REVIEW

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Approaches and challenges in targeting memory T cells in transplant tolerance

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Abstract

Memory T cells are an important cell type in the immune system and are vital to protective immunity against invading pathogens. However, a significant fraction of memory T cells is found to be alloreactive in transplant models, i.e. they can readily attack and dismantle allografts in transplant models. As memory T cells are not as easily amenable as naïve T cells, memory T cells constitute a potent barrier to the induction of transplant tolerance. The key issues concerning memory T cells in transplantation are related to the tolerability of alloreactive memory T cells and the effects of commonly used immunosuppressive drugs on the memory response in transplant recipients. The real challenge in the future is to selectively tolerize alloreactive memory T cells but spare those involved in protective immunity following organ transplantation. This review will discuss recent advances in our understating of memory T cells in transplant models, with specific emphasis on the problems and challenges in targeting memory T cells in the induction of transplant tolerance.

Key words: transplantation, rejection, tolerance, memory, alloreactivity.

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INTRODUCTION

The remarkable success of tolerance induction strategies in transplantation has been largely restricted to naïve hosts that do not harbor significant numbers of memory T cells, for example mice housed in a pathogen-free environment. These strategies often produce immunological tolerance to a foreign transplant by exploiting the same principles that underlie tolerance to self antigens, and these principles include deletion, anergy, suppression, and immune deviation [13, 14, 16]. However, few such tolerizing protocols can withstand vigorous tests in large animal models and humans, and most protocols that work brilliantly in rodents often fail miserably when tested in primates [8, 11]. Obviously, many factors can potentially contribute to such a striking dichotomy between rodent and primate models, but one outstanding issue that has attracted considerable attention is the presence of a large number of memory T cells in large animal models. Because of their distinct features, memory T cells are becoming a growing concern in the induction of transplant tolerance in the clinic.

UNIQUE FEATURES OF MEMORY T CELLS

One of the fundamental features of adaptive immunity is the development of memory T cells. Phenotypically and functionally, memory T cells are extremely heterogeneous and consist of many different subsets. Most memory T cells in the immune system are progenies of effector cells following antigen stimulation, and these memory T cells therefore often have well-defined antigen specificities. As a population, antigen-specific memory T cells carry the entire immune history of an individual. However, certain T cells exhibit phenotypic features of memory T cells (i.e. high levels of CD44), but develop spontaneously, without known foreign antigen exposure [33, 34]; such memory T cells have less well-defined antigen specificities and are often called "memory-like T cells" [29, 30, 33, 34]. As compared with their naïve counterparts, all memory T cells can replenish themselves by slow but constant dividing in the periphery [34, 43], and therefore they are long-lived cells in the immune system.

Memory T cells are endowed with several unique features that make such cells quite distinct from their

naïve counterparts. First, memory T cells have a much lower activation threshold than naïve T cells and are less dependent on CD28 and CD154 costimulation for activation [20]. Second, memory T cells have a clear survival advantage over naïve cells; they are highly resistant to apoptotic cell death and to antibody-induced depletion therapies [19]. Third, the memory response to recall antigens is much more robust than that of naïve T cells, and on a per-cell basis, memory T cells often generate far more effector cells than their naïve counterparts [30]. Fourth, memory T cells have disseminated tissue distribution and reside in both the lymphoid and the non-lymphoid tissues (e.g. the liver, lung, and gut) [4, 18]. Finally, in contrast to naïve T cells, activation of memory T cells is not contingent on the presence of secondary lymphoid organs [2]. Clearly, memory T cells are well equipped and uniquely positioned to mount effective recall responses against invading pathogens. However, the heightened responses of memory T cells also create significant problems in transplant settings.

A combination of cell surface markers can further divide memory T cells into different subtypes. Based on the expressions of CD44, CD62L (L-selectin), CD45 isoforms, CCR5, CCR7, and an interleukin (IL-2) receptor subunit (e.g. CD122), distinct subsets of memory T cells have been described in different model systems [30]. Perhaps the identification of "**central memory**" and "**effector memory**" T cells is among the most significant findings [29]. Phenotypically, central memory T cells are $CD44^{hi}CD45RO^{hi}CCR7^{+}CD62L^{+}$ and preferentially reside in the secondary lymphoid organs such as the spleen and lymph nodes. However, effector memory T cells are $CD44^{hi}CD45RO^{hi}CCR7^{-}CD62L^{-}$ and located primarily in the non-lymphoid tissues. Importantly, central memory T cells and effector memory T cells also have striking functional differences. For example, effector memory T cells exhibit potent cytotoxicity against target cells, but central memory T cells lack such cytotoxic effects. Furthermore, central memory T cells readily produce copious amounts of IL-2, but very little interferon (IFN)-γ, whereas effector memory T cells often produce large amounts of IFN-γ and perforin, but very little IL-2 [30]. Effector memory T cells, in contrast to central memory T cells, can readily mount potent effector responses upon antigen stimulation [6]. The exact relationship between central memory T cells and effector memory T cells remains to be defined. It has been suggested that central memory T cells are the precursors of effector memory T cells, although such a distinction is not absolute in all models. Also, the mechanisms that govern the preferential development of central memory over effector memory cells or vice versa are unclear.

Several mechanisms collectively contribute to the generation and maintenance of a memory pool in the immune system. Besides immunization with specific antigens, other mechanisms also play an important role in the generation of memory T cells, such mechanisms including heterologous immunity [31] and homeostatic proliferation [39]. It has been recognized recently that memory T cells developed in response to immunization with one particular antigen can respond to other unrelated antigens, thereby affecting the subsequent memory responses to a wide range of different antigens, and this phenomenon is called heterologous immunity [30]. In transplant settings, there is solid evidence demonstrating that memory T cells that are specific to pathogens such as *Leishmania major* or lymphocytic choriomeningitis virus can respond to a defined set of transplant antigens [1, 23]. A major implication of heterologous immunity is that in humans with a normal history of vaccinations and infections, memory T cells that are potentially reactive to transplant antigens may be numerous. Indeed, as much as 50% of the alloreactive T cells in the periphery express a memory phenotype in humans [17]. Furthermore, T cells can spontaneously undergo extensive proliferation under lymphopenic conditions. This type of cell proliferation occurs in the absence of foreign antigen stimulation and is often called homeostatic proliferation [26]. Homeostatic or lymphopenia-induced proliferation is thought to be driven by cytokine availability as well as T cell receptor engagement, although it is unclear under conventional conditions whether the antigens driving T cell proliferation are self peptides, peptides from commensal microbes in the gut, other exogenous non-self antigens, or a combination of all of these [35]. One of the key features of homeostatic expansion is the acquisition of phenotypic and functional characteristics of memory T cells [7]. In experimental models, memory T cells after homeostatic proliferation are potent alloreactive T cells and can mediate prompt allograft rejection [38].

Homeostasis of memory T cells is controlled primarily by the γc-cytokines IL-7 and IL-15 [33, 34]. Some costimulatory molecules such as 4-1BB and OX40 also contribute to the generation and survival of memory T cells [3]. Although IL-7 and IL-15 have some overlapping functions, IL-7 appears to be particularly important for cell survival, whereas IL-15 is necessary to drive homeostatic proliferation of memory T cells [10]. This applies especially to memory $CD8^{+}$ T cells, while for memory $CD4^{+}$ T cells, IL-7 seems to play a more conspicuous role than IL-15 [15, 32].

CRITICAL ROLE OF MEMORY T CELLS IN TRANSPLANT REJECTION

Memory T cells are extremely diverse, both phenotypically and functionally. This raises an important question as to whether all types of memory T cells are equally effective in mediating transplant rejection or in resistance to tolerance induction. There is no doubt that the donor-specific memory T cells are potent effector cells in mediating the rejection response. In animal models, the most effective means of generating donor-specific memory T cells is by priming the transplant recipients with donor antigens [12]. In the clinical settings, donor-

-specific memory cells are often generated by blood transfusions, pregnancy, or failed first transplants. The donor-specific memory T cells are known to mount a second-set rejection response, which is extremely difficult to inhibit when it happens [37]. It has been shown that purified memory T cells, unlike their naïve counterparts, mediate allograft rejection without the need to home first to the secondary lymphoid tissues, and the rejection response is not inhibited by agents that block CD28 and CD154 costimulation [37]. Furthermore, central memory cells and effector memory cells appear to be equally potent in mediating the rejection response [21].

There is considerable interest in the role of memory-like T cells generated by homeostatic proliferation or by heterologous immunity in transplant rejection [31]. We and others have demonstrated that memory T cells post homeostatic proliferation are potent effector cells in mediating transplant rejection [38, 39]. In contrast to naïve T cells, memory T cells developed after homeostatic proliferation are highly resistant to certain tolerizing therapies [38, 39]. Similarly, heterologous immunity also results in the generation of memory T cells that are alloreactive in a transplant model. For example, stimulation of B6 mice with parasitic or viral antigens has been shown to induce effector/memory T cells that are highly responsive to alloantigens, and transplantation of allografts onto such pathogen-challenged mice often results in accelerated rejection [23]. Although the pathogen-initiated "danger signals" may contribute to the accelerated rejection response, the pathogen-induced memory T cells selected from the challenged mice are clearly responsive to the donor-derived alloantigens [23]. In certain models, memory T cells have been suggested to be key mediators in the chronic loss of allografts, suggesting a possibility that memory T cells and chronic rejection may be intimately associated. Hence, regardless of their phenotypes and the means by which they develop, memory T cells are key players in mediating transplant rejection.

MEMORY T CELLS AS A BARRIER TO TRANSPLANT TOLERANCE

Clearly, memory T cells are potent effector cells in transplant rejection. A key question concerning memory T cells in transplantation is whether they are as amendable as their naïve counterparts in tolerance induction. This is an important and clinically relevant issue and has been actively pursued by many different groups around the world. In spite of different model systems used to address this issue, the conclusions reached by different groups are quite similar, i.e. memory T cells are highly resistant to tolerance induction. In most experimental models, tolerizing therapies that consistently produce allograft tolerance in naïve animals often completely fail to do so in memory-rich animals. For example, donor-specific transfusion (DST) plus anti-CD154 (MR1) induces uniform transplant tolerance to cardiac and islet allografts in mice [37]. However, the same protocol completely fails to block rejection in mice pre-sensitized with the skin allografts from the same donor [41]. Similarly, adoptive transfer of primed donor-specific T cells into recipient mice prevents the induction of cardiac allograft tolerance in naïve mice by the DST and MR1 protocol [37]. Other costimulation blockade-based tolerizing protocols also fail to induce tolerance in mice harboring memory T cells specific for pathogens [1, 23]. The role of pathogen-specific memory T cells that are cross-reactive with alloantigens in resistance to tolerance induction is elegantly demonstrated in a recent report showing that virally induced memory T cells can interfere with the most robust form of transplant tolerance [1]. Hence, memory T cells generated either by prior exposure to alloantigens or by pathogen infections are potent barriers to tolerance induction in transplant models.

The overall resistance of memory T cells to tolerance induction also applies to memory T cells generated by homeostatic proliferation. It has been shown that treatment of naïve B6 mice with depleting anti-CD4 and anti-CD8 monoclonal antibodies (mAbs) induces profound depletion of peripheral T cells [24, 39]. However, not all T cells are equally sensitive to the depletion therapy and a subset of residual T cells can undergo extensive homeostatic proliferation in the treated mice [22, 39]. Interestingly, memory T cells generated by homeostatic proliferation are highly resistant to the induction of allograft tolerance by DST plus CD154 blockade treatment [39]. In our own study, we used immunodeficient mice as a tool to generate memory T cells [38]. Memory T cells generated by homeostatic proliferation in the immunodeficient mice are also highly resistant to CD28 and CD154 blockade-induced tolerance [38]. Thus, resistance to tolerance induction appears to be a general feature of all types of memory T cells that are alloreactive.

NEW APPROACHES TO TARGETING ALLOREACTIVE MEMORY T CELLS

Clearly, memory T cells are potent effector T cells in transplant rejection, and the presence of memory T cells in transplant recipients hinders the induction of allograft tolerance. Thus, development of therapeutic protocols that can effectively and reliably target alloreactive memory T cells is a pressing issue in tolerance induction in the clinic.

Most of the current immunosuppressive drugs that are effective in blocking naïve T cells have minimal effects in preventing memory T cell-mediated rejection [36], suggesting that the activation requirement of memory T cells is quite different from that of naïve T cells in rejection. In fact, there have been reports on the correlation between the presence of pre-transplant alloreactive memory T cells and acute rejection episodes that

occurred despite tacrolimus- and sirolimus-based therapies. Moreover, leukocyte depletion therapies using antithymocyte globulin, alemtuzumab, or anti-human CD52 mAb are less effective at eliminating pre-existing memory T cells. Indeed, following leukocyte-depletion treatments, effector memory $CD4^+$ T cells are a dominant remaining cell type and appear to be capable of initiating rejection episodes [24]. In some studies, the commonly used immunosuppressive agents may impact the ability of memory T cells to respond to alloantigens *in vitro* [24]. However, their efficacy *in vivo* in limiting memory T cell-mediated rejection is often less striking.

Thus there is urgent need to develop alternative approaches to targeting alloreactive memory T cells in transplant models. Most studies in this area are focused on means to prevent activation and survival of memory T cells and ways to avoid their accumulation in the grafts. It appears that, in contrast to naïve T cells, which rely on CD28 and CD154 for activation, memory T cells may need other alternative T cell costimulatory molecules for activation and effector functions. For example, interaction of inducible costimulator (ICOS) on T cells with B7h (B7RP-1) on antigen-presenting cells is crucial for the activation of previously primed T cells, including memory T cells. Blocking the ICOS costimulatory pathway prolongs allograft survival in rodents, particularly if the blockade is administered at a delayed time point after transplantation [9], suggesting that it interferes with the recall response of primed T cells. Also, 4–1BB/4–1BBL interactions have been shown to be important in $CD8^+$ T cell recall responses [5]. Another costimulatory pathway that may be important for the recall response of memory T cells, particularly the $CD4^+$ population, is the OX40/OX40L pathway [25, 28]. In certain models, simultaneous blockade of the OX40/OX40L and B7/CD28 pathways prolongs cardiac allograft survival in recipients that had received primed T cells [40]. Furthermore, blockade of the CD27/CD70 costimulatory pathway has been shown to lead to indefinite allograft survival despite the presence of memory $CD8^+$ T cells [27]. This finding is consistent with the role of CD70/CD27 costimulation in the activation of antigen-experienced $CD8^+$ T cells. Therefore, it seems that memory T cells may require a distinct set of costimulatory molecules to function properly, which may open new opportunities for the therapeutic intervention of memory T cells in transplant settings. Further studies of the costimulatory requirements for memory T cells may lead to the design of new strategies to manipulate memory responses to allografts in addition to those already effective in preventing rejection mediated by naive T cells.

There have been other attempts to control memory T cell responses in transplant models, and the findings are equally exciting. For example, the NF-κB nuclear translocation blocker 15-deoxyspergualin prevented activation of donor antigen-specific memory CD8 T cells and synergized with costimulatory blockade to induce long-term skin allograft survival in a mouse model [1]. Administration of the sphingosine-1 phosphate receptor agonist FTY720 resulted in lymphoid sequestration of donor-specific memory CD4 T cells in the peripheral lymph nodes, thus delaying the heart allograft rejection in mice [42]. However, all of these new strategies have yet to be tested and validated in large animal models.

FUTURE CHALLENGES IN TARGETING MEMORY T CELLS IN TRANSPLANTATION

Several key questions need to be addressed before new strategies can be successfully designed to prevent memory T cell-mediated rejection. These questions include the following: 1) What are the mechanisms and key molecular pathways involved in the generation, persistence, and effector functions of alloreactive memory T cells? 2) What are the events that regulate the survival advantage of memory T cells in the periphery? 3) Are alloreactive memory T cells susceptible to Treg-mediated suppression? If not, can they be rendered susceptible by targeting certain key molecular pathways involved in memory T cell function? 4) Are memory T cells subject to deletion, anergy, suppression, or immune deviation in the same way as naïve T cells in tolerance induction?

Of course, the greatest challenge in the future is how to tolerize memory T cells in an antigen-specific manner, i.e. selective deletion or suppression of alloreactive memory T cells without compromising the host's entire protective immunity against pathogens. However, the sheer size of the alloreactive T cell repertoire, its cellular diversity, and the presence of extensive cross-reactivity within the memory compartment may present new challenges, even if tolerance is successfully established. It is highly desirable that tolerization of the alloreactive T cells in transplant recipients should avoid drastic alterations of the host's T cell repertoire and the loss of protective immunity against certain pathogens. Otherwise, the risk of a compromised T cell repertoire will be high.

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REFERENCES

1. Adams A. B., Williams M. A., Jones T. R., Shirasugi N., Durham M. M., Kaech S. M., Wherry E. J., Onami T., Lanier J. G., Kokko K. E., Pearsib T. C., Ahmed R. and Larsen C. P. (2003): Heterologous immunity provides a potent barrier to transplantation tolerance. J. Clin. Invest., **111**, 1887–1895.
2. Chalasani G., Dai Z., Konieczny B. T., Baddoura F. K. and Lakkis F. G. (2002): Recall and propagation of allospecific memory T cells independent of secondary lymphoid organs. Proc. Natl. Acad. Sci. USA, **99**, 6175–6180.
3. Croft M. (2003): Co-stimulatory members of the TNFR

family: keys to effective T cell immunity? Nat. Rev. Immunol., **3**, 609–620.
4. Cush J. J., Pietschmann P., Oppenheimer-Marks N. and Lipsky P. E. (1992): The intrinsic migratory capacity of memory T cells contributes to their accumulation in rheumatoid synovium. Arthritis Rheum., **35**, 1434–1444.
5. Dawicki W., Bertram E. M., Sharpe A. H. and Watts T. H. (2004): 4-1BB and OX40 act independently to facilitate robust CD8 and CD4 recall responses. J. Immunol., **173**, 5944–5951.
6. Geginat J., Sallusto F. and Lanzavecchia A. (2001): Cytokine-driven proliferation and differentiation of human naive, central memory, and effector memory CD4+ T cells. J. Exp. Med., **194**, 1711–1720.
7. Goldrath A. W., Bogatzki L. Y. and Bevan M. J. (2000): Naive T cells transiently acquire a memory-like phenotype during homeostasis-driven proliferation. J. Exp. Med., **192**, 557–564.
8. Hale D. A., Dhanireddy K., Bruno D. and Kirk A. D. (2005): Induction of transplantation tolerance in non-human primate preclinical models Philos. Trans. R Soc. Lond B Biol. Sci., **360**, 1723–1737.
9. Harada H., Salama A. D., Sho M., Izawa A., Sandner S. E., Ito T., Akiba H., Yagita H., Sharpe A. H., Freeman G. J. and Sayegh M. H. (2003): The role of the ICOS-B7h T cell costimulatory pathway in transplantation immunity. J. Clin. Invest., **112**, 234–243.
10. Kieper W. C., Tan J. T., Bondi-Boyd B., Gapin L., Sprent J., Ceredig R. and Surh C. D. (2002): Overexpression of interleukin (IL)-7 leads to IL-15-independent generation of memory phenotype CD8+ T cells. J. Exp. Med., **195**, 1533–1539.
11. Koehn B., Gangappa S., Miller J. D., Ahmed R. and Larsen C. P. (2006): Patients, pathogens, and protective immunity: the relevance of virus-induced alloreactivity in transplantation. J. Immunol., **176**, 2691–2696.
12. Lakkis F. G. and Sayegh M. H. (2003): Memory T cells: a hurdle to immunologic tolerance. J. Am. Soc. Nephrol., **14**, 2402–2410.
13. Lechler R., Garden O. A. and Turka L. A. (2003): The complementary roles of deletion and regulation in transplantation tolerance. Nat. Rev. Immunol., **3**, 147–158.
14. Lechler R., Sykes M., Thomson A. W. and Turka L. A. (2005): Organ Transplantation-how much of the promise has been realized? Nat. Med., **11**, 605–613.
15. Lefrancois L. (2002): Dual personality of memory T cells. Trends Immunol., **23**, 226–228.
16. Li X. C., Strom T. B., Turka L. A. and Wells A. D. (2001): T cell death and transplantation tolerance. Immunity, **14**, 407–416.
17. Lombardi G., Sidhu S., Daly M., Batchelor J. R., Makgoba W. and Lechler R. I. (1989): Are primary alloresponses truly primary? Int. Immunol., **2**, 9–13.
18. Masopust D., Vezys V., Marzo A. and Lefrancois L. (2001): Preferential localization of effector memory cells in nonlymphoid tissue. Science, **291**, 2413–2417.
19. Minamimura K., Gao W. and Maki T. (2006): CD4+ regulatory T cells are spared from deletion by antilymphocyte serum, a polyclonal anti-T cell antibody. J. Immunol., **176**, 4125–4132.
20. Neujahr D. C., Chen C., Huang X., Markmann J. F., Cobbold S., Waldmann H., Sayegh M. H., Hancock W. W. and Turka L. A. (2006): Accelerated memory cell homeostasis during T cell depletion and approaches to overcome it. J. Immunol., **176**, 4632–4639.
21. Obhrai J. S., Oberbarnscheidt M. H., Hand T. W., Diggs L., Chalasani G. and Lakkis F. G. (2006): Effector T cell differentiation and memory T cell maintenance outside secondary lymphoid organs. J. Immunol., **176**, 4051–4058.
22. Ogawa N., List J. F., Habener J. F. and Maki T. (2004): Cure of overt diabetes in NOD mice by transient treatment with anti-lymphocyte serum and exendin-4. Diabetes, **53**, 1700–1705.
23. Pantenburg B., Heinzel F., Das L., Heeger P. S. and Valujskikh A. (2002): T cells primed by leishmania major infection cross-react with alloantigens and alter the course of allograft rejection. J. Immunol., **169**, 3686–3693.
24. Pearl J. P., Parris J., Hale D. A., Hoffmann S. C., Bernstein W. B., McCoy K. L., Swanson S. J., Mannon R. B., Roederer M. and Kirk A. D. (2005): Immunocompetent T-cells with a memory-like phenotype are the dominant cell type following antibody-mediated T-cell depletion. Am. J. Transplant., **5**, 465–474.
25. Prell R. A., Evans D. E., Thalhofer C., Shi T., Funatake C. and Weinberg A. D. (2003): OX40-mediated memory T cell generation is TNF receptor-associated factor 2 dependent. J. Immunol., **171**, 5997–6005.
26. Prlic M., Blazar B. R., Khoruts A., Zell T. and Jameson S. C. (2001): Homeostatic expansion occurs independently of costimulatory signals. J. Immunol., **167**, 5664–5668.
27. Rothstein D. M. and Sayegh M. H. (2003): T-cell costimulatory pathways in allograft rejection and tolerance. Immunol. Rev., **196**, 85–108.
28. Salek-Ardakani S., Song J., Halteman B. S., Jember A. G.-H., Akiba H., Yagita H. and Croft M. (2003): OX40 (CD134) controls memory T helper 2 cells that drive lung inflammation. J. Exp. Med., **198**, 315–324.
29. Sallusto J., Lenig D., Forster R., Lipp M. and Lanzavecchia A. (1999): Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature, **401**, 708–712.
30. Seder R. A. and Ahmed R. (2003): Similarities and differences in CD4+ and CD8+ effector and memory T cell generation. Nat. Immunol., **4**, 835–842.
31. Selin L. K. and Brehm M. A. (2007): Frontiers in nephrology: heterologous immunity, T cell cross-reactivity, and alloreactivity. J. Am. Soc. Nephrol., **18**, 2268–2277.
32. Selin L. K. and Welsh R. M. (2004): Plasticity of T cell memory responses to viruses. Immunity, **20**, 5–16.
33. Sprent J. (2003): Turnover of memory-phenotype CD8+ T cells. Microbes Infect., **5**, 227–231.
34. Sprent J. and Surh C. D. (2001): Generation and maintenance of memory T cells. Curr. Opin. Immunol., **13**, 248–254.
35. Surh C. D., Boyman O., Purton J. F. and Sprent J. (2006): Homeostasis of memory T cells. Immunol. Rev., **211**, 154–163.
36. Valujskikh A. and Li X. C. (2007): Frontiers in nephrology: T cell memory as a barrier to transplant tolerance. J. Am. Soc. Nephrol., **18**, 2252–2261.
37. Valujskikh A., Pantenburg B. and Heeger P. S. (2002): Primed allospecific T cells prevent the effects of costimulatory blockade on prolonged cardiac allograft survival in mice. Am. J. Transplant., **2**, 501–509.
38. Vu M. D., Clarkson M. R., Yagita H., Turka L. A., Sayegh M. H. and Li X. C. (2006): Critical, but conditional, role of OX40 in memory T cell-mediated rejection. J. Immunol., **176**, 1394–1401.
39. Wu Z., Bensinger S. J., Zhang J., Chen C., Yuan X., Huang X., Markmann J. F., Kassaee A., Rosengard B. R., Han-

cock W. W., Sayegh M. H. and Turka L. A. (2004): Homeostatic proliferation is a barrier to transplantation tolerance. Nat. Med., **10**, 87–92.
40. Yuan X., Salama A. D., Dong V., Schmitt I., Najafian N., Chandraker A., Akiba H., Yagita H. and Sayegh M. H. (2003). The role of the CD134-CD134 ligand costimulatory pathway in alloimmune responses *in vivo*. J. Immunol., **170**, 2949–2955.
41. Zhai Y., Meng L., Gao F., Busuttil R. W. and Kupiec-Weglinski J. W. (2002): Allograft rejection by primed/memory CD8+ T cells is CD154 blockade resistant: therapeutic implications for sensitized transplant recipients. J. Immunol., **169**, 4667–4673.
42. Zhang Q., Chen Y., Fairchild R. L., Heeger P. S. and Valujskikh A. (2006): Lymphoid sequestration of alloreactive memory CD4 T cells promotes cardiac allograft survival. J. Immunol., **176**, 770–777.
43. Zheng X., Sun S., Hwang I., Tough D. F. and Sprent J. (1998): Potent and selective stimulation of memory phenotype CD8+ T cells *in vivo* by IL-15. Immunity, **8**, 591–599.