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Tolerance in Kidney Transplantation

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1. Introduction

Advances in immunosuppressive treatments led us to better control acute rejection and improve graft survival in organ transplantation. However, immunosuppressive drugs, due to their toxicity, are also responsible for many side effects as opportunistic infections, renal failure, cardiovascular disease and malignancy (Stegall et al, 1997; Soulillou et al, 2001; Ojo et al, 2003; Fishman et al, 2007). Then, establishing long-term graft acceptance without the continuous utilisation of immunosuppression, also called “tolerance” is a highly desirable therapeutic goal.

Many strategies have been developed to achieve this goal in transplantation but whereas achievable in rodent models (Tomita et al., 1994), it remains very difficult in human because of many differences between their immune system. The definition of true tolerance has been proposed by Billingham et al in 1953, as a well-functioning graft lacking histological lesions of rejection, in the absence of immunosuppression in an immunocompetent host accepting a second graft of the same donor, while able to reject a third-party graft. In clinic some cases of spontaneous tolerance, who stopped their immunosuppressive treatments and display a good graft function, were reported in the last decades in 20 % of liver transplanted recipients (Leruta et al., 2006) but also in kidney transplantation (Roussey-Kesler et al., 2006) suggesting that tolerance exist in human. Because several keys elements of transplant tolerance in rodents cannot be demonstrated in humans, this state has been referred to as “operational tolerance”. Thanks to these patients, the scientific community aims to identify prognostic and diagnostic biomarkers that could help physicians to detect tolerance (Brouard et al, 2007; Newell et al, 2010; Sagoo et al) to safely reduce immunosuppression in transplanted recipients.

2. Long-term graft acceptance exploiting the central tolerance

Billingham et al. first demonstrated in 1953 the feasibility of “actively acquired tolerance” in contrast with “actively acquired immunity” in their neonatal mouse model (Billingham et al., 1953). They demonstrated that injection of foreign antigens to mice at a foetal stage induced tolerance to a skin graft of the same donor at the adult stage. They thus reported on a phenomenon of “acquired tolerance” defined as a well-functioning graft lacking histological lesions of rejection, in the absence of immunosuppression, in an immunocompetent host accepting a second graft of the same donor, while able to reject a third-party graft. Moreover, they deduced from these experiments that immune system formation and lymphocyte education to self-antigens were taking place early during

embryonic development. Mechanisms of central tolerance are based on positive and negative selection of T lymphocytes in the thymus permitting the discrimination of self and nonself (Von Boehmer et al., 1990; Nossal., 1994). Consequently, two main strategies were developed in experimental and clinical transplantation to exploit the natural process of self-reactive T lymphocyte depletion in the thymus: intrathymic injection of alloantigens (Ildstad et al, 1985; Ildstad et al, 1986; Posselt et al, 1990) and mixed chimerism (Kurtz et al., 2004) to induce central tolerance to foreign antigens, allowing the acceptance of the graft.

2.1 Tolerance induction by intrathymic injection of alloantigens

One strategy for the induction of tolerance is the introduction of foreign alloantigens into the adult thymus to re-educate T cells of the host to recognize such antigens as self and tolerate them. There was a huge interest in this approach after the demonstration by Posselt et al that intrathymic injection of allogeneic islets induced donor-specific transplant tolerance in rat (Posselt et al., 1990). Many reports have since confirmed this observation. In experimental kidney transplantation, Remuzzi et al generated tolerance in Lewis rats by injecting in the thymus isolated glomeruli from Brown-Norway rat kidneys. They observed a donor specific unresponsiveness that permitted the renal allograft to survive indefinitely without immunosuppression (Remuzzi et al., 1991). Later, Nick D. Jones and colleagues demonstrated that the delivery of alloantigens to the thymus could lead to the induction of tolerance in vivo in adult mice (Jones et al., 1998). Indeed they showed that intrathymic injections of H-2k^{b+} splenocytes combined with peripheral T cell depletion trigger the long-term graft survival of H-2k^{b+} cardiac allograft in transgenic mice expressing a specific TCR against H-2k^{b+} (Jones et al., 1998). In their mouse model, tolerance was performed by clonal deletion of alloreactive T cells.

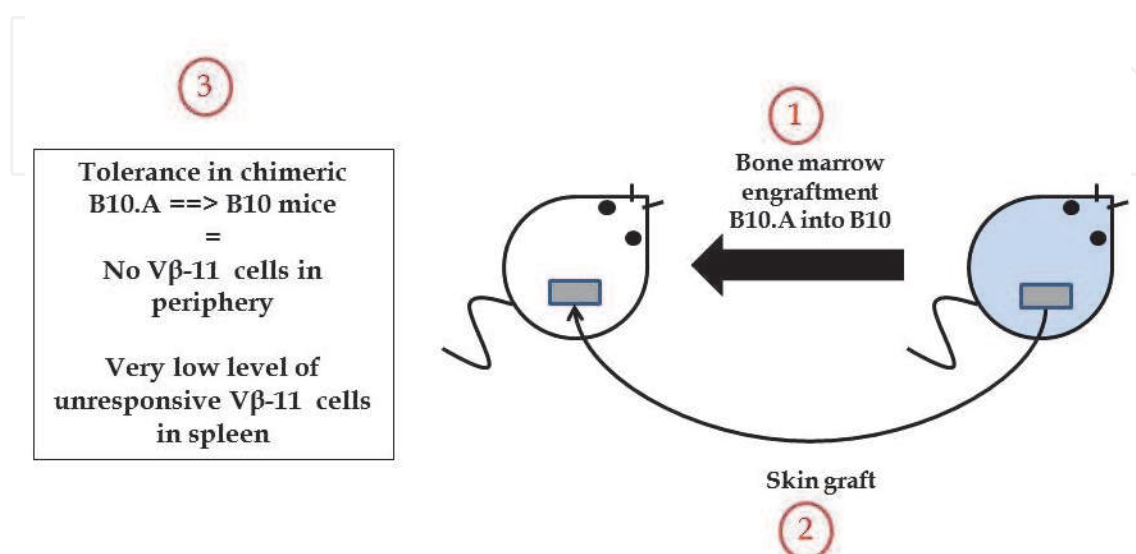
Similarly, Oluwole and colleagues showed that intrathymic injections of a combination of seven major histocompatibility peptides from RT1.Au rat to ACI rat induced tolerance to cardiac and islet allografts from RT1.Au donor. In a second report they identified five immunodominant peptides inducing tolerance in ACI rats and studied the cytokine profile in grafts, thymus and lymphoid tissues of each tolerant and rejecting rat by ELISA and RT-PCR (Oluwole et al., 1993). They demonstrated that injection of a single immunodominant tolerant peptide induced an antigen specific down-regulation of Th1 responses, in both graft and lymphoid tissues, and an augmentation of Th2 cytokines (IL-4 and IL-10) in the graft. In contrast they observed a strengthless Th1 response in rejected graft correlating with the events in lymphoid tissues (Oluwole et al., 1993). These different reports showed that direct intrathymic injection of donor cells generates specific unresponsiveness and clonal deletion of host T cells. The first attempt to extend this approach in human has been performed in cardiac allografts (Remuzzi et al., 1995). This study showed that the injection of donor cells in thymus before transplantation was safe but did not allow a continuous provision of donor alloantigen and was insufficient to induce long term graft survival.

2.2 Tolerance induction by mixed chimerism in rodents

Other studies demonstrated that bone marrow infusions of the donor associated with total body or thymic irradiation to deplete peripheral T cells could provide a source of stem cells able to establish mixed chimerism (recipient and donor) and induce tolerance in transplantation (Kurtz et al., 2004). The engraftment of allogeneic bone marrow in the recipient allows having a permanent source of donor antigens and produces cells involved in the T lymphocyte selection, such as thymic progenitors which repopulate the peripheral T

cell repertory, and dendritic cells which allow negative selection in the thymus. All new mature T lymphocytes of host and donor, recognizing donor and host antigens, are eliminated during the step of central tolerance. Finally, the donor is considered as «self» by the new developing immune system. As long as donor and host bone marrow coexist, the thymus will not generate mature T cells with reactivity against the donor or the host (Kurtz et al., 2004). This intrathymic deletion of donor-reactive thymocytes was shown to be the dominant mechanism for the maintenance of tolerance in mixed chimerism transplantation (Kurtz et al., 2004). First animal studies with antisera or monoclonal antibodies against lymphocytes showed that engraftment of donor bone marrow could enhance long-term survival of transplanted tissues without the need of a complete and potentially lethal ablation of host's immune system induced by irradiation (S.P.Cobbold et al., 1986). Later, Yedida Sharabi and David H. Sachs were the first to induce tolerance by mixed chimerism using a nonlethal conditioning regimen in mice skin allograft model (Sharabi et al., 1989). They showed that mixed hematopoietic chimerism can induce robust donor-specific tolerance, even across full MHC mismatched. This method involved a nonmyeloablative conditioning regimen in which mice were pretreated with an anti-CD4 and an anti-CD8 to deplete peripheral T cells, following total body and thymic irradiations and an injection of donor bone marrow cells. In their experiment, all mice displayed a stable chimerism and long-term graft survival without graft versus host diseases. Most of their tolerant mice also displayed a cell-mediated lympholysis and a mixed lymphocyte reaction tolerance (Sharabi et al., 1989). Megan Sykes's team clearly identified in 1994 the mechanism of B10.A skin allograft tolerance in B10.A ==> B10 chimeric mice after specific conditioning regimen followed by B10.A bone marrow cell injection (Figure 1). For that, they followed the clonal

B10 mice	B10. A mice
H-2b; Kb Ab E- Db I-E- TCR V β -11 +	H2-a; Kk Ak E+ Dk Dd Ld TCR V β -11 - I-E+ (no antigen recognized by TCR V β -11)



deletion of VB11+T cells in their tolerant mice, these cells being normally deleted in I-E+ B10.A mice, but not in B10 mice. In their work, they demonstrated that most of VB11+ T cells of tolerant chimeras B10.A ==> B10 were deleted. They didn't detect VB11+ cells in periphery but very low level in spleen of tolerant mice. These cells were anergic following TCR stimulation in vitro (Tomita et al., 1994).

No evidence of peripheral mechanisms could be found in these models (Khan et al., 1996). Indeed, depletion of donor chimeric cells with donor class I MHC-specific monoclonal antibody broke tolerance in these mice, and was associated with the appearance in blood of T cells with receptors recognizing donor antigens (Khan et al., 1996). But if the thymus was removed just before depletion, specific tolerance to the donor persisted in the absence of donor chimerism, and donor-reactive T cells did not appear in the periphery. Thus, the major factor for tolerance in this model is to give a constant source of donor antigen presenting cells to permit intrathymic deletion of new thymocytes, which continued to be generated (Khan et al., 1996). Similar approaches were performed in monkeys with success. But in this model, tolerance was associated with the loss of mixed chimerism suggesting the implication of peripheral mechanisms to maintain tolerance in non-human primates (Kawai et al., 1995).

2.3 Tolerance induction by mixed chimerism in human kidney transplantation

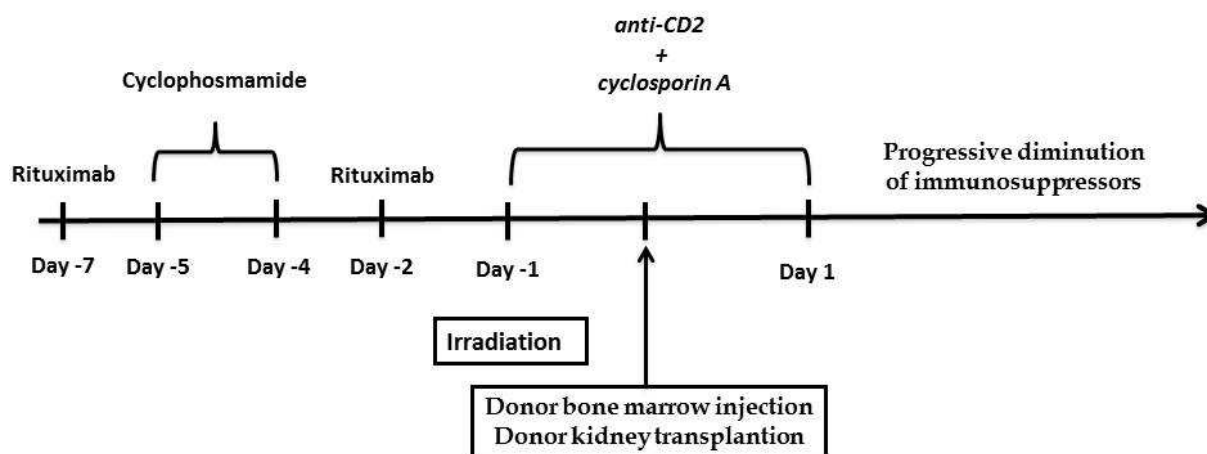
The proof of concept that the tolerance of an organ can be obtained when the transplanted organ is followed by engrafting of bone marrow of the same donor was shown in humans in a few cases. Indeed two patients, who received a HLA-matched bone marrow transplantation, were able to accept few years later a kidney graft from the same donor without immunosuppressive drugs (Sayegh et al., 1991). Some teams developed a clinically relevant non-myeloablative preparative regimen permitting an induction of tolerance in human kidney transplantation. They performed this approach in both HLA-matched (Scandling et al., 2008) and HLA-mismatched situation (Kawai et al., 2008).

For the HLA-matched study six patients were enrolled in the protocol but only results of one patient were published. This patient has undergone a post-transplantation conditioning regimen of total lymphoid irradiation and injection of rabbit anti-thymocyte immunoglobulins allowing the engraftment of donor's kidney and bone marrow. In these patients, they observed a stable mixed chimerism and a well-functioning graft despite the withdrawal of all immunosuppressors. Also, few experiments were accomplished in order to study the immune system of these operationally tolerant recipients. They tested immune responses and showed a good immune reconstitution after the conditioning regimen without opportunistic infections, normal in vitro T-cells responses against virus, bacteria and third-party allogenic cells. In contrast, there was a global unresponsiveness of host T cells against donor dendritic cells. This study demonstrated that it was possible to achieve persistent chimerism and tolerance to the graft without graft versus host disease (Scandling et al., 2008).

The study by Kawai et al. has reported a stable renal allograft-function after complete removal of all immunosuppressors (Kawai et al., 2008). Five patients with end-stage renal disease have undergone combined bone marrow and kidney transplantation from HLA mismatched donors after specific conditioning regimen including a strong immunosuppressive treatment and a thymic irradiation before transplantation (figure 2). Because of the death of one patient during the study, the conditioning regimen protocol was modified. Then, physicians performed a progressive diminution of immunosuppressive

drugs during the first months until complete withdrawal. The clinical follow-up of the patients was achieved by controlling creatinine and proteinuria levels and making biopsy surveillance (immunofluorescence microscopy including C4d deposition). Thus, all patients displayed stable creatinine level and graft function despite the presence of antidonor HLA II antibodies and C4d deposits in three of the four recipients. Authors were unable to detect mixed chimerism after 14 days. The authors noticed a specific unresponsiveness of host T cells against donor antigens in vitro (Kawai et al., 2008). Tolerated grafts exhibited a high level of Foxp3 expression and no expression of granzyme B suggesting a role of regulatory T cells (Tregs) in the maintenance of tolerance as previously described in monkey (Kawai et al., 1995). This study suggests some evidences for a cooperation of central and peripheral tolerance mechanisms in operational tolerance. Indeed, mixed chimerism permits to suppress alloreactive T cells whereas intra-graft regulatory T cells maintain a global unresponsiveness of allogenic surviving T cells permitting the long term survival of the graft. In spite of encouraging results, a few patients waiting for an allograft can receive an HLA-identical allograft, used in most of these protocols and giving the best results. Moreover, this protocol is uneasy to apply in clinic because of the possibility for the patient to develop a graft versus host disease, associated with the bone marrow engraftment. Finally, the conditioning regimen must be mastered and safe for patients. There are too much non acceptable conditions just to induce tolerance.

Conditioning regimen undergone by each patient to induce mixed chimerism and tolerance (Kawai et al., 2008)



3. Kidney transplantation tolerance induction by manipulating peripheral mechanisms

Clinicians use immunosuppressive drugs to suppress immune reactions against the graft (Philip et al., 2004). Basically, these drugs can be classified in three groups: anti-inflammatory of the corticosteroid family as prednisone; cytotoxic treatment as cyclophosphamide; and fungus or bacteria derived molecule as Cyclosporin A, Tacrolimus and Sirolimus inhibiting T cell signaling. All these drugs have a large spectrum of action and suppress deleterious functions as well as protective functions of our immune system

(Galon et al., 2002). Thus, although immunosuppressive drugs demonstrated good impact in graft survival, they are responsible for large dangerous side effects.

The development of monoclonal antibodies gave the possibility to target particular processes of the immune response (Kohler et al., 1975). These antibodies were used in clinical transplantation to deplete reactive T lymphocytes (Strober et al., 1984) to improve long term survival of the graft, but also to induce tolerance notably through costimulatory blockade and induction of regulatory immune mechanisms (Kirk et al., 1997). Another approach for tolerance induction is to rebalance the pool of regulatory cells in transplanted patients in order to restore the cellular homeostasis. During the last decades, many regulatory populations were identified in animals and also in humans. They represent a strong potential clinical tool for the establishment of tolerance in human transplantation. Thus, many studies try to develop different protocols able to generate specific allogenic regulatory cells in order to promote donor-specific tolerance.

3.1 The use of monoclonal antibodies: T cell depletion and blockade of costimulatory signals

T cell activation requires three signals to enhance a strong immune response. The two first signals depend on the interaction of T cells with antigen presenting cells. Interaction between MHC-peptide and TCR provides the specificity of the response. The second signal, called the “costimulatory signal”, is given by molecules on antigen presenting cells that interact with particular costimulatory receptors on T cells. In the absence of costimulation, T cells that recognize antigen either fail to respond and die or enter a state of unresponsiveness known as anergy (Schwartz et al., 1990). Thus, costimulation is a key determinant of T cell response. The third signal is provided by cytokines and their respective receptors. There are different kinds of cytokines that can enhance proliferation, survival, but also orientate the immune response. Anti-thymocyte globulin preparations were first used to deplete alloreactive peripheral T cells, in combination with total lymphoid irradiation (Strober et al., 1984, Strober et al 1989). However, it was suggested that the T cell depletion induced by ATG was not sufficient to induce tolerance (ref). OKT3, a monoclonal murine antibody directed against CD3 molecule of the TCR (Cosimi et al., 1981) was then used to block activation of T cell in vitro and induce depletion of T cells in vivo. Although several studies demonstrated the efficacy of OKT3 in the prevention and treatment of acute rejection (Vincenti et al., 1998; Webster et al., 2006) its clinical use was limited by many serious side effects. Administration of the drug is often followed by a cytokine storm with high fever, arterial hypertension and pulmonary oedema as result of capillary leak. Secondly, some patients can develop antibodies against the xenogeneic epitope that are responsible for decreased efficacy. Lastly, a higher incidence of infectious complications and malignancies has been reported, suggesting a too strong immunosuppression (Ortho Multicenter Transplant Study Group et al., 1985).

To limit the over-immunosuppression generated by OKT3, another monoclonal antibody was developed that was targeting the interleukin 2 receptor, a molecule specifically involved in proliferation and activation of T lymphocytes. Such treatments spare T lymphocytes not involved in the recognition of donor antigen, decreasing the over-immunosuppression. Monoclonal antibodies that are specific for rodents IL-2R can abrogate proliferation of activated T cells in vitro, prevent and reverse acute heart rejection in mice (Kirkman et al., 1985) and delay kidney rejection in monkeys (Shapiro et al., 1987). In human kidney transplantation, the efficacy of a rat monoclonal antibody (33B1.3) was studied and

confirmed in a randomized clinical trial in combination with immunosuppressors (Soulillou et al., 1987). The 33B1.3 blocks the α and β chain association preventing the interaction between IL-2 and its receptor. The efficacy of this treatment to prevent acute rejection is similar to rabbit antithymocyte globulin treatment with fewer side effects (Soulillou et al., 1990). Nowadays it's clearly demonstrated that treatments with anti-IL2R associated with cyclosporin A and steroids ameliorate the survival of the graft and decrease opportunistic infections, but nevertheless with a little more acute rejection (Brennan et al., 2006) and a decrease of Tregs in periphery (Bluestone et al., 2008).

Alentuzumab (Campath-1H), a humanized rat monoclonal antibody, binds CD52, a glycoprotein expressed by T and B lymphocytes, monocytes and granulocytes (Xia et al., 1993). Injection of Alentuzumab leads to massive depletion of peripheral lymphocytes. It has been used for the treatment of lymphoma (Hale et al., 2002) but also in kidney transplantation. Indeed, in combination with low dose of cyclosporin A, this treatment could induce tolerance (Calne et al., 1998). Moreover, it has been showed that Alentuzumab treatment followed by low dose of tacrolimus permit to decrease acute rejection and opportunistic infections but also increase the number of Tregs (Ciancio et al., 2008). But recent data demonstrated that the use of high dose of Alentuzumab to treat acute rejection must be made with caution because of the high risk of early infection-associated death (Clatworthy et al., 2009).

Belatacept (LEA29Y), a selective costimulation blocker, binds surface costimulatory ligands (CD80 and CD86) of antigen-presenting cells. Then there is a blockade of second signal inducing death and anergy of effector T cells (Schwartz et al., 1990; Sayegh et al., 1998). Belatacept is derived from Abatacept, a human fusion protein combining the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 with the constant region fragment of human IgG1 (CTLA4Ig). Treatment with Belatacept permit to have effective immunosuppression, superior renal function and reduced incidence of chronic allograft nephropathy than in patients treated with cyclosporin A (Vincenti et al., 2005). Treatments with Belatacept have no adverse effects on Tregs and even improve their infiltration in the graft (Bluestone et al., 2008). A recent study has tested the immunoregulatory effect of selective CD28 blockade on kidney and heart allograft in primates (ref). It has been showed that CD28 blockade reduced alloreactivity and increased the pool of peripheral T regulatory cells. In addition, authors observed a strong infiltration of Tregs in graft. Thus, this treatment permits to manipulating and rebalance the regulatory mechanisms in transplanted primates (Poirier et al., 2010). Selective CD28 blockade has significant advantages relative to CD80/86 blockade by Belatacept (Vincenti et al., 2005). Indeed with Belatacept, all B7 molecules are targeted, preventing activator and inhibitory signals by CD28 and CTLA-4 respectively. With CD28 antagonist we block just effector T cells and not Tregs that constitutively express CTLA-4 for their immunosuppressive activity (Wing et al., 2008)

Blockade of CD40 pathway in non-human primates also allows the long term graft survival. The first study in monkey demonstrated the good effect with an anti-CD40 injection in kidney transplantation (Kirk et al., 1999). But the first generation of this antibody induced serious side effects as thromboembolic complications (Kawai et al., 2000). Recently a new human monoclonal anti-CD40 antibody (4D11) was developed and studied in kidney graft model in cynomolgus monkeys. 4D11 was described as a potential effective immunosuppressive drug inducing a diminution of graft lesions and alloantibody production (Imai 2007). Thus, it was shown that the blockade of both CD40 and ICOS pathways in a rat heart transplantation model ameliorates the graft survival (Guillonnet et

al 2005). Also, injection of anti-ICOS in transgenic CD40Ig rat preferentially inhibits chronic rejection, decreases leucocyte infiltration in the graft and cytotoxic activity of T cells.

A lot of differences, in the immune system, exist between human and animal, notably the strong presence of human memory cells which play a central role in chronic rejection. They present different characteristics which prevent their manipulation *in vivo*. Indeed, it was shown that memory cells are resistant to depletion (Gallon et al., 2006), costimulatory blockade (Yang et al., 2007) and apoptosis (Wu et al., 2004) and can be activated by low antigenic signal and without costimulation (Cho et al., 2000). A lot of studies thus try to specifically target human memory T cells by neutralizing the tumor necrosis factor which is an important factor for the generation of memory T cells (Croft, 2003; Yuan et al., 2003) or by blocking adhesion molecules, then inhibiting the infiltration of such T cells in the graft (Ellis and Krueger., 2001; Dedrick et al., 2002; Vicenti et al., 2007).

3.2 Tolerogenic cellular therapy

Recently, new protocols to induce tolerance were developed in experimental transplantation. It is a “tolerogenic cellular therapy” approach mainly developed in rodents (Bluestone et al., 2005; Morelli et al., 2007) (figure 5). In fact, in the last decades a lot of regulatory immune populations were isolated and identified as potential suppressors of allogenic responses. Thus, Tregs (Sakaguchi et al., 1995; Qin et al., 1998; Hori et al., 2003) tolerogenic dendritic cells, myeloid-derived suppressor cells, NKT cells (Seino et al., 2001) and B cells (Fuchs and Matzinger., 1991) were described to induce and transfer tolerance in experimental transplantation. Thus, CD4⁺ T cells with regulatory function have been shown to play a critical role in the maintenance of transplantation tolerance (Qin et al., 1998). The CD25⁺ fraction of CD4⁺ T cells mediates tolerance on adoptive transfer into a naive host (Hara et al., 2001; Graca et al., 2002). These cells were shown to be potent suppressors of activated T cells *in vitro* (Thornton et al., 1998) and to be crucial for the control of the effector function of alloreactive CD4⁺ and CD8⁺T cells in transplantation models *in vivo* (Maurik et al., 2002). The precise mechanisms by which these Treg cells exert their suppressive function remain to be defined, but we know that surface molecules such as CTLA-4 (Read et al., 2000), the glucocorticoid-induced tumor necrosis factor receptor (GITR) (Shimizu et al., 2002), and cytokines such as TGF- β and IL-10 (Hara et al., 2001) play roles for the maintenance of tolerance. Several studies have demonstrated that the regulation mediated by Treg cells is dependent on a continuous supply of alloantigens (Scully et al., 1998; Sanchez-Fueyo et al., 2001) suggesting that these cells have specificity for alloantigens. In transplantation, alloreactive CD4⁺ T cells with indirect allospecificity are thought to play a key role in chronic rejection, and the control of these pathogenic effector cells by donor-specific Treg cells could, therefore, result in transplantation tolerance (Wise et al., 1998; Graca et al., 2002). However, the possibility of using Treg cells as immunotherapy for the induction of antigen-specific tolerance is limited by cell number. Indeed, the entire pool of Treg cells accounts for only 5% to 10% of CD4⁺T cells in the peripheral blood of healthy persons. Consequently, a lot of teams focused their efforts on the possibility to expand *ex-vivo* human allogenic Tregs. In mice, *ex-vivo* stimulation of Tregs by anti-CD3 and anti-CD28 promotes strong proliferation of these cells (Nadig et al., 2010; Issa et al., 2010). In humans other studies described the possibility to induce specific allogenic Tregs by using tolerogenic dendritic cells (Bacchetta et al., 2010) or CD40-activated B cells (Zheng et al., 2010). The success of “Treg cell therapy” in solid organ transplantation is subject to confirmation of many clinical trials.

3.2 Induction of tolerance: How far are we?

Manipulating the host immune system to develop antigen-specific immune tolerance leading to graft acceptance is an attractive alternative and is the objective of an increasing number of studies. Two key factors must be considered to induce immune tolerance: firstly, decrease potentially harmful immune effector and memory cells responding to donor tissue, and secondly, increase donor-reactive tolerant cells. The comprehension of how we can harness the immune response towards tolerant cells should permit us to switch the balance from rejection towards long-term tolerance of donor grafts, without the need for immunosuppressive drugs (Long et al., 2009). The evaluation of the impact of therapeutic agents for tolerance is not clearly mastered and understood. Today we know that intense immunosuppressive therapy is not the solution for long term graft survival. Manipulating the immune system by mixed chimerism, monoclonal antibody and tolerogenic cell therapy remains in a clinical trial state because of the lack of knowledge and potential lethal and deleterious effects of these approaches. But all studies try to display the perfect balance between donor cells, recipient effector and regulatory cells and treatments. Unfortunately we still lack tools to identify such perfect tolerance balance. Thus, for the moment no protocol of induction of tolerance is used in routine in clinic.

4. Dissecting the operational tolerance phenotype

Operational tolerance is a state referred as long term graft survival, with a stable function of the graft without immunosuppression in an immunocompetent recipient (Ansari and Sayegh, 2004). Other factors can help to complete the definition of operational tolerance as the lack of anti-donor antibodies, no infiltration of effector cells in graft and a global unresponsiveness against the donor in vitro (Ferah and Sykes 2004). Phenomena of operational tolerance remain very rare in kidney but are real. Indeed, some patients have been tolerant for more than ten years with a stable function of their graft (Roussey-Kesler et al., 2006). The clinical history of these operationally tolerant patients, who stopped IS mostly by incompliance, is not different from kidney recipients (Roussey-Kesler et al., 2006). Moreover these patients do not seem to be immunosuppressed because they do not have more significant opportunistic infections following immunosuppression withdrawal. A small proportion of patient also presents anti-donor class II antibody without showing any signs of graft degradation. Finally, some of them lost their graft decades after transplantation suggesting that this phenomenon of “operational tolerance” is a metastable process that likely corresponds to an absence of “lesional response” in a protective environment.

Although these patients display heterogeneous characteristics, they offer the opportunity (i) to understand mechanisms responsible for tolerance in human kidney transplantation and (ii) to identify molecules that can induce, predict or diagnostic tolerance. Many teams are fundamentally interested in developing a better understanding of the basic processes of operational tolerance in kidney transplantation. They have engaged multiples studies to determine if there is a specific phenotype of tolerance in the blood of patients. The identification of pertinent biomarkers of tolerance is very important to predict and diagnose long term graft survival and potentially adapt therapy in stable patients under immunosuppression.

Whereas studies in animals put on light the role of Tregs in transplantation tolerance, first studies in human kidney transplantation showed no alteration in phenotype and functions

of T cells in the blood of tolerant patients compared to healthy volunteers and stable patients under immunosuppressive therapy (Louis et al., 2006). Nevertheless, other studies showed an increase of Tregs in the blood of tolerant patients (Braudeau et al., 2007), a global unresponsiveness against the graft (Brouard et al., 2005) and a decreased expression of Myd88 and TLR4 in the PBMCs (Braudeau et al., 2008) compared to patients with chronic rejection. Moreover, a decrease of perforin and granzyme A, cytotoxic molecules, was reported in the CD8⁺ CD28⁻ T cell subset in tolerant patients compared to patients with chronic rejection (Baeten et al., 2006) confirming the quiescence of the immune system in tolerant recipients. A study by our team identified by microarray a 49 gene signature of tolerance in operationally tolerant patients (Brouard et al., 2007). This signature can discriminate tolerant recipients from healthy volunteers, stable patients and recipients with chronic rejection. Moreover, this fingerprint of tolerance can predict and classify stable patients as potential tolerant patients, which would permit a progressive diminution of immunosuppressive drugs. It was also shown that tolerant patients display a lower expression of genes involved in effector immune responses confirming the global unresponsiveness against the graft (Brouard et al., 2007). Interestingly, this differential profile was composed of several genes specific of B cells (Brouard et al., 2007, Pallier et al., 2010) that also correlated with an increased number of peripheral B cells in these patients (Louis et al., 2006). We characterized more specifically the phenotype of these B lymphocytes (Pallier et al., 2010) and reported a global inhibitory phenotype of B cell compartment (Pallier et al., 2010). The genetic and B cell signature of these patients was independently verified by the ITN and IOT networks (Newell et al., 2010; Sagoo et al., 2010). It is nowadays a need to validate these biomarkers using larger multicentric cohorts in order to move from potential biomarkers into clinically useful biomarkers. Indeed a combination of several parameters is necessary to predict long-term graft survival. To increase the sensitivity and the specificity of the prediction, the composite score needs to be infusing with immunological parameters. Large cohort of patients has to be enrolled in order to take into account potential confounding factors when evaluating diagnostic or prognostic biomarkers. Finally, it will be necessary to move from snapshot studies into longitudinal studies in order to define the fluctuation of these biomarkers and better evaluate, understand and why not induce tolerance in transplantation.

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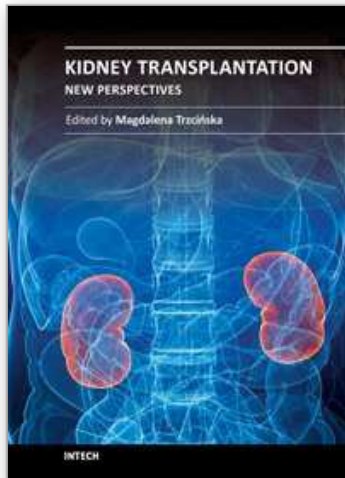
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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and that's why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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