J Med Dent Sci 2006; 53: 85−91

Review

CD83: A Regulatory Molecule of The Immune System with Great Potential for Therapeutic Application

Yoko Fujimoto and Thomas F. Tedder

Department of Neurology and Neurological Science, Tokyo Medical and Dental University

CD83 has been known for a decade to be one of the best markers for mature dendritic cells (DCs). The recognition of CD83 was greatly changed since CD83 in thymus was unveiled to be essential for the generation of $CD4^+$ T cells by the study using CD83-deficient mice. It was recently shown that both activated DCs and B cells release soluble form of CD83 and that low levels of soluble CD83 are present in normal human sera. Both in vivo and in vitro studies demonstrated that soluble CD83 has immunosuppressive roles such as the inhibition of DC-mediated T cell stimulation and the maturation of DCs. CD83 appears to have regulatory functions for immune response in light of observations that the soluble form of CD83 can inhibits immune reactions while being strongly up-regulated during DC maturation and activation. In addition, the fact that various cell types including thymic epithelial cells, activated T and B cells and activated DCs express CD83 suggests the universal role in immune function. Because of these immuno-regulatory functions, the therapeutic application of CD83 is highly anticipated in many pathological states including malignancy and autoimmune disease.

Key words: CD83, Dendritic cells, Immune modulation, Soluble form, CD83-deficient mice

Corresponding Author: Yoko Fujimoto
Department of Neurology and Neurological Science, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
Tel: +81-3-5803-5234 Fax: +81-3-5803-0134
Duke University Medical Center, Durham, NC 27710, USA
Received January 30; Accepted March 17, 2006

Introduction

Dendritic cells (DCs) are the best antigen-presenting cells to induce primary immune response. Upon exposure to inflammatory stimuli in the peripheral tissues, immature DCs uptake antigens, are activated and migrate to the peripheral lymph nodes, where they undergo phenotypic and functional maturation. As a consequence, they express major histocompatibility complex (MHC) and other co-stimulatory molecules that can induce T cell stimulation. The best known maturation marker for human DCs is CD83.

CD83 is a 45-kD, type-1 membrane glycoprotein belonging to the Ig superfamily[1]. Although CD83 does not share significant sequence homologies with other known proteins, human and mouse CD83 are well conserved (~63%) in amino acid sequence[2,3]. Homologs of CD83 are found in elasmobranch and teleost fish, suggesting that the role of CD83 in cell-mediated immunity has been conserved for over 450 million years of vertebrate evolution[4]. CD83 is expressed at the surface of most DCs including thymic DCs, Langerhan cells in the skin, circulating DCs, monocyte-derived DCs and interdigitating reticulum cells present in the T cell zones of lymphoid organs[5,6,7,8]. Together with co-stimulatory molecules such as CD80 and CD86, CD83 is strongly up-regulated during the maturation of DCs[6]. Based on the pattern of CD83 expression and its structural similarity with other members of the immunoglobulin superfamily[6,9], CD83 is considered to play important roles during interactions between cells of the immune system.

Additional evidence in support of the functional importance of CD83 is provided by studies showing that mature DCs infected with herpes simplex virus type 1 (HSV-1) strongly down-modulate CD83 from the cell

surface 10h post infection, whereas CD80 and CD86 are not affected[10]. The identification of potential ligands also directed attention towards the function of CD83 on DCs and on their interaction with T cells[11,12,13].

Recognition of the importance of CD83 has evolved rapidly since its role in thymic function was revealed by the study of CD83-deficient (CD83-/-) mice[14]. CD83-/- mice have a specific block in $CD4^+$ thymocyte development, suggesting that CD83 expression represents an additional regulatory component for the development $CD4^+$ T cells in the thymus. Recent data has shown that CD83 is released from activated cells and the soluble form of CD83 has a strong immunosuppressive effect[12].

The characteristics of CD83 and potential therapeutic roles for this molecule are summarized in this review.

CD83 plays an essential role in the thymus

Although CD83 had been considered to play important roles during intercellular interactions, little is known about its function on DCs or on other cell types. We have therefore previously generated CD83-deficient (CD83-/-) mice in an attempt to understand these possible functions. Surprisingly, a specific block in thymocyte development was observed in CD83-/- mice and this was characterized by a severe reduction in peripheral $CD4^+$ T cells (Figure 1A, B)[14]. Identical defects in $CD4^+$ T lymphocyte development were also found in CD83-/- AND transgenic mice, a model system used to examine positive selection (Figure 2A). Despite the dramatic effect of CD83 deficiency on $CD4^+$ T cell development, $CD8^+$ T cell development and numbers were generally normal. A study using mouse mutagenesis screening shows the consistent observation that CD83 impairs the development of $CD4^+$ T cells.[15]

Whether abnormal $CD4^+$ T cell development in CD83-/- mice was due to intrinsic thymocyte defects or to an altered thymic microenvironment was further assessed by our group using adoptive transfer experiments. Bone marrow cells from CD83-/- AND and AND littermates were transplanted into irradiated CD83-/- and wild-type littermates. Four weeks later, $V\alpha11^+$ thymocytes from both CD83-/- AND and AND donors had developed normally into $CD4^+$ Single positive (SP) thymocytes in wild-type recipients (Figure 2B). In contrast, $V\alpha11^+$ thymocytes from either CD83-/- AND or AND donors failed to develop into $CD4^+$ SP

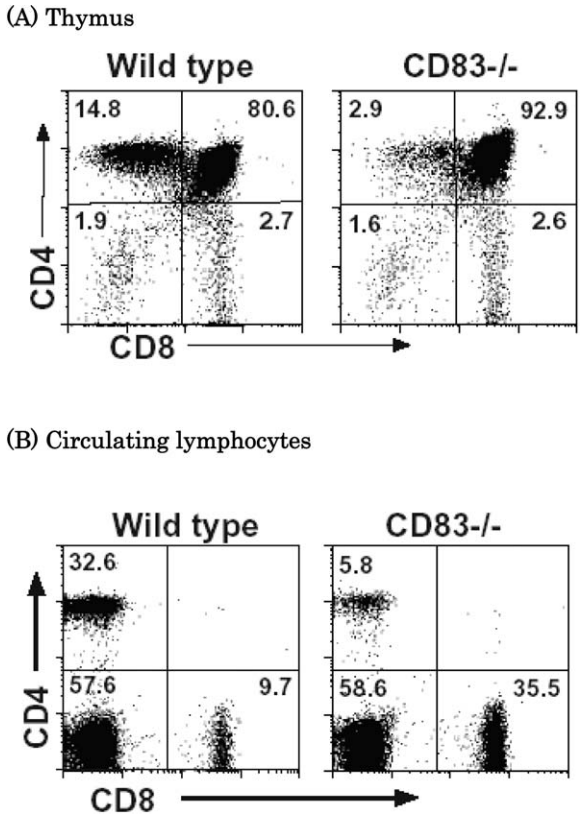


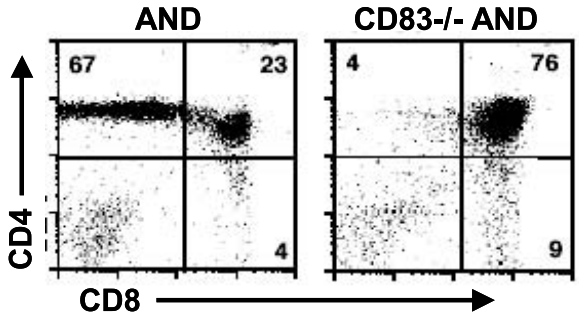
Fig. 1. (A) Immunofluorescence staining of thymocytes from CD83-/- and wild type littermates. The percentage of cells with $CD4^+$ SP, $CD8^+$ SP, DN or DP phenotypes are shown for each quadrant. Mean numbers of thymocytes in each subset are shown for 6 littermate pairs. (B) Circulating lymphocytes from CD83-/- and wild type littermates.

cells in CD83-/- littermates. Peripheral $V\alpha11^+$ $CD4^+$ T cell numbers were equivalent in wild-type recipients transplanted with either CD83-/- AND or AND bone marrow cells. In contrast, $V\alpha11^+$ $CD4^+$ T cell numbers were significantly reduced in CD83-/- recipients transplanted with either CD83-/- AND or AND bone marrow.

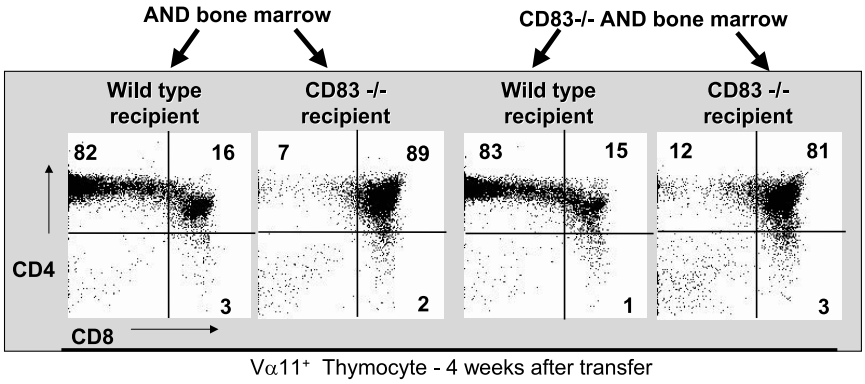
To further confirm that impaired $CD4^+$ T cell development in CD83-/- mice was due to an intrinsic defect in the thymic microenvironment, thymocytes from CD83-/- AND and AND mice were directly transferred into the thymi of irradiated CD83-/- and wild type littermates. $V\alpha11^+$ thymocytes from both CD83-/- AND and AND donors failed to develop into $CD4^+$ SP thymocytes in CD83-/- recipients after one and three weeks, but developed in normal proportions in wild-type

Footnote Figure No.1, 2A and 3A are reprinted from the publication titled “CD83 expression influences CD4+ T cell development in the thymus” Cell 2002, 108: 755-67, authored by Fujimoto et al, with permission from Elsevier.

(A) AND Thymus



(B) Bome Marrow Transplantation



(C) A Model of CD83 function for T cell development in the thymus

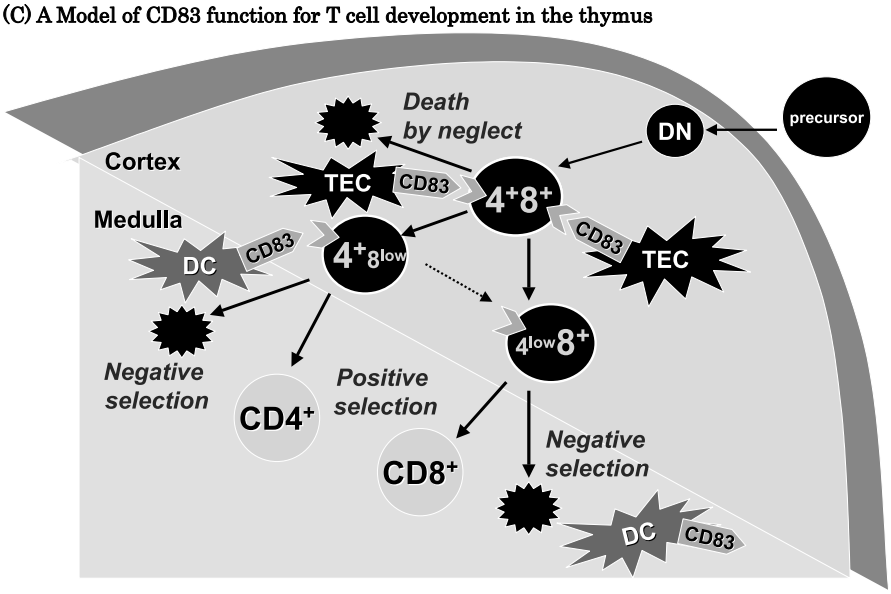


Fig. 2. (A) Immunofluorescence staining of thymocytes from CD83-/- AND and AND littermates. Mean numbers from 4 littermate pairs are shown. (B) Bone marrow cells from CD83-/- AND and AND littermates were transplanted into irradiated CD83-/- and wild type littermates. Four weeks later, the relative percentages of Vα11$^+$ cells expressing CD4 and/or CD8 were assessed in the thymus. (C) A Model of CD83 function for T cell development in the thymus. A signaling step from CD83 on thymic epithelial cells and dendritic cells to thymocytes is required for the development of CD4$^+$ T cells.

littermates. Peripheral Vα11$^+$ CD4$^+$ T cell numbers were equivalent when wild-type recipient mice were injected with either CD83-/- AND or AND thymocytes. Consistent with this, CD83 was expressed by mouse thymic DCs and epithelial cells. Therefore, the lack of CD4$^+$ T cells in CD83-/- mice results primarily from a deficiency in CD83 expression by thymic DCs and epithelial cells.

The process by which immature thymocytes undergo lineage commitment and selection is the subject of intense investigation. Precursor cells enter the thymus as double negative (DN, CD4$^-$CD8$^-$) thymocytes but up-regulate the expression of both CD4 and CD8 co-receptor molecules to become CD4$^+$CD8$^+$ double positive (DP) thymocytes. DP thymocytes develop into mixed transitional CD4$^+$CD8^{low} thymocytes before commitment to either the CD4$^+$ or CD8$^+$ lineages as SP T cells[16,17,18,19]. Immature DP thymocytes with a T cell antigen receptor (TCR) of high affinity for MHC molecules and self-peptide complexes are deleted in a process referred to as negative selection, while those with a TCR of low affinity for self-peptide/MHC complexes are positively selected and survive[20].

Although little is known about the signals and cell surface molecules involved, transitional thymocytes require signals from thymic stromal cells in order to become mature CD4$^+$ or CD8$^+$ T cells[18,21,22,23,24]. Amongst stromal cells, cortical epithelial cells provide the signals required for positive selection and lineage commitment[25,26]. A role for DCs as antigen-presenting cells during thymocyte selection and survival has also been proposed[27,28,29]. CD83-/- mice revealed there is a requirement for CD83 signaling from thymic epithelial and dendritic cells during the development of CD4$^+$ T cells, as well as additional regulatory steps in the complex network of molecular interactions that control thymocyte and peripheral T cell generation (Figure 2C). Future investigations into the interaction between thymocytes and CD83 expressed on thymic epithelial cells and DCs will be important to clarify the function of CD83 and to elucidate the mechanism for thymocyte lineage commitment.

Soluble CD83 and T cells

Inhibitory functions for the soluble form of CD83 were reported recently. Recombinant human CD83 extra cellar domain completely inhibited DC-mediated T cell stimulation in a concentration-dependent manner[12,30,31]. Another interesting finding was that immature DCs when incubated with soluble CD83 protein could no longer become fully mature even in the presence of a potent maturation cocktail[12]. Treatment with soluble CD83 protein led to specific down-modulation of CD80 expression at the cell surface, as well as that of CD83 itself. These observations suggest that soluble CD83 might induce a maturation block in DCs and hence could represent a mechanism to control and down-modulate the *in vivo* immune response. The biological importance of soluble CD83 protein was highlighted by the fact soluble CD83 is also present in the serum of healthy donors[32]. Furthermore, it was recently found that soluble CD83 was present at elevated levels in patients with hematological disorders including chronic lymphocytic leukemia and mantle cell lymphoma[33,34]. The mechanism proposed for generation of soluble CD83 was the shedding of cell surface-associated CD83 on DCs and B cells[32,33,34]. However, in addition to the hypothesis of receptor endoproteolytic release of cell surface, generation of soluble form by microsomes can be also considered as a possible mechanism. Recent study reported that three alternative spliced transcripts of CD83 were identified in human peripheral blood mononuclear cells and alternative splicing could generate soluble forms of CD83[35]. Further research is expected to reveal the generation of soluble form of CD83 with the regulatory mechanism to produce the soluble form.

The function of soluble CD83 *in vivo* has been investigated using as a model murine experimental autoimmune encephalomyelitis (EAE)[36]. It was reported that as few as three injections of soluble CD83 almost completely prevented the paralysis associated with EAE in different therapeutic settings. Importantly, even when the treatment was delayed until the disease symptoms were fully established, soluble CD83 still clearly reduced the paralyses. Complete reduction of leukocyte infiltration into the brain and spinal cord was also reported. Thus, therapeutic intervention with soluble CD83 appears to have profound clinical effects.

Recent study shows that engagement with the CD83 ligand preferentially enriches and significantly amplifies the number of antigen-specific CD8$^+$ T cells[37]. Co-engagement of the T cell receptor, CD28, with CD83 ligand supports the priming of naive CD8$^+$ T cells that retain antigen specificity and cytotoxic function for greater than 6 months. Therefore, engagement of the CD83 ligand provides a unique signal to activated CD8$^+$ T cells that could be exploited to generate long-lived, antigen-specific cytotoxic T cells for the treatment of cancer and infection[37]. Future studies aimed at

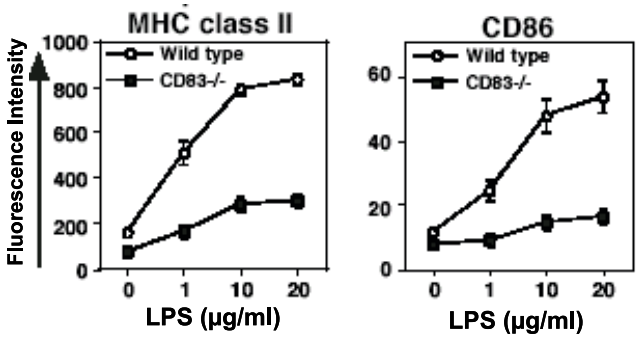
characterizing $CD8^+$ T cells from CD83-/- mice should provide a better understanding of CD83 function in the activation of $CD8^+$ T cells. This may eventually lead to therapeutic use against cancer and infectious diseases.

CD83 on B cells

Splenic B cells from CD83-/- mice express cell surface MHC class II antigens and CD86 at ~50% and ~20% lower levels, respectively, than wild-type littermates[14]. CD86 expression by CD83-/- B cells was also reduced by ~20%. The expression of MHC class II and CD86 by CD83-/- B cells remained 3-4-fold below normal levels following activation with LPS (Figure 3A). Similar results were obtained following B cell stimulation with IL4, IgM or interferon. Decreased MHC class II and CD86 expression following LPS, IL4 or IgM stimulation was also observed in heterozygous CD83+/- mice. The decrease in CD86 expression cannot be explained by a decrease in MHC class II, since MHC class II-deficient mice show increased levels of CD86 expression. CD83-deficiency significantly affected the activation status of peripheral B cells and inhibited antigen-specific humoral immune responses, but does not appear to affect intrinsic B cell proliferative function.

The characteristics by which CD83 reacts immedi-

(A) MHC class II antigen and CD86 expression by resting and LPS-stimulated splenic B cells



(B) MHC class II antigen and CD86 expression by resting and LPS-stimulated microglia

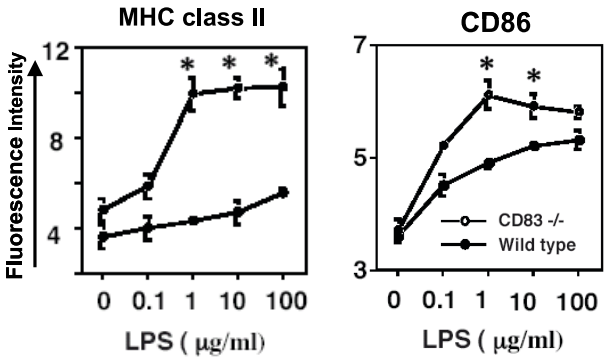


Fig. 3. (A) MHC class II antigen and CD86 expression by resting and LPS-stimulated splenic B cells after 24 hours. Values represent the mean fluorescence intensity of antigen expression as determined by flow cytometry analysis of cells from three CD83-/- and wild type littermates. (B) MHC class II antigen and CD86 expression by resting and LPS-stimulated microglia after 24 hours. Values represent the mean fluorescence intensity of antigen expression as determined by flow cytometry analysis of cells from three CD83-/- and wild type littermates.

ately upon stimulation of cells and directly influences the surface expression of MHC class II could explain why this molecule has been assumed for many years to be the activation marker. On the other hand, the experimental finding that despite the failure in activation, CD83-deficiency does not result in a clear defect of B cell function seems consistent with an immune modulation function shown by studies with soluble CD83.

CD83 and the Central Nervous System

Microglia are brain-specific, immune-mediating cells. It is well known that activated microglia play an important role in many types of central nervous system disease[38]. We have previously shown that microglia express CD83[39]. To investigate a possible functional role, microglia from new-born CD83-/- and wild-type mice were cultured and the expression of MHC class II and other cell surface molecules including CD80, CD86, CD40 and ICAM-1 was compared before and after LPS or IFN-γ stimulation. CD83-/- microglia expressed MHC class II and CD86 at significantly lower levels after stimulation compared to wild type microglia (Figure 3B), indicating that CD83 regulates microglial activation. Moreover, this consistent observation amongst different cell types such as DCs, B cells and microglia tends to confirm the universal importance of CD83 on antigen-presenting cells. Further research into the functional mechanism using tools such as CD83-/- mice and soluble CD83 molecules may allow elucidation of CD83 function in the brain. Together with experimental findings from the EAE model, a more detailed understanding of CD83 function could lead to its therapeutic use for diseases related to inflammation in the brain.

Discussion

The acquired immune response depends crucially on antigen presentation by cells that emit pathogens or that take up pathogens or their metabolic products. As the first step in this process, DCs and other antigen-presenting cells are activated and MHC class II molecules present the antigen peptides at the cell surface. The importance of CD83 for this step is demonstrated not only by the regulation of MHC Class II expression but also by the intrinsic example for the regulation of antigen presentation; thymic development of T cells. CD83 is up-regulated by activation and soluble form of CD83 is released from the activated cells.The soluble CD83 has inhibitory functions within the immune reaction. Together, the best marker for mature dendritic cells, CD83, is now recognized to be an essential molecule for $CD4^+$ T cell generation and one of the central regulatory molecules in immune function. The biological importance of CD83 suggests that it has potential for therapeutic use. In addition to the results obtained using EAE as a model of autoimmune disease, other published data demonstrate an immunomodulative role with anti-tumor effects. The ability of CD83 to potentiate anti-tumor immune responses was reported in mice implanted subcutaneously with the poorly immunogenic melanoma cell line K1735 and transfected with CD83. Cells from the M2 clone of mouse melanoma K1735 cells transfected to express human CD83 were shown to be rejected by syngeneic mice, some of which also rejected a subsequent transplant of nontransfected cells from the M2 clone[31]. Additionally, it is known that CD83 expression on DCs decreases promptly by the infection of HIV[40] and the expression on DCs actually decrease in AIDS patients[41].

In conclusion, recent investigations into CD83 have provided new clues regarding autoimmune disease and immune therapy for malignant tumors. CD83 could also prove to be a key molecule for the inhibition of transplant rejection, T cell-mediated allergies and infectious disease. Thus, the possibility of therapeutic applications for CD83 through its regulation of immune function is highly anticipated over the next decade.

Acknowledgements

We would like to thank Dr. Hidehiro Mizusawa for his valuable guidance and support throughout the entire research.

References

1. Zhou, LJ, Schwarting R, Smith HM, et al. A novel cell-surface molecule expressed by human interdigitating reticulum cells, Langerhans cells, and activated lymphocytes is a new member of the Ig superfamily. J Immunol 1992;149:735-42.
2. Berchtold S, Mühl-Zürbes P, Heufler C, et al. Cloning, recombinant expression and biochemical characterization of the murine CD83 molecule which is specifically upregulated during dendritic cell maturation. FEBS Letters 1999;461:211-6.
3. Twist CJ, Beier DR, Disteche MC, et al. The mouse CD83 antigen: structure, domain organization and chromosome localization. Immunogenetics 1998;48:383-3.

4. Ohta Y, Landis E, Boulay T, et al. Homologs of CD83 from elasmobranch and teleost fish. J Immunol 2004;173:4553-60.
5. Zhou LJ, Tedder TF. A distinct pattern of cytokine gene expression by human CD83+ blood dendritic cells. Blood 1995;86:3295-301.
6. Zhou LJ, Tedder TF. Human blood dendritic cells selectively express CD83, a member of the immunoglobulin superfamily. J Immunol 1995;154:3821-35.
7. Weissman D, Li Y, Orenstein JM, et al. Both a precursor and a mature population of dendritic cells can bind HIV. However, only the mature population that expresses CD80 can pass infection to unstimulated CD4+ T cells. J Immunol 1995;155:4111-7.
8. Kruse M, Rosorius O, Kratzer F, et al. Inhibition of CD83 cell surface expression during dendritic cell maturation by interference with nuclear export of CD83 mRNA. J Exp Med 2000;191:1581-90.
9. Kozlow EJ, Wilson GL, Fox CH, et al. Subtractive cDNA cloning of a novel member of the Ig gene superfamily expressed at high levels in activated B lymphocytes. Blood 1993;81:454-61.
10. Kruse M, Rosorius O, Kratzer F, et al. Mature dendritic cells infected with herpes simplex virus type 1 exhibit inhibited T-cell stimulatory capacity. J Virol 2000;74:7127-36.
11. Cramer SO, Trumpfheller C, Mehlhoop U, et al. Activation-induced expression of murine CD83 on T cells and identification of a specific CD83 ligand on murine B cells. Intl Immunol 2000;12:1347-51.
12. Lechmann M, Krooshoop DJEB, Dudziak D, et al. The extracellular domain of CD83 inhibits dendritic cell-mediated T cell stimulation and binds to a ligand on dendritic cells. J Exp Med 2001;194:1813-21.
13. Scholler N, Hayden-Ledbetter M, Hellström KE, et al. CD83 is a sialic acid-binding Ig-like lectin (Siglec) adhesion receptor that binds monocytes and a subset of activated CD8+ T cells. J Immunol 2001;166:3865-72.
14. Fujimoto Y, Tu L, Miller AS, et al. CD83 expression influences CD4+ T cell development in the thymus. Cell 2002; 108: 755-67.
15. Garcia-Martinez LF, Appleby MW, Staehling-Hampton K, et al. A novel mutation in CD83 results in the development of a unique population of CD4+ T cells. J Immunol 2004;173:2995-3001.
16. Lucas B and Germain RN. Unexpectedly complex regulation of CD4/CD8 coreceptor expression supports a revised model for CD4+CD8+ thymocyte differentiation. Immunity 1996;5:461-77.
17. Lundberg K, Heath W, Kontgen F, et al. Intermediate steps in positive selection : differentiation of CD4+ 8int TCRint thymocytes into CD4-8+ TCRhi thymocytes. J Exp Med 1995;181:1643-51.
18. Sant'Angelo DB, Lucas B, Waterbury PG, et al. A molecular map of T cell development. Immunity 1998;9:179-86.
19. Suzuki H, Guinter TI, Koyasu S, et al. Positive selection of CD4+ T cells by TCR-specific antibodies requires low valency TCR cross-linking: implications for repertoire selection in the thymus. Eur J Immunol 1998;28:3252-8.
20. Jameson SC, Bevan MJ. T-cell selection. Curr Opin Immunol 1998;10:214-9.
21. Brugnera E, Bhandoola A, Cibotti R, et al. Coreceptor reversal in the thymus; signaled CD4+ CD8+ thymocytes initially terminate CD8 transcription even when differentiating into CD8+ T cells. Immunity 2000;13:59-71.
22. Anderson G, Jenkinson EJ, Moore NC, et al. MHC class II-positive epithelium and mesenchyme cells are both required for T-cell development in the thymus. Nature 1993;362:70-3.
23. Cibotti R, Punt JA, Dash KS, et al. Surface molecules that drive T cell development in vitro in the absence of thymic epithelium and in the absence of lineage-specific signals. Immunity 1997;6:245-55.
24. Wilkinson RW, Anderson G, Owen JJT et al. Positive selection of thymocytes involves sustained interactions with the thymic microenvironment. J Immunol 1995;155:5234-40.
25. Laufer TM, Dekoning J Markowitz JS, et al. Unopposed positive selection and autoreactivity in mice expressing class II MHC only on thymic cortex. Nature 1996;383:81-5.
26. Matzinger P, Guerder S. Does T-cell tolerance require a dedicated antigen-presenting cell? Nature 1989;338;74-6.
27. Ardavin C. Thymic dendritic cells. Immunol Today 1997;18: 350-61.
28. Steinman RM. DC-SIGN: A guide to some mysteries of dendritic cells. Cell 2000;100:491-4.
29. Yasutomo K, Lucas B, Germain RN. TCR signaling for initiation and completion of thymocyte positive selection has distinct requirements for ligand quality and presenting cell type. J Immunol 2000;165:3015-22.
30. Lechmann M, Berchtold S, Hauber J, et al. CD83 on dendritic cells: more than just a marker for maturation. Trends Immunol 2002;23:273-5.
31. Scholler N, Hayden-Ledbetter M, Dahlin A, et al. CD83 regulates the development of cellular immunity. J Immunol 2002;168:2599-602.
32. Hock BD, Kato M, McKenzie JL, et al. A soluble form of CD83 is released from activated dendritic cells and B lymphocytes, and is detectable in normal human sera. Int Immunol 2001;13:959-67.
33. Senechal B, Boruchov AM, Reagan JL, et al. Infection of mature monocyte-derived dendritic cells with human cytomegalovirus inhibits stimulation of T-cell proliferation via the release of soluble CD83. Blood 2004;103:4207-15.
34. Hock BD, Haring LF, Steinkassered A, et al. The soluble form of CD83 is present at elevated levels in a number of hematological malignancies. Leuk Res 2004;28:237-41.
35. Dudziak D, Nimmerjahn F, Bornkamm GW, et al. Alternative splicing generates putative soluble CD83 proteins that inhibit T cell proliferation. J Immunol 2005;174:6672-6.
36. Zinser E, Lechmann M, Golka A, et al. Prevention and treatment of experimental autoimmune encephalomyelitis by soluble CD83. J Exp Med 2004;200:345-51.
37. Hirano N, Butler MO, et al. Engagement of CD83 ligand induces prolonged expansion of CD8+ T cells and preferential enrichment for antigen specificity. Blood 2006;107:1528-36
38. McGeer PL, Kawamata T, Walker DG, et al. Microglia in degenerative neurological disease. Glia 1993;7:84-92.
39. Fujimoto Y, Fujimoto M, Yoshitake S, et al. CD83 expression regulates microglial activation. Neuroimmunology 2002; 10:243-9 (Japanese).
40. Kawamura DL, et al, Candidate microbicides block HIV-1 infection of human immature Langerhans T, Cohen SS, Borris cells within epithelial tissue explants. J Exp Med 2000;192:1491-500.
41. McIlroy D, Autran B, Clauvel JP, et al, Low CD83, but normal MHC class II and costimulatory molecule expression, on spleen dendritic cells from HIV+ patients. AIDS Res Hum Retroviruses 1998;14:505-13.