Immunology Letters 148 (2012) 53–58

Contents lists available at SciVerse ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

Memory T-cell-specific therapeutics attenuate allograft rejection via mediation of alloreactivity in memory cells

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ARTICLE INFO

Article history:
Received 17 May 2012
Received in revised form 30 July 2012
Accepted 1 August 2012
Available online xxx

Keywords:
Memory T cell
Immunosuppressant
Tolerogenic dendritic cells
Regulatory T cells
Alloreactivity

ABSTRACT

Many means in inbred rodent models promoted long-term graft survival or donor-specific tolerance, but less so in nonhuman primates, outbred rodents or human patients. A diverse repertoire of memory T cells, derived from heterologous immunity or prior to exposure to alloantigen, has been believed to be an important part of this barrier. Memory T cells have a unique capacity to generate effector functions quickly upon re-exposure to antigen, and this capacity is achieved by reduced activation thresholds, and expressed high level trafficking and adhesion molecules, which is likely responsible for their exhibiting differential susceptibility to immune therapeutics compared with naïve T cells. This review outlines recent progress on characteristics of memory T cells and focuses on these potential therapies targeting memory T cells which are likely to ameliorate allograft rejection by inducing transplant tolerance.

1. Introduction

Immunological memory is a fundamental hallmark of adaptive immunity and plays a critical role in providing antigen-specific protective immunity in higher vertebrates [1]. The immune repertoire is constantly being imprinted through exposure to environmental antigens, resulting in their rapid clearance following re-exposure to the same antigen [1]. In adults, 40–50% of T cells in the peripheral blood have memory phenotypes [2]. It is thought that memory T cells (T_Ms) are generated through continuous exposure to bacterial and viral pathogens [3], blood transfusions or pregnancies, as well as transplantation [4–6]. Primed T cells take on characteristics indicative of prior activation and give rise to a population of cells collective referred to as T_Ms. These T_Ms mediate protective immune responses by invading pathogens and are thought to provide an evolutionary survival advantage [1]. However, there is an increasing amount of evidence to indicate that T_Ms can cross-react with alloantigens, partially accounting for the high frequency of alloreactivity [7,8]. Alloreactive T_Ms can become activated by specific pathogens, or due to a molecular resemblance between a microbial antigen/self major histocompatibility complex (MHC) and cross-reactivity with an allogeneic MHC T cell [9]. Such cross-reactivity of T_Ms can lead to pre-sensitization in a potential recipient despite lack of exposure to tissues from a donor [10,11]. In the context of transplantation, emerging evidence has revealed the issues associated with T_Ms for transplant recipients. The T_Ms generate antigen-specific protective immunity, and pose a barrier to longtime allograft survival and transplant tolerance by cross-reactivity with allogeneic antigens [3]. In this review, we describe recent advances related to the characteristics of T_Ms, and discuss their roles in allograft rejection and potential therapies.

2. Characteristics of T_Ms

Naïve T cells (T_Ns) emerge from the thymus with a non-activated phenotype characterized by T cell receptor (TCR) density and limited adhesion molecules. The phenotypes of T_Ns remain constant until they are primed by an antigen, at which point they are then considered T_Ms [1]. The expression of chemokine, selectin, and integrin receptors is altered after the activation of T_Ms. T_Ms also express higher levels of CD2, CD11a and CD44 as compared with their naïve counterparts. In humans, T_Ms express the RO isoform of CD45 as opposed to the RA isoform, and possess direct cytolytic functions in vivo [1]. In contrast to T_Ns, T_Ms exhibit enhanced

Abbreviations: T_Ms, memory T cells; MHC, major histocompatibility complex; T_Ns, naïve T cells; TCR, T cell receptor; T_{CM}s, central memory T cells; T_{EM}s, effector memory T cells; T_Es, effector T cells; HLA, human leukocyte antigen; EBV, Epstein–Barr virus; CTLA4, cytotoxic T-lymphocyte antigen 4; LFA-3, leukocyte function-associated antigen-3; GVHD, graft-versus-host disease; mAb, monoclonal antibody; S1P, sphingosine 1-phosphate; JAKs, janus kinases; γc, γ chain; IκB, inhibitor of kappa-light-chain-enhancer of activated B; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B; Tregs, regulatory T cells; Tol DCs, tolerogenic dendritic cells; pDCs, plasmacytoid dendritic cells.

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http://dx.doi.org/10.1016/j.imlet.2012.08.001

activation, distinct phenotype trafficking, and functions related to adhesion. Upon re-exposure to an antigen, they secret cytokines faster than naïve T cells with reduced activation thresholds [12].

Emerging evidence has shown that T_Ns and T_Ms can cross-react with alloantigens, and the specificity of T_Ns and T_Ms pools is likely to be quite different [13]. The issue of whether alloreactive frequencies in T_Ms pools are higher, lower or equivalent as compared with T_Ns has been thoroughly discussed over the last two decades. Recently, research has shown that alloreactive T_Ms are likely to be limited to a few discrete TCR clones when compared with T_Ns. This is likely owing to the restricted TCR repertoires of T_Ms. However, the frequency of a given clone is higher in T_Ms pools compared with T_Ns pools [14,15]. TCR clones among T_Ms are therefore thought to be responsible for higher alloreactivity than that seen in T_Ns. In the context of transplantation, pre-existing donor-specific T_Ms are believed to participate in the development of acute and chronic rejection.

2.1. T_M subsets

The phenotype of heterogeneous T_Ms has been classified into two subsets: central T_Ms (T_{CM}s; CD62L^{hi}CCR7^{+}), which circulate in non-lymphoid or lymphoid tissues and proliferate in response to stimulation when an antigen is encountered; and effector T_Ms (T_{EM}s; CD62L^{lo}CCR7^{-}), which migrate to non-lymphoid tissues and release cytokines thereby providing an effector function at peripheral sites [1,16,17]. This classification highlights that the overall frequency within T_Ms pools may be similar, but their behavior may be distinct, depending on differentiation status.

2.2. Models of T_M generation

Whether T_Ms arise from naïve or effector T cells (T_Es) remains unclear, four models have been suggested to describe the generation of T_Ms. First, a separate lineage model suggests that effector and T_Ms can be directly generated by homeostatic turnover of different naïve precursors [18–20] (Fig. 1A). Second, naïve cells undergoing their first division produced unequal numbers of effector and memory populations [21] (Fig. 1B). Third, a linear progression model postulates that memory populations are derived from a pool of primed effector cells that experienced expansion and contraction before finally becoming T_Ms [22,23] (Fig. 1C). Fourth, during the latter stages of an immune response, a remaining, small amount of antigen fails to adequately stimulate T cells; therefore, naïve T cells differentiate into memory populations [24] (Fig. 1D).

3. The role of T_Ms in allograft rejection

Using inbred rodent models, long-term graft survival or donor-specific tolerance has been achieved several times. Success has been limited in nonhuman primates, outbred rodents, and human patients. A diverse range of T_Ms derived from heterologous immunity or prior exposure to alloantigens, are believed to be an important part of this barrier [3,25–27]. A study by Felix and Allen suggested that alloreactive T cells have the ability to recognize many unrelated peptide sequences [28]. Burrows et al. demonstrated that human leukocyte antigen (HLA)-B8-restricted Epstein–Barr virus (EBV)-specific T cells were cross-reactive with HLA-B14, -44, and -35 [29,30]. Therefore, alloreactive T_Ms could mediate allograft rejection by cross-reacting with donor antigens. It has been reported that pre-transplant frequency of donor-specific T_Ms correlates with the risk of post-transplant acute rejection episodes [31]. Donor-reactive T_Ms can migrate into allograft tissues within 24 h post-transplant [32]. Tolerance induction protocols in naïve mice based on a co-stimulatory blockade of cytotoxic T-lymphocyte antigen 4 (CTLA4-Ig) and anti-CD40L have been found to be ineffective in mice infected with lymphocytic choriomeningitis virus [33]. In another study, depletion of CD8 T_Ms effectively improved induction of chimerism and renal survival [34]. Taken together, these data suggest that donor-specific T_Ms contributed to graft destruction and a resistance in the induction of tolerance.

4. T_Ms and immunosuppressants

Allograft recipients require long-term immunosuppression to prevent acute and chronic rejection. Immunosuppressive agents act in different ways to elicit their effects. Immunosuppression can be carried out by blocking co-stimulatory signals (CTLA4-Ig); blocking TCR and cytokine receptor signaling (cyclosporine A, FK506); T cell depletion (antithymocyte globulin); mixed chimerism (bone marrow transfusion); and blocking trafficking (alefacept, FTY720). The majority of immunosuppressive agents mentioned above focus on naïve T cells. In renal transplant patients, treatment with antithymocyte globulin resulted in a 90% depletion of T_Ms and T_Ns, with CD45RO^{+}CD62L^{lo} T_Ms comprising the dominant lymphocyte population [35]. A blockade of co-stimulatory molecules (CD154/CD40 or ICOS/ICOSL) inhibited rejection response and prolonged graft survival, but not in alloantigen-primed mice [36–38]. It has been reported that using cyclosporine A alone shows a dose-dependent enhancement of memory recall [39,40]. Growing evidence has revealed that T_Ms exhibit different susceptibilities to immune therapeutics, and this distinguishes them from T_Ns. Because of this property, the potential number of immunosuppressive agents available for targeting T_Ms is impressive (Table 1).

4.1. Effect of blocking T_Ms trafficking

T_Ms express higher levels of CD2 and CD11 compared with T_Ns, and can rapidly traffic into grafts and mediate rejection by initiating effector functions [41]. Thus, blockade of trafficking might be one potential immunosuppressive strategy. A candidate agent is alefacept, a dimeric, fusion protein consisting of the extracellular CD2-binding portion of human leukocyte function-associated antigen-3 (LFA-3) linked to the Fc portion of human immunoglobulin G. Several mechanisms are thought to attenuate allograft rejection including complement-mediated lysis and blocking of LFA-3 as the CD2 pathway is important in reactivation of T_{EM}s [42,43]. Alefacept is approved for the clinical treatment of psoriasis by the FDA, and its therapeutic effects have been associated with the ability to eliminate T_Ms. It has been reported that alefacept prolongs traditional co-stimulatory blockades. This is based on renal allograft survival times in nonhuman primates [43]. Data acquired from Shapira et al. showed that alefacept preferentially decreases circulating T_M subsets in refractory chronic extensive graft-versus-host disease (GVHD) in humans [44]. In non-human primates, islet transplantation with alefacept treatment prolonged allograft survival by targeting co-stimulatory blockade-resistant T_{EM}s [45].

Efalizumab, an anti-human leukocyte function-associated antigen-1 (LFA-1) monoclonal antibody (mAb), inhibits the interaction of LFA-1 with CD11a to interrupt T_M trafficking (Fig. 2A). It has been reported that anti-LFA-1 mAbs attenuate donor-reactive memory recall responses and reduce T-cell trafficking to the allograft in murine models of transplantation [46,47]. Phase 2 clinical trials involving renal transplantation demonstrated that anti-LFA-1 mAbs have potential inhibitory effects on T_Ms [48].

FTY720 is a high-affinity agonist for sphingosine 1-phosphate (S1P) receptors. It can inhibit lymphocyte migration from the thymus and peripheral lymphoid tissues by down-regulating surface expression of the S1P receptor [49] (Fig. 2A). FTY720 leads to peripheral blood lymphopenia within 3–24 h after administration to rats [50]. FTY720 promoted cyclosporine A-based skin, cardiac

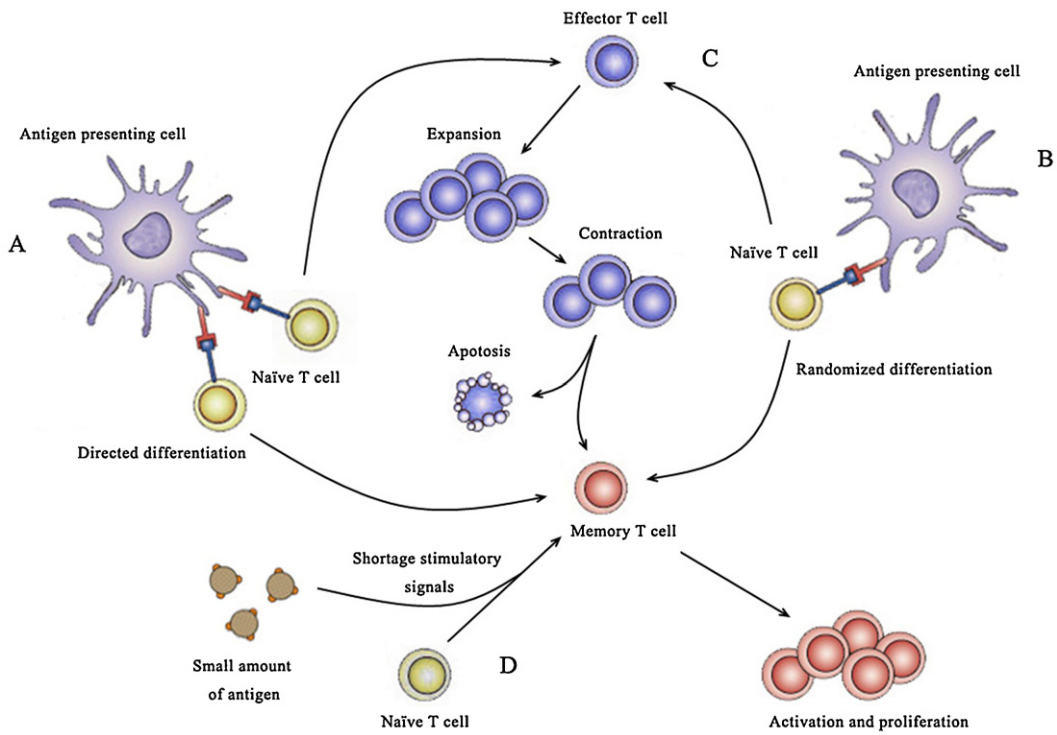

Fig. 1. Four different models of T_M generation. (A) T_Es and T_Ms are directly generated by homeostatic turnover of different T_Ns; (B) T_Ns undergoing their first division produced unequal numbers of T_Es and T_Ms; (C) memory populations are derived from a pool of primed T_Es that experienced expansion and contraction; (D) T_Ns differentiate into memory populations by shortage stimulation of a small amount of antigen in the latter stages of an immune response.

and renal allograft survival in rats and dogs [50–54]. Further studies have proposed that FTY720 prolongs graft survival by inhibiting alloantigen-specific CD4 memory T cells from trafficking to graft sites.

4.2. Effects of blocking signaling through the cytokine receptor

In mammals, Janus kinases (JAKs) are a family of cytoplasmic tyrosine kinases consisting of four members: Jak1, Jak2, Jak3, and tyrosine kinase 2 which are predominantly expressed in hematopoietic cells and highly regulated with cell development and activation. JAKs share a common γ chain (γc) surface receptor for IL-2, -4, -7, -9, -15, -17, and -21, which regulates the development, activation, proliferation, and survival of T, B, NK, and NKT cells [55]. Recent studies have suggested that cytokines, including IL-2, -7 and -15, play an important role in generation, maintenance and proliferation of T_Ms [56] (Fig. 2A). Therefore, JAKs are a potential molecular target for blockade of cytokine signals used by T_Ms. A highly selective and potent JAK3 inhibitor, tasocitinib (also known as CP-690550), has been shown to prevent allograft rejection in mice subjected to heart transplants, and in non-human primates that have undergone kidney transplants [57,58].

4.3. Effects of inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) nuclear translocation

Bortezomib (Velcade), an FDA-approved dipeptidyl boronic acid analog, is the first proteasomal inhibitor that prevents degradation of inhibitors of κB (IκB) and thus blocks NF-κB nuclear translocation [59] (Fig. 2A). It has been reported that bortezomib mediates apoptosis in alloreactive human T cells [60]. A recent study demonstrated that bortezomib can suppress the proliferation of rapamycin-resistant T_Ms populations in non-human primates [61]. More importantly, bortezomib was shown to preserve the function of regulatory T cells (Tregs) while inhibiting the activation of donor-reactive T_Ms. Thus, Bortezomib and a newer generation

Table 1
Therapeutic agents targeting T_Ms.

Therapeutic agents	Effects on T_Ms	Mechanism of action	References
Alefacept	Blockade of T_Ms trafficking	Block leukocyte LFA-3:CD2 pathway	[35–38]
Efalizumab		Inhibit the interaction of LFA-1 and CD11a, and attenuate T_Ms recall responses	[39–41]
FTY720		Down-modulate of the surface expression of S1P receptor	[42–47]
Tasocitinib	Blockade of signaling through the cytokine receptor	Block the signals of cytokines such as IL-2, IL-7 and IL-15 which play an important role in generation, maintenance and proliferation of T_Ms	[48–51]
Bortezomib	Induction of T_Ms apoptosis	Prevent degradation of IκB and thus blocks NF-κB nuclear translocation	[52–54]
Tolerogenic dendritic cells	Induction of T_Ms tolerance	Inhibit allo-immune responses of T_Ms, induce anergy and hyporesponsiveness in T_Ms	[55,60–67]
Regulatory T cells		Inhibit allo-immune responses of T_Ms	[67,73]

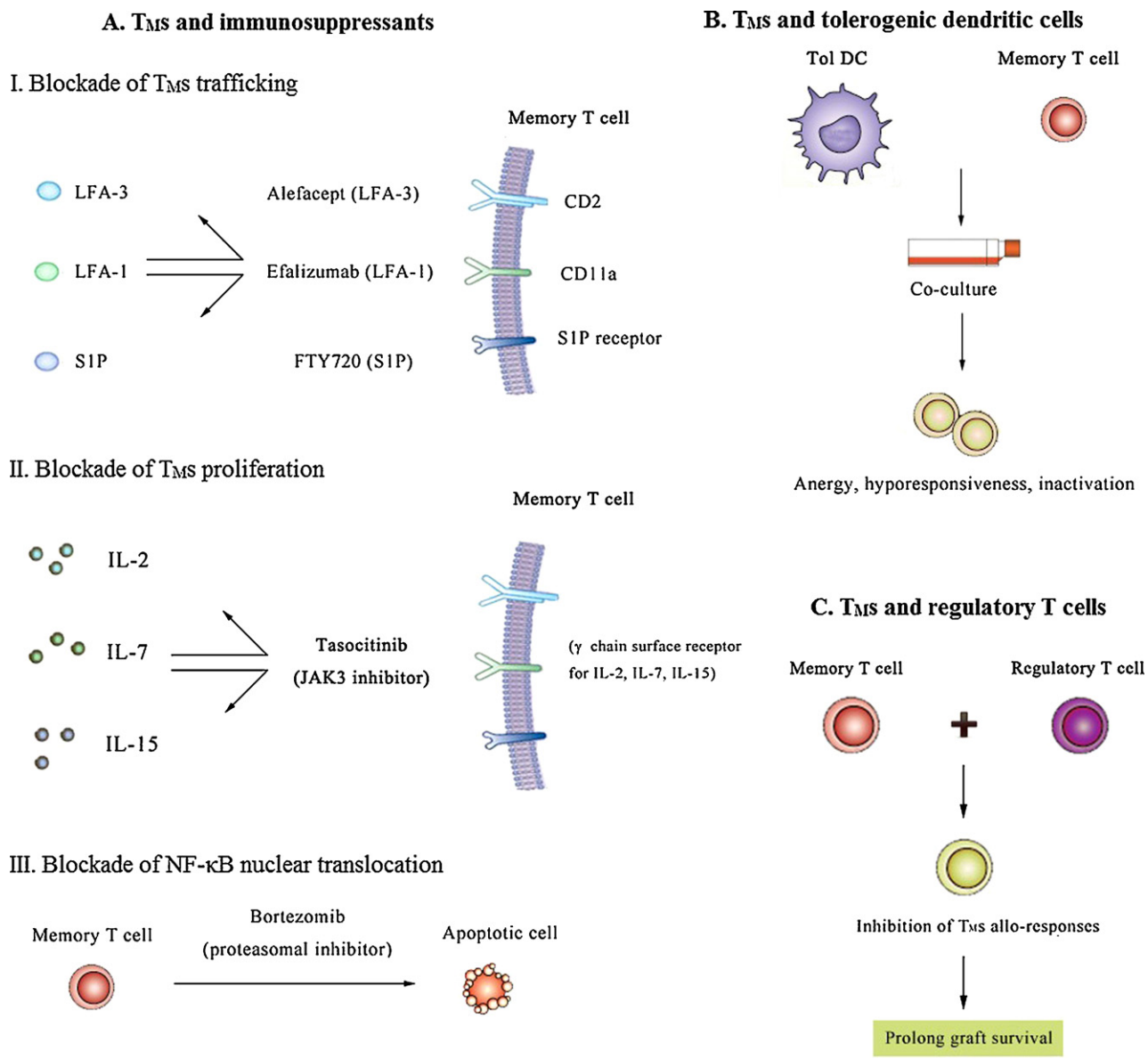

Fig. 2. Therapeutic agents targeting T_Ms. (A) Three types of immunosuppressive agents available for targeting T_Ms, (I) include Alefacept, Efalizumab, and FTY720 which block T_Ms trafficking, (II) include Tasocitinib which blocks T_Ms proliferation, (III) include Bortezomib which induces T_Ms apoptosis; (B) Tol DCs could induce tolerance of T_Ms which suggested its potential to regulate allo-immune responses in transplant patients; (C) Tregs could inhibit allo-responses of T_Ms which may prolong graft survival.

of more selective and less toxic proteasome inhibitors are showing promise as inhibitors of donor-reactive T_Ms responses.

5. T_Ms and tolerogenic dendritic cells (Tol DCs)

Overcoming the resistance of T_Ms to tolerance induction continues to present a serious challenge in transplantation. Tol DCs are a promising, novel immunotherapeutic tool for inhibiting naïve T cell-mediated immune rejection [62] (Fig. 2B). The mechanisms by which Tol DCs induce tolerance include T_Ns deletion, anergy, cytokine deviation, and/or the induction of Tregs [63–66]. Several recent studies have addressed the importance of Tol DCs in tolerance induction of T_Ms. It was previously shown that monoclonal anti-CD3 or fixed DCs induced hyporesponsiveness in T_Ms but not in T_Ns [67–69]. Co-cultures of dexamethasone-conditioned human DCs induced anergy in terms of proliferation and cytokine production [70]. Tolerance induction protocols based on human Tol DCs generated with dexamethasone induced anergy in allogeneic $CD4^+$ T_Ms, which retained their capacity to produce large amounts of IL-10. Anergy in T_Ms did not induce Tregs and could be partially reversed by IL-2 [62]. Our data demonstrated that RelB-silenced DCs induced hyporesponsiveness in $CD4^+$ T_Ns and $CD4^+$ T_Ms. Upon re-stimulation with mature DCs, $CD4^+$ T_Ns primed with RelB-silenced DCs maintain responsiveness, while $CD4^+$ T_Ms primed by RelB-silenced DCs maintain hyporesponsiveness in terms of proliferation and cytokine production. This would suggest that RelB-silenced DCs induce a hyporesponsive state in $CD4^+$ T_Ns and $CD4^+$ T_Ms in a distinct manner [71]. $CD8^+$ T_Ms also are potent barrier to transplant tolerance induction. Research has demonstrated that $CD8^+$ T_Ms are susceptible to tolerance induction when cognate antigens are expressed in DCs [72]. A recently study has shown that $CD4^+$ T_Ms responses could be terminated by steady-state DCs expressing cognate antigen [73]. Plasmacytoid dendritic cells (pDCs) are associated with tolerance to allografts in experimental animal models, and adoptive transfusion of donor-derived pDCs significantly prolonged allogeneic heart graft and skin graft survival. Moreover, pDCs could suppress responses in unfractionated allogeneic $CD_3{}^+$ T cells that contain both T_Ns. and T_Ms [74]. The

important ability of Tol DCs to induce tolerance of T_Ms underscores the potential of these cells to regulate allo-immune responses in transplant patients.

6. T_Ms and Tregs

Tregs are a subpopulation of T cells, defined by their role in inhibiting immune reactions and inducing tolerance [75]. Tregs play a crucial role in maintaining donor-specific hyporesponsiveness in renal and liver transplant patients [76–78]. In rodent models, adoptive transfer of Tregs prevents allograft rejection and prolongs survival of grafts [79] (Fig. 2C), suggesting that Tregs could function as a potential therapy by inhibiting T_Ns. Because of the resistance of T_Ms immunomodulation, researchers have addressed the impact of Tregs on T_Ms. Anti-OX40L prolonged graft survival by inhibition and apoptosis of T_Ms in pre-sensitized recipients. Anti-OX40L, LF-15-0195, and anti-CD45RB restored heart allograft tolerance in pre-sensitized model by induction of Tregs. However, following $CD25^+$ T-cell depletion, heart grafts were rapidly rejected, despite pre-sensitized recipients being co-administered three immunosuppressants [80]. This indicates that Tregs targeting T_Ms are crucial for tolerance induction in pre-sensitized heart transplant recipients. $CD8^+$ Tregs induced by pDCs suppressed the allo-responsiveness of T_Ms [74]. These finding are highly relevant to clinical transplantation, and support the use of Tregs as a potential approach to induce tolerance of recipient allo-reactive T_Ms.

7. Conclusion

Over the past decade, studies published have definitively demonstrated that T_Ms pose a potent barrier in obtaining long-term allograft survival and transplant tolerance because heterogeneous T_Ms develop different susceptibilities to traditional immunosuppressive agents. In this study, we summarized two strategies for immunosuppressive and cellular therapy. Immunosuppressants can be divided into three types according to their different effects on T_Ms. Cellular therapies mainly use two cell types: Tol DCs and Tregs. Some immunosuppressants are already used clinically. However, because their effects are mainly based on inhibition of T_M activation and proliferation, there can be many side effects on transplant patients, thereby limiting their extensive use. Because the aim of cellular therapy is to induce tolerance of T_Ms, leading to anergy and hyporesponsiveness of T_Ms to transplant allografts, it is more likely to have fewer side effects and maintain allograft functions. Although most cellular therapies are still in the early stages, some animal studies have already showed great potential in preventing rejection, prolonging survival time, and maintaining the functions of allografts. We believe that cellular therapy will become the preferred solution for clinical transplant rejection in the future.

In summary, with advances in understanding the mechanisms of T_M generation, activation, function, or trafficking, and the identification of biomarkers, potential approaches targeting T_Ms should eliminate or attenuate allograft rejection.

Acknowledgment

This study is supported by the Guizhou Science and Technology Agency Fund (J[2012]2232).

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