two other transgenic TCRs. One of these TCRs is the 2C TCR, which is positively selected by K+b and is specific for the p2Ca peptide by L4 class I MHC molecules. The other is the AND TCR, which is specific for the pigeon cytochrome c peptide presented by E1 class II MHC molecules. As shown in Fig 4, downregulation of the CD43 130-kD glycoform was observed on 2C DP thymocytes but not on AND DP thymocytes. Each figure represents data from a single
Fig 2. Differential regulation of CD43 130 kD, CD5, CD69, and TCR during positive selection. (A) Panned DP thymocytes from H-2b (thin line and shaded area) and H-2d (bold line and clear area) H-Y transgenic mice were stained with a control MoAb, 1F10, anti-CD5, anti-CD69, or T3.70 (anti-H-Y α-TCR) and the plots overlaid. (B) Panned DP H-2d and H-2b H-Y thymocytes were double stained with 1B11 and either anti-CD5, anti-CD69, or T3.70. Expression of 1B11 was compared by gating on CD5, CD69, and T3.70 positive populations in (A) and overlaying the 1B11 profiles. In both panels fluorescence exceeding that of the control MoAb was used as the positive gate for these antibodies. The figures in (B) represent the percentage of cells positive for 1B11 in H-2d and H-2b mice (bold), respectively.

In each experiment and in each experiment the 1B11 positive gate was set above the level of staining of the 1F10 control MoAb. Thus, the observed difference in 1B11 signal reflects experimental variation. The important conclusion is that 1B11 was downregulated on DP thymocytes from 2C mice relative to AND mice. As observed for the H-Y DP thymocytes, there was no significant difference in the expression level of CD43 115 kD on DP thymocytes from AND mice. Surprisingly, the expression of CD43 115 kD was upregulated on DP thymocytes from 2C mice relative to B6 and AND TCR transgenic mice. This observation questions the validity of using the CD43 115-kD molecule as a cell-surface marker whose expression level is uninfluenced by thymic positive selection. The following considerations provide a likely explanation for the higher expression of S7 on DP thymocytes from 2C mice that is independent of thymic positive selection. Previous studies have shown that the 2C TCR has an apparently higher affinity for the positively selecting ligand in H-2b mice than the H-Y TCR. Evidence supporting this hypothesis is that immature DP thymocytes expressing the H-Y TCR in H-2b mice can tolerate a high level of transgenic CD8 expression whereas those expressing the 2C TCR cannot.29,30 Consistent with the hypothesis that DP thymocytes express a TCR with a higher-than-normal affinity for its selecting ligand, we found that DP thymocytes from H-2b 2C mice are considerably larger than DP thymocytes from B6 or AND transgenic mice (mean forward scatter of 480 channel units for 2C DP thymocytes vs 320 channel units for B6 and AND DP thymocytes). This increase in cell size likely accounted for the increase in S7 expression on DP thymocytes from 2C mice. More importantly, despite the increase in cell size, the expression of 1B11 was specifically downregulated on DP thymocytes from 2C mice relative to those from B6 and AND mice. These observations further support the conclusion that downregulation of CD43 130 kD is uniquely associated with the positive selection of class I MHC–restricted TCRs.

CD43 expression on mature lymphocytes is not affected by TCR transgenes. Previous studies have shown that whereas the 115 kD-glycoform of CD43 is common to all
DOWNREGULATION OF CD43 IN POSITIVE SELECTION

GATED ON DP T CELLS

CD5

CD69

F23.1

CD44

S7

1B11

Relative Cell Number

Relative Fluorescence Intensity

Fig 3. TCR stimulation is insufficient to induce CD43 130 kD down-regulation in DP thymocytes. Thymocytes from female H-2b H-Y TCR transgenic mice with the β2-microglobulin null mutation were stimulated with (bold line and clear area) or without (thin line and shaded area) 10 μg/mL of immobilized 2C11 (anti-CD3e) for 16 hours. After this culture period the thymocytes were triple stained with anti-CD4 and anti-CD8 and either CD5, CD69, F23.1 (specific for the transgenic TCR β chain), CD44, S7, or 1B11. Expression of the indicated cell-surface antigen on gated DP thymocytes are shown.

Peripheral T cells, the 130-kD glycoform of CD43 is differentially expressed on peripheral SP T cells. In particular, the high MW glycoform was expressed at a higher level on CD8 SP T cells than on CD4 SP T cells. Since we observed that the positive selection of DP thymocytes committed to the CD8 SP lineage was associated with a downregulation of the CD43 130-kD glycoform, it was important to determine that this downregulation of the CD43 130 kD during positive selection was a transient event. Therefore, we examined S7 and 1B11 expression on peripheral T lymphocytes isolated from lymph nodes of control C57BL/6 and H-2b transgenic mice. In accordance with our previous results, we found that S7 was expressed at a uniformly high level on both CD4 and CD8 SP T cells from either C57BL/6 mice or H-Y TCR transgenic mice. Importantly, the 1B11 epitope was differentially expressed on SP T cells, being expressed at a much higher level on CD8 than on CD4 SP T cells (Fig 5). These results indicate that the downregulation of CD43 130 kD during positive selection is a transient event and that the differential expression of CD43 glycoforms on T cells occurs at different developmental stages of the T-cell differentiation pathway.

DISCUSSION

Changes in carbohydrate antigens have been observed in the early stages of T-lymphocyte ontogeny, suggesting regulation of membrane glycoproteins by specific glycosyltransferase enzymes in this differentiation process. Other studies showed that the α2,3-sialyltransferase and the C2GnT are also expressed in a developmentally regulated manner in the thymus and C2GnT activity has been correlated with changes in cell surface oligosaccharides on CD43 and CD45. Furthermore, these O-glycan changes can modulate lymphocyte adhesion to TE cells via galectin-1-poly lactosamine interactions and modulate T cell apoptosis in vitro. Thus, differential expression of CD43 glycoforms may alter binding to CD43 ligands and modulate cellular signaling as well as change temporal interactions between thymocytes and TE cells.

The present study examines expression of the 115-kD resting CD43 glycoform and the 130-kD C2GnT modified activation CD43 glycoform in transgenic models of positive selection. We have shown that positive selection of class I (H-Y and 2C) but not class II (AND) MHC-restricted TCRs is associated with a downregulation of CD43 130 kD on DP thymocytes. These data indicate that CD43 may be involved in the process of positive selection and suggest that the C2GnT modification of CD43 may affect T-lymphocyte development at the DP stage. Interestingly, Baum et al have shown that the C2GnT was high in subcapsular and cortical human thymocytes and low in medullary thymocytes, suggesting that the level of enzyme activity drops as T lymphocytes mature. A role for the C2GnT-mediated downregulation of O-linked lactosamine side chains on CD43 at the DP stage of thymocyte development is supported by data from Perillo et al, which implicates an inhibition of O-glycan elongation in potentiation of the galectin-1 induced apoptosis of T cells.

In addition to CD43 130 kD, a novel 65-kD thymocyte surface protein referred to as F3Ag is also downregulated during the positive selection process. However, this antigen is downregulated during selection of both class I– and class II–restricted T cells in a manner that correlates with the efficacy of positive selection. Interestingly, whereas F3Ag remains low on CD4 SP T cells, it is re-expressed on a proportion of CD8 SP cells. Our data suggest that the downregulation of CD43 130 kD in mice carrying MHC class I–restricted transgenic
TCRs is also a transient event during positive selection, because CD8 SP T cells express moderate levels of CD43 130 kD. Downregulation of CD43 130 kD also occurs on CD4 SP T cells because DP T cells express CD43 130 kD whereas CD4 SP T cells express low levels of the antigen. However, results from the AND MHC class II-restricted TCR suggest that this downregulation occurs late in the selection process as opposed to the early downregulation associated with selection of MHC class I-restricted T cells.

Several studies suggest that the CD43 molecule can act as an accessory signaling molecule in monocytes and T lymphocytes. Recently, Sperling et al. showed that murine CD43 can provide a CD28-independent, costimulatory signal to antigen-specific T-cell responses resulting in T-lymphocyte proliferation. In addition, Manjunath and Ardman have evidence that CD43 regulates a 93-kD tyrosine phosphoprotein in the T-cell line CEM. However, in contrast to CD69 and CD5, which are upregulated during positive selection in a manner similar to activation of peripheral T lymphocytes, the CD43 130-kD glycoform is downregulated in this process. Furthermore, we showed that the in vitro cross-linking of the TCR on DP thymocytes did not result in the downregulation of CD43 expression. CD43 130 kD is a late-activation antigen in the periphery and we observed that the late-activation marker CD44 which has been reported to be upregulated during positive selection was also unaffected after 16 hours of 2C11 stimulation. Being a late-activation antigen, a role for CD43 glycoforms in negative selection seems unlikely because T-cell deletion is a rapid event as evidenced in male H-Y TCR mice that have very few DP T cells. These observations suggest that signals transmitted through the TCR are more distally coupled to CD43 than to CD5 and CD69. They also suggest that the activity of C2GnT is indirectly regulated by TCR signaling.

We have previously shown that CD43 glycoforms are differentially regulated on peripheral CD4 and CD8 SP T cells. Although CD43 115 kD is a pan-T-cell marker, CD43 130 kD is expressed on all CD8 SP T cells but only 10% to 15% of CD4 SP T cells. After in vivo immune stimulation, both CD43 115 kD and CD43 130 kD are upregulated on CD4 SP T cells; however, on CD8 SP T cells, CD43 115 kD is downregulated whereas CD43 130 kD is dramatically upregulated. The present study provides additional support for our previous finding that the 115-kD and 130-kD glycoforms of CD43 are functionally distinct. It also suggests a role for CD43 in regulating the positive selection of CD8 SP T cells. The presence of CD43 is clearly not necessary for positive selection of T lymphocytes to occur because CD43 knockout mice have normal numbers and proportions of CD4 and CD8 SP T cells. However, CD43-deficient T cells do show altered behavior such as enhanced proliferation and adhesion and impaired viral clearance. The downregulation of antigens such as CD43 130 kD and F3Ag during class I-restricted selection events may be important in the maturation of functionally competent cells. Further studies will be required to address these subtle effects.
then gated on either CD4 or CD8 and levels of S7 and lB11 compared
affected by the TCR transgene. Lymphocytes from C57BL/6 control
mice and female H-2b H-Y TCR transgenic mice were stained with
anti-CD4 and S7 or l811 or with anti-CD8 and S7 or 1811. Cells were
discussed and Soo-Jeet Teh for technical assistance.

Fig 5. CD43 expression on resting peripheral T lymphocytes is not
affected by the TCR transgene. Lymphocytes from C57BL/6 control
mice and female H-2b H-Y TCR transgenic mice were stained with
anti-CD4 and S7 or l811 or with anti-CD8 and S7 or 1811. Cells were
then gated on either CD4 or CD8 and levels of S7 and 1811 compared
between control (thin line and shaded area) and transgenic mice
(bold line and clear area).

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REFERENCES

1. Ritter MA, Boyd RL: Development in the thymus: It takes two
tango. Immunol Today 14:462, 1993
Curr Opinion Immunol 7:188, 1995
LFA-1 and thymic epithelial cell ICAM-1 molecules mediate
binding of activated human thymocytes to thymic epithelial cells. J
Immunol 144:2931, 1990
epithelial cells function as accessory cells for autologous mature
SR, Fukuda M, Frelinger JG: Characterization of cDNAs encoding
human leukosialin and localization of the leukosialin gene to chro-
7. Cyster J, Somoza C, Killeen N, Williams AF: Protein sequence
and gene structure for mouse leukosialin (CD43), a T lymphocyte
activation is associated with changes in O-glycan biosynthesis. J
Biol Chem 263:15146, 1988
9. Fukuda M, Carlson SR, Klock JC, Dell A: Structures of O-
linked oligosaccharides isolated from normal granulocytes, chronic
myelogenous leukemia cells, and acute myelogenous leukemia cells.
10. Manjunath N, Johnson RS, Staunton DE, Pasqualini R, Ard-
man B: Targeted disruption of CD43 gene enhances T lymphocyte
11. Baum LG, Pang M, Perillo NL, Wu T, Delegeane A, Uittenfo-
gaart CH, Fukuda M, Seilhamer JJ: Human thymic epithelial cells
express an endogenous lectin, galec-tin-1, which binds to core 0-
Structure and function of a large family of animal lectins. J Biol
Chem 269:20807, 1994
13. Drickamer K: Two distinct classes of carbohydrate-recogni-
14. Lundberg K, Heath W, Königs F, Carbone FR, Shortman
K: Intermediate steps in positive selection: Differentiation of CD48
selection of antigen-specific T cells in thymus by restricting MHC
H, von Boehmmer H: Thymic major histocompatibility complex anti-
gens and the alpha beta T-cell receptor determine the CD4/CD8
phenotype of T cells. Nature 335:229, 1988
development of mice deficient in β2, MHC class I proteins, and
CD8 T cells. Science 248:1227, 1990
18. Dutz JP, Ong CJ, Marth J, Teh H-S: Distinct differentiative
stages of CD4/CD8 thymocyte development defined by the lack of
19. Sha WC, Nelson CA, Newberry RD, Kranz DM, Russell JH,
Loh DY: Selective expression of an antigen receptor on CD8-bearing
20. Sha WC, Nelson CA, Newberry RD, Kranz DM, Russell JH,
Loh DY: Positive and negative selection of an antigen receptor on
Hedrick SM: Selective development of CD4 T cells in transgenic
mice expressing a class II MHC-restricted antigen receptor. Nature
341:746, 1989
London, UK, Academic, 1986
Kisielov P: Early deletion and late positive selection of T cells
expressing a male-specific receptor in T-cell receptor transgenic
mice. Dev Immunol 1:1, 1990
24. Kisielov P, Bluthmann H, Staerz UD, Steinmetz M, von
Boehmmer H: Tolerance in T cell receptor transgenic mice involves
deletion of nonmature CD4CD8 thymocytes. Nature 333:742, 1988
25. Tomlinson Jones AT, Federspill B, Ellies LG, Williams MJ,
Burgener R, Duronio V, Smith CA, Takei F, Ziltener HJ: Character-
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LG Ellies, W Tao, W Fellinger, HS Teh and HJ Ziltener