ONKOLOGIE

Review Article · Übersichtsarbeit

Onkologie 2004;27:91–95
DOI: 10.1159/000075612

ICOS: A New Costimulatory Ligand/Receptor Pair and Its Role in T-Cell Activion

G. Richter S. Burdach

Labor für Transplantationsbiologie, Kinderklinik und Poliklinik des Klinikums rechts der Isar der Technischen Universität München, Germany

Key Words
ICOS · Ligand/receptor pair, costimulatory · T-cell activation

Summary
The inducible costimulator (ICOS) is a new member of the CD28/CD152 receptor family that regulates T-cell activation and function. ICOS binds to a specific ligand on antigen-presenting cells (APC) and cells of the peripheral tissue different from the CD28/CD152 ligands CD80 and CD86. ICOS-L can be induced by inflammatory stimuli in peripheral tissue and on some APC, including monocytes, but is downregulated in B-cell and myeloid leukemia. ICOS-L delivers distinct signals to T cells, presumably important for the maintenance of certain types of immune response, providing the rationale for the development of new therapeutic strategies for the treatment of diseases.

Schlüsselwörter
ICOS · Liganden/Rezeptor–Paar, kostimulatorisch · T-Zellaktivierung

Zusammenfassung
Der induzierbare Kostimulator (ICOS) ist ein neues Mitglied der CD28/CD152 Rezeptorfamilie, die die Aktivierung und Funktion von T-Zellen regulieren. ICOS bindet an einen spezifischen Liganden auf Antigen-präsentierenden Zellen (APC) und Zellen des peripheren Gewebes, der verschieden ist von den CD28/CD152-Liganden CD80 und CD86. Die Expression des ICOS-L kann durch inflammatorische Stimuli auf peripherem Gewebe und einigen APC, einschließlich Monozyten induziert werden, ist aber herunter reguliert bei B-Zell- und myeloiden Leukämien. ICOS-L induziert spezifische Signale in T-Zellen, die wahrscheinlich für die Aufrechterhaltung bestimmter Immunantworten notwendig sind. Diese Beobachtungen sind die Grundlage für die Entwicklung neuer therapeutischer Strategien zur Behandlung von Erkrankungen.

ICOS: A New Member of CD28 Receptor Family

Antigen-specific T-cell stimulation via the T-cell receptor/CD3 complex (TCR/CD3) requires costimulatory receptors such as CD28. During this process, CD28 or CD152 (CTLA-4) expressed on T cells is engaged by the ligands CD80 (B7–1) or CD86 (B7–2) expressed on antigen-presenting cells [1]. The inducible costimulator (ICOS) is a recently defined new member of the CD28 family, but unlike CD28, it is not constitutively expressed on T cells [2]. ICOS expression requires the activation of T cells via the TCR/CD3 complex. It shows structural homology to CD28 and CD152 but it differs in the MYPPPY homology domain necessary for binding of CD28/CD152 to CD80 or CD86 [3]. Similarly, the cytoplasmic tail of ICOS lacks the PXXP site necessary for IL-2 production after CD28 engagement [4]. ICOS is expressed on T cells in lymphoid or-

KARGER

Fax +49 761 4 52 07 14
E-mail Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/onk

Dr. rer. nat. Günther Richter
Labor für Transplantationsbiologie, Kinder- und Poliklinik
Klinikum rechts der Isar der TU München
Kölner Platz 1, D-80804 München
Tel. +49 89 3068-3235, Fax -3954
E-mail guenther.richter@lrz.tum.de

Table 1. Regulation of ICOS/ICOS-L expression

ICOS expression		
Naive T cells	no	
Activated T cells	yes, TH2 >TH1 cells, CD8+ T cells	
Memory T cells	yes	
Activated NK cells	yes	
Tissue location of ICOS	human fetal and new-born thymus; thymic medulla and cortico-medullary junction in mice; germinal centres in lymphoid tissues	
ICOS-L expression in lymphoid tissues	expressed on B cells, CD33+ cells in bone marrow, monocytes, DCs and T cells	
Regulation	induced by IFN-γ on B cells, monocytes and DCs; induced by GM-CSF/TNF-α or GM-CSF/IL-3 on CD34+ cells earlier than B7–1/B7–2; not induced by progenitor Ig or CD40 crosslinking on B cells or CD3+ T cells	
ICOS-L expression in nonlymphoid tissues	expressed on a variety of tissues including kidney, liver, peritoneum, lung, testes, embryonic fibroblasts, epithelial cells	
Regulation	induced by TNF-α, LPS and IFN-γ on fibroblasts, epithelial cells and other nonlymphoid tissues	
ICOS-L expression in leukemia and lymphoma		
Acute myeloid leukemia	CD13+/CD33+	0%
B cell lymphoblastic leukemia	CD19+	0%
Chronic lymphocytic leukemia	CD19+	20%
B cell prolymphocytic leukemia	CD19+	40%
Hairy cell leukemia	CD19+	66%
Folicular lymphoma	CD19+	0%

gans, including spleen, lymph nodes, and Peyer's patches (table 1) [2, 5–7]. ICOS is expressed in the medulla and the cortico-medullary junction of the thymus [6]. In humans, ICOS expression was detected in fetal and newborn thymuses, with expression primarily in the medulla [5]. However, mice deficient for ICOS have a normal thymus and normal numbers of peripheral $CD4^+$ and $CD8^+$ T cells, indicating that ICOS does not play a critical role in T-cell development [8–10]. In addition, it was recently observed that ICOS can be upregulated on IL-2 or IFN-γ activated NK cells [11].

ICOS Binds to a New Ligand (ICOS-L) That is Differentially Expressed Compared to CD80/CD86

CD80 is expressed on antigen presenting cells after induction by microbes, cytokines or CD40 ligation and is also expressed on fibroblasts, while CD86 is constitutively expressed on monocytes and is inducible upon stimulation [12]. Most lymphoma and leukemia cells lack CD80 but about 50% of cases express CD86. Recently, new homologues of CD80 and CD86 were described. One of these, B7h (also designated B7RP-1, GL50 or B7-H2) binds to ICOS but not to CD28 or CD152/CTLA-4 [6, 7, 13–16]. The ligand for ICOS (ICOS-L) shares only ~20% amino acid identity with CD80 and CD86. A soluble form of the ICOS receptor was generated and used, together with a subsequently developed mouse anti-human ICOS-L mAb 13C1 that has been generated by DNA vaccination [17], to characterize the ICOS-L. We found that ICOS-L is expressed on human antigen presenting cells of myeloid origin and on about 40% of peripheral blood $CD19^+$ B cells [18]. Expression of ICOS-L was induced on monocytes after integrin-dependent plastic adhesion and was further upregulated by IFN-γ but not TNF-α. Unlike CD152-L expression, ICOS-L expression did not change when monocytes were differentiated into dendritic cells (DCs) or after DCs were induced to mature by LPS, TNF-α, or CD40 ligation.

Flow cytometry and ICOS-L-specific RT-PCR of immunomagnetically purified subpopulations revealed an ICOS-L expression level on $CD19^+$ B cells in bone marrow that was similar to that observed in peripheral blood, while $CD3^+$ T cells and $CD34^+$ stem cells were ICOS-L^-. $CD33^+$ meloid cells were ICOS-L positve and 3-color staining further suggested that ICOS-L expression is acquired as soon as hematopoetic progenitor cells show a clear myeloid commitment as indicated by strong CD33 expression and beginning loss of CD34 antigen expression.

When immuno-magnetically purified $CD34^+$ cells were grown in a cocktail of GM-CSF and TNF-α that induces differentiation of hematopoietic progenitor cells into DCs, they rapidly acquired, already after 12 hours of culture, ICOS-L expression at the cell surface. ICOS-L was equally expressed

in the GM-CSF/TNF-α induced $CD11c^+CD14^-$ DC and $CD11c^+CD14^+$ monocyte fraction. TNF-α appeared to be the crucial cytokine for induction of expression of ICOS-L, while GM-CSF alone and G-CSF alone were not able to induce ICOS-L expression. Significant expression of the costimulatory molecules CD80/CD86 (as judged by binding of the CD152Ig fusion protein (or anti-CD80 and CD86 mAb) appeared later at day 6 (table 1). Dendritic cells distinctive from those that give rise to Langerhans cells can be generated by stimulation with IL-3 or IL3 + GM-CSF [19]. These cells are also called 'lymphoid dendritic cells' and are positive for CD4, CD33, CD54, CD58, CD86 and HLA-DR, but negative for CD1a and CD80. The combination of GM-CSF and IL-3 induced an up-regulation of ICOS-L that was earlier and stronger as compared to CD80/CD86. Highest ICOS-L expression, however, was achieved at a later time than in TNF-containing cultures.

Early during the discovery of ICOS-L it was shown that ICOS-L is not only expressed on cells of hematopoietic origin, but also on peripheral tissue, such as brain, heart liver, kidney and endothelial cells and can be further induced by TNF-α or other inflammatory stimuli (table 1) [7, 15–17, 20].

Myeloid and Lymphoid Leukemic Cells Do Not Express ICOS-L

When myeloid (AML) and lymphoid leukemic cells (ALL) were investigated for ICOS-L expression, none of 7 cases of $CD13^+CD33^+$ AML nor any of 6 cases of B-lineage ALL examined were bound by ICOSIg (table 1) [17]. These data suggest that the very early myeloid cells and B-cell progenitor cells do not express ICOS-L. 4/5 cases of chronic lymphocytic leukemia, which is thought to represent a disease of immature, virgin B-lymphocytes, were $ICOS\text{-}L^-$; whereas 2/4 PLL and 4/6 HCL were $ICOS\text{-}L^+$. None of 7 cases of follicular lymphoma (which correspond to germinal center B cells) reacted with our ICOSIg reagent. Similarly, ICOS-L mRNA expression in pediatric c-ALL was found to be down-regulated when compared to normal controls (Uwe Hattenhorst, personal comunication). Since ICOS-L expression in the periphery seems to provide costimulatory activity to T cells, down-regulation of ICOS-L on leukemic cells could be part of possible mechanisms of tumor cells to escape immuno surveillance not only by T cells but also by NK cells, for which ICOS expression on activated NK cells was recently demonstrated [11].

Stimulatory Potential of ICOS-L Depends on the State of T-Cell Activation and Phenotype of APC

Engagement of ICOS, like CD28, can mediate potent costimulation of T cells [2, 21], and promotes T-cell proliferation at levels similar to those observed after CD28 triggering but without the accompanying increase in IL-2 production. Instead, ICOS up-regulates expression of IL-4, IL-5, GM-CSF, IFN-γ, TNF-α and is particularly effective in enhancing IL-10 production [2, 22]. In Ag-specific T-cell proliferation assays, the presence of tetanus toxoid increased T-cell proliferation by 3-fold. This T-cell proliferation was inhibited about 50% in the presence of ICOSIg. Comparable results were observed using influenza HA. The presence of CD152Ig efficiently blocked T-cell proliferation in both cases by more than 80%. Similarly, addition of ICOSIg to allogeneic MLRs between mature DCs and T cells reduced T-cell proliferative responses but did so less efficiently than CTLA4Ig (CD152Ig) did [18]. However, when purified $CD4^+$ T cells had been preactivated with suboptimal doses of anti-CD3 sufficient to induce ICOS expression, and were subsequently stimulated in an allogeneic MLR with $CD34^+$ cells pretreated with TNF-α to express optimal amounts of ICOS-L, these TNF-activated $CD34^+$ cells were potent stimulators of allogeneic T cells [17]. The results also suggested that the CD28 costimulatory pathway is not necessary for ICOS-L-mediated costimulation, since inhibition of CD80/86:CD28 interaction by CD152Ig in this situation was less effective. Similarly, when MHC class II^+ endothelial cells together with superantigen were cocultured with resting memory $CD4^+$ T cells, different cytokines (IL-2, IFN-γ, IL-4, IL-10, and IL-13) were produced. Inhibition with blocking anti-ICOS-L mAb reduced the amount of cytokines produced to 20–50%, indicating that ICOSL is a major costimulator in endothelial cell mediated costimulation [20]. Likewise, Yoshinaga and colleagues [7] found that T cells from $CD28^{-/-}$ mice could still be stimulated via ICOS-L. Villegas et al. [23] in addition observed in a model of parasite infection with *Toxoplasma gondii* in $CD28^{-/-}$ mice that infection resulted in increased expression of ICOS coming along with an increased parasite burden and mortality when ICOS/ICOS-L interaction is blocked.

The prominent role of ICOS-L in B-cell responses has been demonstrated in transgenic mice overexpressing soluble ICOS-L [7]. These mice are characterized by lymphoid hyperplasia in the spleen, lymph node, and Peyer's patches, and have high serum IgG levels. In addition, ICOS-deficient mice show a severe decrease in serum IgG1 levels [8, 9], and immunization of mice with TNP-KLH in the absence of adjuvant or with alum or IFA reveals a deficit in IgG_1 and IgG_{2a} antibody production [8]. Immunization of mice with NP-OVA in alum [9] or with aerosolized antigen in the lung [10] also demonstrated a deficit in IgE production in ICOS-deficient mice, consistent with defects in overall germinal center formation and T-cell dependent B-cell responses [8–10]. Similarly, for patients with common variable immunodeficiency (CVID) that lack the ICOS gene, it was observed that their T cells appeared normal, but naïve, switched and memory B cells were reduced, suggesting a critical role for ICOS in late B-cell differentiation, class switching and memory B cell generation [24].

Therapeutic Implications

It appears that the clone size of T_H cells responding to their antigen critically depends on ICOS as shown recently in a adoptive transfer system. Moreover, results by Kopf et al. [29] reveal that blockade of ICOS/ICOS-L interaction also inhibits T_H1-regulated effector phases. They observed that both the T_H1 cytokine IFN-γ and T_H2 cytokines IL-4 and IL-5 are reduced by administration of ICOSIg at the time of infection with *Nippostrongylus brasiliensis*, indicating that the ICOS pathway is relevant for both T_H1 and T_H2 cytokine production in vivo. Studies on experimental induction of autoimmune encephalomyelitis (EAE), a T_H1-mediated autoimmune disease, similarly suggest that ICOS costimulation may play an important role in the effector phase of T_H1 responses, in that disease is ameliorated by blockade of ICOS only during the effector phase [25] by preventing encephalitogenic T cells from attacking brain tissue where ICOS-L is abundantly expressed. However, induction of EAE is not dependent upon ICOS, since ICOSIg at the time of antigen priming does not prevent the disease [25]. Likewise, inhibiting ICOS/ICOS-L interaction in a heart transplant model suppressed intragraft T-cell activation and prolonged allograft survival, and in combination with cyclosporin A promoted long-term allograft acceptance [26]. Iwai et al. [27] in a model of collagen-induced arthritis found that ICOLS-L blockade could ameliorate and delay the onset of the disease by blocking both T_H1- and T_H2-mediated inflammatory reactions.

In addition, it was observed that ICOS engagement can also stimulate $CD8^+$ T cell responses. Immunogenic, ICOS-L^+ tumors can be efficiently rejected in immunocompetent mice [21], in these studies, ICOS-L costimulation of $CD8^+$ T cells was found to enhance IL-2 and IFN-γ production preferentially in recall responses compared with naïve responses. However, ICOS-L does not enhance cytolytic T-cell function, which is consistent with experiments showing that ICOS blockade had no effect on CTL responses after LCMV or VSV infection [28, 29], indicating that the lytic function of T cells is ICOS-independent.

Interestingly, ICOS seems to be critically important for the generation of IL-10-secreting regulatory $CD4^+$ T cells [30]: In a model of allergen-induced airway hypersensitivity (AHR) IL-10-secreting T_R cells expressed significant in vivo and in vitro inhibitory activity and blocked the development of allergen-induced AHR. DC-induced development of T_R was prevented by neutralization of IL-10 or by blockade of ICOS:ICOS-ligand signaling. A finding that is supported by Witsch et al. [31] observing that IL-10 production of $CD4^+$ T cells stimulated with mature DC in the presence of superantigen critically depends on ICOS/ICOS-L interaction.

It will be interesting to investigate whether ICOS is also effective in other therapeutic settings: Graft versus host disease (GVHD) remains a major complication after allogeneic bone marrow transplantation (BMT), thereby preventing the widespread use of this therapeutic approach for the treatment of malignant and nonmalignant diseases [32, 33]. Acute GVHD is initiated by alloreactive donor T cells that recognize MHC class I and II molecules on the surface of host cells as well as peptides presented by them. The infiltration of several target organs such as gut, liver, and skin by donor leukocytes including T cells is thought to be one of the key processes in the early phase of GVHD. The activation and expansion of the donor T cells, leading to the secretion of proinflammatory cytokines and the recruitment of additional inflammatory effector cells to these sites, further damages the affected tissues. The apparent involvement of ICOS/ICOS-L interaction in several T-cell effector functions and the abundant expression of ICOS-L in a variety of tissues also affected in a GVHD provides the rationale to investigate whether it will be possible to ameliorate a GVHD with anti-ICOS-L treatment and to determine the influence of this treatment on a protective graft versus leukemia (GvL) reactivity of the BMT. Likewise, it is not understood why a high percentage of leukemic cells downregulate ICOS-L on their cell surface and on the other hand the blockade of ICOS-L has no influence on cytolytic T-cell function, but is hoped to be determined in the near future.

Acknowledgements

Preparation of the manuscript was supported by a grant from the Deutsche Krebshilfe, Projekt 70–2787-Bu 3.

References

1 Slavik JM, Hutchcroft JE, Bierer BE: CD28/CTLA-4 and CD80/CD86 families: Signaling and function. Immunol Res 1999;19:1–24.
2 Hutloff A, Dittrich AM, Beier KC, Eljaschewitsch B, Kraft R, Anagnostopoulos I, Kroczek RA: ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. Nature 1999;397:263–266.
3 Peach RJ, Bajorath J, Brady W, Leytze G, Greene J, Naemura J, Linsley PS: Complementarity determining region 1 (CDR1)- and CDR3-analogous regions in CTLA-4 and CD28 determine the binding to B7–1. J Exp Med 1994;180:2049–2058.
4 Burr JS, Savage ND, Messah GE, Kimzey SL, Shaw AS, Arch RH, Green JM: Cutting edge: Distinct motifs within CD28 regulate T cell proliferation and induction of Bcl-X(l). J Immunol 2001;166:5331–5335.
5 Beier KC, Hutloff A, Dittrich AM, Heuck C, Rauch A, Buchner K, Ludewig B, Ochs HD, Mages HW, Kroczek RA: Induction, binding specificity and function of human ICOS. Eur J Immunol 2000;30:3707–3717.
6 Mages HW, Hutloff A, Heuck C, Buchner K, Himmelbauer H, Oliveri F, Kroczek RA: Molecular cloning and characterization of murine ICOS and identification of B7h as ICOS ligand. Eur J Immunol 2000;30:1040–1047.
7 Yoshinaga SK, Whoriskey JS, Khare SD, Sarmiento U, Guo J, Horan T, Shih G, Zhang M, Coccia MA, Kohno T, Tafuri-Bladt A, Brankow D, Campbell P, Chang D, Chiu L, Dai T, Duncan G, Elliott GS, Hui A, McCabe SM, Scully S, Shahinian A, Shaklee CL, Van G, Mak T, Senaldi G: T-cell co-stimulation through B7RP-1 and ICOS. Nature 1999;402:827–832.

8 Dong C, Juedes AE, Temann UA, Shresta S, Allison JP, Ruddle NH, Flavell RA: ICOS co-stimulatory receptor is essential for T-cell activation and function. Nature 2001;409:97–101.
9 McAdam AJ, Greenwald RJ, Levin MA, Chernova T, Malenkovich N, Ling V, Freeman GJ, Sharpe AH: ICOS is critical for CD40-mediated antibody class switching. Nature 2001;409:102–105.
10 Tafuri A, Shahinian A, Bladt F, Yoshinaga SK, Jordana M, Wakeham A, Boucher LM, Bouchard D, Chan VS, Duncan G, Odermatt B, Ho A, Itie A, Horan T, Whoriskey JS, Pawson T, Penninger JM, Ohashi PS, Mak TW: ICOS is essential for effective T-helper-cell responses. Nature 2001;409:105–109.
11 Ogasawara K, Yoshinaga SK, Lanier LL: Inducible costimulator costimulates cytotoxic activity and IFN-gamma production in activated murine NK cells. J Immunol 2002;169:3676–3685.
12 McAdam AJ, Schweitzer AN, Sharpe AH: The role of B7 co-stimulation in activation and differentiation of CD4+ and CD8+ T cells. Immunol Rev 1998;165:231–475.
13 Ling V, Wu PW, Finnerty HF, Bean KM, Spaulding V, Fouser LA, Leonard JP, Hunter SE, Zollner R, Thomas JL, Miyashiro JS, Jacobs KA, Collins M: Cutting edge: Identification of GL50, a novel B7-like protein that functionally binds to ICOS receptor. J Immunol 2000;164:1653–1657.
14 Swallow MM, Wallin JJ, Sha WC: B7h, a novel costimulatory homolog of B7.1 and B7.2, is induced by TNFalpha. Immunity 1999;11:423–432.
15 Wang S, Zhu G, Chapoval AI, Dong H, Tamada K, Ni J, Chen L: Costimulation of T cells by B7-H2, a B7-like molecule that binds ICOS. Blood 2000;96: 2808–2813.
16 Yoshinaga SK, Zhang M, Pistillo J, Horan T, Khare SD, Miner K, Sonnenberg M, Boone T, Brankow D, Dai T, Delaney J, Han H, Hui A, Kohno T, Manoukian R, Whoriskey JS, Coccia MA: Characterization of a new human B7-related protein: B7RP-1 is the ligand to the co-stimulatory protein ICOS. Int Immunol 2000;12:1439–1447.
17 Richter G, Hayden-Ledbetter M, Irgang M, Ledbetter JA, Westermann J, Korner I, Daemen K, Clark EA, Aicher A, Pezzutto A: Tumor necrosis factor-alpha regulates the expression of inducible costimulator receptor ligand on CD34(+) progenitor cells during differentiation into antigen presenting cells. J Biol Chem 2001;276:45686–45693.
18 Aicher A, Hayden-Ledbetter M, Brady WA, Pezzutto A, Richter G, Magaletti D, Buckwalter S, Ledbetter JA, Clark EA: Characterization of human inducible costimulator ligand expression and function. J Immunol 2000;164:4689–4696.
19 Olweus J, BitMansour A, Warnke R, Thompson PA, Carballido J, Picker LJ, Lund-Johansen F: Dendritic cell ontogeny: A human dendritic cell lineage of myeloid origin. Proc Natl Acad Sci U S A 1997; 94:12551–12556.
20 Khayyamian S, Hutloff A, Buchner K, Grafe M, Henn V, Kroczek RA, Mages HW: ICOS-ligand, expressed on human endothelial cells, costimulates Th1 and Th2 cytokine secretion by memory CD4+ T cells. Proc Natl Acad Sci U S A 2002;99:6198–6203.
21 Wallin JJ, Liang L, Bakardjiev A, Sha WC: Enhancement of CD8+ T cell responses by ICOS/B7h costimulation. J Immunol 2001;167:132–139.
22 McAdam AJ, Chang TT, Lumelsky AE, Greenfield EA, Boussiotis VA, Duke-Cohan JS, Chernova T, Malenkovich N, Jabs C, Kuchroo VK, Ling V, Collins M, Sharpe AH, Freeman GJ: Mouse inducible costimulatory molecule (ICOS) expression is enhanced by CD28 costimulation and regulates differentiation of CD4+ T cells. J Immunol 2000; 165:5035–5040.
23 Villegas EN, Lieberman LA, Mason N, Blass SL, Zediak VP, Peach R, Horan T, Yoshinaga S, Hunter CA: A role for inducible costimulator protein in the CD28- independent mechanism of resistance to *Toxoplasma gondii*. J Immunol 2002;169:937–943.
24 Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Drager R, Eibel H, Fischer B, Schaffer AA, Mages HW, Kroczek RA, Peter HH: Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 2003;4:261–268.
25 Rottman JB, Smith T, Tonra JR, Ganley K, Bloom T, Silva R, Pierce B, Gutierrez-Ramos JC, Ozkaynak E, Coyle AJ: The costimulatory molecule ICOS plays an important role in the immunopathogenesis of EAE. Nat Immunol 2001;2:605–611.
26 Ozkaynak E, Gao W, Shemmeri N, Wang C, Gutierrez-Ramos JC, Amaral J, Qin S, Rottman JB, Coyle AJ, Hancock WW: Importance of ICOS-B7RP-1 costimulation in acute and chronic allograft rejection. Nat Immunol 2001;2:591–596.
27 Iwai H, Kozono Y, Hirose S, Akiba H, Yagita H, Okumura K, Kohsaka H, Miyasaka N, Azuma M: Amelioration of collagen-induced arthritis by blockade of inducible costimulator-B7 homologous protein costimulation. J Immunol 2002;169:332–339.
28 Bertram EM, Tafuri A, Shahinian A, Chan VS, Hunziker L, Recher M, Ohashi PS, Mak TW, Watts TH: Role of ICOS versus CD28 in antiviral immunity. Eur J Immunol 2002;32:3376–3385.
29 Kopf M, Coyle AJ, Schmitz N, Barner M, Oxenius A, Gallimore A, Gutierrez-Ramos JC, Bachmann MF: Inducible costimulator protein (ICOS) controls T helper cell subset polarization after virus and parasite infection. J Exp Med 2000;192:53–61.
30 Akbari O, Freeman GJ, Meyer EH, Greenfield EA, Chang TT, Sharpe AH, Berry G, DeKruyff RH, Umetsu DT: Antigen-specific regulatory T cells develop via the ICOS-ICOS-ligand pathway and inhibit allergen-induced airway hyperreactivity. Nat Med 2002;8:1024–1032.
31 Witsch EJ, Peiser M, Hutloff A, Buchner K, Dorner BG, Jonuleit H, Mages HW, Kroczek RA: ICOS and CD28 reversely regulate IL-10 on re-activation of human effector T cells with mature dendritic cells. Eur J Immunol 2002;32:2680–2686.
32 Korholz D, Kunst D, Hempel L, Sohngen D, Heyll A, Bonig H, Gobel U, Zintl F, Burdach S: Decreased interleukin 10 and increased interferon-gamma production in patients with chronic graft-versus-host disease after allogeneic bone marrow transplantation. Bone Marrow Transplant 1997;19: 691–695.
33 Nurnberger W, Michelmann I, Burdach S, Gobel U: Endothelial dysfunction after bone marrow transplantation: Increase of soluble thrombomodulin and PAI-1 in patients with multiple transplant-related complications. Ann Hematol 1998;76:61–65.