Study Progress of the Relationship of Memory T Cells with Transplantation Immunity

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Abstract

Memory T cells are widely distributed in the body's tissues and plays a very important role in the fight against pathogenic microorganisms infections. On the other hand, these characteristics of memory T cells become a huge obstacle to induce transplantation tolerance. This paper describes the characteristics of memory T cells, and the mechanism of producing and maintaining. Also, the relationship between the memory T cells and transplant rejection, and the process of possible measures to suppress the rejection are summarized.

Keywords: Memory T cells, Transplantation Immunity

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Introduction

The T cell population of a normal organism is consisted of two parts: naive T cells and memory T cells. With respect to Naive T Cells, memory T cells are provided with stronger phagocytic ability and immune-reactivity. Memory T cells usually locate in lymphatic and non-lymphoid tissues [1], and the Homing Receptors expressed by them may drive the memory T cells to migrate to the phlogistic or transplanted parts [2, 3]. memory T cells are able to differentiate into more effector T cells when being stimulated by antigens and the immunoreaction mediated by them is more intense than that by naive T cells [4, 5]. Thus memory T cells play a crucial role in the fighting against the pathogenic microbial infection. However, these characteristics of memory T cells bring about a lot of trouble for induction of generation of transplantation immune tolerance. So far there have been a plenty of tests which indicate that if the acceptor has plentiful in vivo memory T cells, it will still be very difficult to induce it to generate immune tolerance even if those memory T cells are specific to the anti-pathogenic microbes [6]. For this reason, how to suppress the generation of memory T cells and thus form antigen-specific immunosuppression has become a key problem of induction of immune tolerance. This article gives a summarization over the research progress of the relationship of memory T cells with transplantation immunity.

Characteristics of Memory T Cells

Compared to naive T cells, memory T cells are provided with stronger power to clean up extrinsic antigens regardless of whether they are pathogenic microbes or allogeneic grafts (Table 1). Firstly, compared to naive T cells, memory T cells have stronger and faster reactivity against extrinsic antigens. After having been stimulated by antigens for hours, memory T cells can soon generate a great deal of effector T cells to clean up antigens while naive T cells need days to generate just a small number [7, 8]. Secondly, memory T cells may survive in the human body for several years and even lifelong, not to mention that this is independent of antigens and MHC complex [9, 10]. Although mature naive T cells can live in the human body for months and even years, they need low-level and incessant stimulation of MHC-autoantigen peptide complex for survival [11-13]. Thirdly, naive T cells locate only in secondary lymphoid tissues and the extrinsic antigens can only activate them by invasion into the secondary lymphoid tissues. Memory T cells are distributed in both lymphatic and non-lymphoid tissues and may directly meet with the extrinsic antigens at non-lymphoid tissues, which may thus be cleaned up before entering the secondary lymphoid tissues [1, 14, 15]. Based on the aforesaid characteristics, memory T cells, compared to naive T cells, give rise to tremendous obstruction against generation of transplantation immune tolerance while being more helpful to the protective effect of the organism against extrinsic antigens.

Generation and maintenance of Memory T Cells

Antigen-specific T cells can differentiate into effector T cells and clean up extrinsic antigens while meeting with them, and along with the process of immunoreaction, most of the effector T cells face apoptosis while a small number of them survive and become memory T cells that can survive for long. So far it has been proved that antigen stimulation on naive T cells is the requirement to generate memory T cells [16], and the number of generated memory T cells is determined by the strength of the initial immune response [17].

Activation and propagation of T cells need the existence of costimulatory molecules and it has been proved that there are several pairs of costimulatory molecules relating to the generation of memory T cells. Experiments indicate that the propagation of CD4 + T Cells and the generation of memory T cells of murines which are in deficiency of CD28, CD40L (CD154) or OX40 are undergoing suppression, but the generation of memory T cells are not completely interdicted [18]. While the generation of CD8+ Memory T cells of murines that are in deficiency of 4-1BBL, CD40L and CD27 (CD70L) is in decrease. Therefore, mere interdicting a pair of costimulatory molecules cannot suppress the generation of memory T cells [19]. Moreover, insufficiency or deficiency of a certain cytokine cannot block the generation of memory T cells either.

Memory T cells can survive for years and even for the whole life without repeated stimulation of antigens. At least there are two mechanisms that are relating to such 'longevity' of memory T cells: 1. Antigen-independent steady state propagation; 2. Memory T cell itself is provided with characteristics of long-term survival under quiescent status [20]. Presently, it is believed that the steady state propagation of memory T cells is much slower than that caused by invasion of antigens and characterized with decrease of lymphocytes, but still faster than the steady state propagation of naive T Cells [21]. Inside the body of a murine model which has been infected by virus, the T cells with CD8+ antiviral specificity need about 35 days to restore to the status

Characteristics	Naive T Cells	Effector T Cells	Memory T Cells
Lifespan	Months to years	Hours to days	Years to the whole life
Distribution	Secondary lymphoid tissue	Non-lymphoid tissue (Target organ)	Lymphoid tissue and peripheral non-lymphoid tissue
Sensibility	Insensitive to low dosage	Highly sensitive	Highly sensitive
Aging	Long-term with weak effect	Short-term effective	Long-term highly effective
State of Activation	Quiescent	Active	Quiescent
Costimulatory Conditions	Indispensable (such routine constitutive classic costimulatory pathways as CD28 and CD40L needed)	/	Low requirements (routine costimulatory pathways not needed and different subgenera need their own inductive co-stimulator as OX40 and ICOS etc.)
Heterogeneity	Relatively homogeneous	/	Multiple subgenera
Antigen Presenting Cells	Professional (Dendritic Cells)	/	Non-professional (B cells and endothelial cells etc.)
Surface Phenotype	CD45RB hi/Ly-6C (mouse) CD45RA (human) CD44 lo CD11a lo CD62L hi CCR7 hi (human)	CD44 hi CD62 lo	CD45RB/Ly-6C lo (mouse) CD45RO (human) CD44hi CD11ahi CD62L lo/hi CCR7 lo/hi

before infection [9]. Presently, it is considered that IL-15 is prerequisite for the steady state propagation of memory T cells [22], and IL-7 can promote the survival of CD8+ memory T cells by means of up-regulation of anti-apoptotic molecules (such as Bcl-2 and Bcl-XL), while IL-2 suppresses the steady state propagation of memory T cells [23].

Relationship of Memory T Cells with Transplantation Rejection

Compared to laboratory animals, wild animals and human bodies contain plentiful memory T cells. About 40-50% of the T cells in adult Peripheral Blood (PB) are memory T cells phenotype [24]. Allogeneic reactivity memory T cells inside the human body are formed mainly because of gestation, blood transfusion and the previous allogeneic transplantation. However, some people do not have similar contact history, but they still contain plentiful allogeneic reactivity memory T cells in their bodies, which mainly relates to cross reaction between antigens [25]. After having gone through repeated stimulation by pathogenic microbes, the human body produces a great deal of memory T cells targeting corresponding virus or bacteria, and due to the cross reaction between antigens, these memory T cells can also identify allogeneic tissue antigens and thus cause transplantation rejection. This phenomenon is also called immunological heterogeneity [26]. Zhai et al [27] had discovered that CD8+ memory T cells can interdict long-term survival of heart transplant induced by such combined treatment as donor-specific spleenocyte transfusion (DST), CD154 monoclonal antibody and CD40 L monoclonal antibody, etc.. There are direct evidences indicating that Virus Sensitization Allogeneic Reactivity T Cells can reverse immune

tolerance induced by micro-chimeric state [28]. In the same way, Leishmania can induce Allogeneic Reactivity CD4+ T lymphocite subpopulation while the latter is able to directly accelerate rejection reaction of allogeneic skin grafting [25]. And those animals accompanied with Leishmania infection have no way to induce up immune tolerance for skin grafting even if they have been processed with conventional treatment (such as DST+ CD40L antibody). A great deal of researches show that CD4+ and CD8+ T lymphocytes which are not donor-antigen-specific can interdict generation of immune tolerance by means of promoting the rejection reaction of allogeneic transplants through the cross reaction of antigens. A good deal of studies indicate that Allogeneic Reactivity memory T cells are closely related to the generation of acute and chronic rejection reactions, and the conventional immune inhibitors cannot effectively suppress the rejecttion mediated by memory T cells [29].

Inhibiting the rejection mediated by Memory T Cells

Although memory T cells are able to effecttively protect the organism from jeopardy of pathogenic microbes, they also generate very harmful influence on successful induction of transplantation tolerance [30]. Currently existing immunosuppressors are almost directing at suppressing activation of naive T cells and are of no effect on memory T cells. Researches indicate that there are still plentiful memory T cells existing in the bodies of patients who have been treated with large doses of immunosuppressors, which means the immunosuppressors are of no effect on Allogeneic reactivity memory T cells. Therefore, how to solve rejection mediated by memory T cells has become a problem urgently to be solved in the field of transplantation. The comforting news is, specific to this problem, some delightful progresses have been made: (1) Interdicting costimulatory molecules to suppress the activation of T cells. Studies show that some costimulatory molecules (such as ICOS, 4-1BB, OX40 and CD30) may possibly relate to adjustment of functions of memory T cells. Different from CD28, these costimulatory molecules are only expressed on the surfaces of activated T cells and their expression of specificity indicates that they are possibly closely related to the activated T cells [32]. Researches of Minh Diem Vu et al [32] show that joint interdiction of CD28/CD154 and OX40 can obviously extend the survival time of transplants of murines being transplanted for a second time (i.e. rejection model mediated by memory T cells), while mere interdiction of CD28/CD154 or OX40 cannot. Besides, mere interdiction of ICOS/ICOS and 4-1BB/4-1BBL pathways or joint interdiction of CD28/CD154 cannot extend the survival time of transplants. This shows that OX40 is the key target spot for treatment of rejection mediated by memory T cells.

(2) Preventing memory T cells from migrating to the transplant: FTY720 is a kind of new type immunosuppressor derived from cordyceps sinensis and undergone chemical modifycation. It can cause lymphocytes to stay at the secondary lymphoid tissue and suppress their migration to the transplanted organs through influence on the functions of chemo-tactic factors. FTY720 is able to effectively act on central memory T cells and inhibit their entering peripheral tissues [33].

(3) Memory T Cells populations which clean up donor specificity: application of anti-T lymphocyte antibodies can effectively kill and wound the memory T cells or reactivity T cells inside the body and extend the survival time of transplants. Yet disadvantages of this therapy are that the T cells which are protective to the organism are largely killed and wounded along with killing and wounding of the donor-specific memory T cells and thus cause significant impact on the immune system of the

patient. Besides, anti-lymphocyte anti-body cannot completely clean up the T cells inside the body, and the residual T cells differentiate into proportionally increased memory T cells after having undergone decreasing propagation of lymphocytes, lower down the threshold of immunoreaction and generate very disadvantageous impact on the built state of immune tolerance [34]. K. Minaminura [24] et al had found out in their researches that combined application of Rapamycin and large dose of anti-lymphocyte serum can obviously extend the survival time (>100 days) of trans-plants of murines with secondary skin trans-plantation. Although further researches are to be done for the substantial mechanism therein, this kind of therapy has provided a new train of thought for con-quering the rejection mediated by memory T cells.

Conclusion

Extensive tissue distribution, expanded antigen recognition spectrum, special migration features, lower activating conditions and characteristics of quickly mediating immune response allow memory T cells to cause fast and intense rejection reaction in organ transplantation and be very difficult to be supressed by traditional anti-rejection drugs. Thus becoming a difficulty in treatment process. This is one of the major obstacles for inducing immune tolerance [34-38]. Effective control of anamnesis reaction of T cells can not only suppress the memory T cells that have been generated, but also the generation of newborn T cells. Clear understanding of the formation mechanism of memory T cells will bring about great significance for the induction of immune tolerance. Surely, how to selectively suppress donor-specific memory T cells and not to damage the immunological ability of the patient will become a key point for future research.

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