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Immune Monitoring of Kidney Recipients: Biomarkers to Appreciate Immunosuppression- Associated Complications

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1. Introduction

The use of nonspecific immunosuppressive drugs has significantly reduced the incidence of acute kidney graft rejection (Sayegh & Carpenter, 2004). This led to a significant improvement in first-year graft survival rates that are “almost close to perfect”, as mentioned in a recent review (Lamb et al., 2011). However, the benefits of such immunosuppressive therapies on chronic rejection and overall long-term graft survival are uncertain (Meier-Kriescher et al., 2004a; McDonald et al., 2007). Thus, long term graft survival remains unchanged over decades (Meier-Kriescher et al., 2004a; Meier-Kriescher et al., 2004b). Persistent excessive immunosuppression –related to these immunosuppressive drugs– exposes renal transplant recipients to long-term toxicities including: increased incidence of cancers, severe infectious complications and “metabolic” diseases (for instance, diabetes, and accelerated atherosclerosis leading to cardiovascular diseases).

An excess risk of cancer after renal transplantation has been increasingly recognized over recent decades (Penn et al., 1979; Kasiske et al., 2004; Grulich et al., 2007; Villeneuve et al., 2007; Webster et al., 2007; van Leeuwen et al., 2009), as advances in medicine have extended the life of renal transplant recipients. A meta-analysis including five studies of cancer risks in organ transplant recipients, including 31'977 organ transplant recipients –among which 97% have received a kidney graft– from Denmark, Finland, Sweden, Australia, and Canada shows an increase in the incidence of cancers related to infection with Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8), hepatitis viruses B and C (HBV and HCV), and *Helicobacter pylori* with comparison to the general population (Grulich et al., 2007). However, cancer incidence after transplantation is not restricted to virus-induced cancers, since kidney cancer, myeloma, leukaemia, melanoma as well as bladder and thyroid cancers are more frequent in transplant recipients than the general population (Grulich et al., 2007). Common epithelial cancers (e.g., breast and prostate) occur at the same rate as the general population (Grulich et al., 2007). However, despite a cancer incidence similar with the general population, an interesting study reported a highly aggressive course of tumors and unresponsiveness to “classical” anti-tumoral chemotherapy in renal transplant recipients (Fiebiger et al., 2009). This report confirmed a pioneer work (Barrett et al., 1993) showing the more aggressive course of cancers in renal transplant recipients. Thus, malignancy is now one of the leading causes of patient's

death with functional graft. A recent study analyzing 1'606 renal transplant recipients reports that malignancies accounted for 12 % of death among patients with a functioning renal allograft (Kahwaji et al., 2011). Immunosuppression and its extent directly influence cancer occurrence after transplantation (Dantal et al., 1998; van Leeuwen et al., 2009).

The other main cause of patient's death with functional graft is cardiovascular diseases (Kahwaji et al., 2011) related to accelerated atherosclerosis associated with kidney transplantation (Sarnak et al., 2003; Ojo, 2006). The incidence of cardiovascular diseases is at least 3 to 5 times higher than in the general population (Sarnak et al., 2003). For instance, while left ventricular hypertrophy prevalence in the general population is estimated to 20%, this prevalence increases to 50 to 70% in renal transplant recipients (Sarnak et al., 2003). Depending on the considered reports, cardiovascular disease is reported to be the most common cause of death in patients with functional graft ranging from 24% to 55% (Kasiske et al., 1996; Ojo et al., 2000; Sarnak et al., 2003; Kahwaji et al., 2011). Risk factors for cardiovascular diseases in renal transplant recipients are multiple. They include traditional cardiovascular disease risk factors (e.g., tobacco use, exercise, hypertension, diabetes, or hyperlipidemia), which are highly prevalent, as well as nontraditional risk factors related to a long history of poor kidney function (e.g., hyperhomocysteinemia, chronic inflammation or anemia) (Kasiske et al., 1996; Ducloux et al., 2000; Sarnak et al., 2003; Liefeldt & Budde, 2010; Kahwaji et al., 2011). Moreover, factors related to transplantation itself, including the direct effects of immunosuppression or rejection episodes as well as new-onset diabetes after transplant (NODAT), impact on cardiovascular disease occurrence after kidney transplantation (Kasiske et al., 1996; Sarnak et al., 2003; Ducloux et al., 2005a; Liefeldt & Budde, 2010; Kahwaji et al., 2011).

Thus, it appears that excessive immunosuppression is involved in both increased cancer and cardiovascular disease incidence observed after kidney transplantation. A greater understanding of risk factors leading to excessive immunosuppression may help physicians to determine high-risk recipient profiles and optimize pre- and post-transplantation treatment strategies. In other words, identification of biomarkers predictive of immunosuppression-associated complications may improve late kidney transplantation outcome. In this chapter, we will report efforts of our laboratory to identify immunological factors that can predict the two main complications associated with kidney transplantation, namely cancer and accelerated atherosclerosis that leads to cardiovascular diseases. We focus on: i) CD4⁺ T cell lymphopenia, a consequence of anti-thymocyte globulin (ATG) administration and ii) recipient innate immune genetic factors appreciated by single nucleotide polymorphism (SNP) analysis. The analysis of these biomarkers was considered only in the settings of transplantation from deceased donors in a Caucasian population. Identification of biomarkers predicting chronic allograft dysfunction is beyond the scope of this review, despite significant advances reported recently in this field (please see a recent commentary in the *Journal of Clinical Investigation*; Schroppel & Heeger, 2010). In contrast to the search for biomarkers predicting chronic allograft dysfunction where immune monitoring was performed in the serum, peripheral blood mononuclear cells (PBMC), urine and the allograft through biopsy (Mannon, 2010), our investigations were focused on non-invasive blood samples (*i.e.*, serum and PBMC).

2. CD4⁺ T cell lymphopenia as a biomarker for immunosuppression-associated complications

CD4⁺ T cell lymphopenia in renal transplant recipients results mainly from ATG administration. Despite a limited treatment duration (until 4 days), CD4⁺ T cell

lymphopenia persists for several years in some transplanted patients (Muller et al., 1997; Louis et al., 2007). We previously demonstrated that persistent CD4⁺ T cell lymphopenia is correlated with enhanced risks of cancers –including skin cancers (Ducloux et al., 1998a), monoclonal gammopathies (Ducloux et al., 1999), lymphomas as well as other non skin cancers such as colon or lung cancers (Ducloux et al., 2002a)–, of opportunistic infections (Ducloux et al., 1998b) and atherosclerotic events (Ducloux et al., 2003) in renal transplant recipients. In contrast, CD4⁺ T cell lymphopenia seems not to be associated with *de novo* genitourinary malignancies (Guichard et al., 2008). Moreover, we recently associated CD4⁺ T cell lymphopenia and renal transplant recipient mortality (Ducloux et al., 2010). In this work, the two identified main causes of death in these patients were cancers (36% in the prevalent cohort of 302 consecutive stable renal transplant recipients with a mean follow-up of 92 ± 7 months) and cardiovascular diseases (39%)(Ducloux et al., 2010). Thus, CD4⁺ T cell lymphopenia may be considered as an adequate marker for excessive immunosuppression leading to immunosuppression-associated complications, at least in patients receiving depletion therapy. However, all transplanted patients treated with ATG did not present a prolonged CD4⁺ T cell lymphopenia (Ducloux et al., 2003; Ducloux et al., 2010). Thus, the next step was to identify factors responsible for this prolonged severe CD4⁺ T cell lymphopenia allowing us to distinguish patients that will develop prolonged CD4⁺ T cell lymphopenia from patients that will not. Some studies (Willoughby et al., 2009; Cai & Terasaki, 2010) reported a benefit of ATG over nondepleting induction therapy mainly on early acute graft rejection occurrence, but also ultimately in preserving allograft function. The benefit of ATG is, however, not similar in each patient (Brennan et al., 2006; Noel et al., 2009). Thus, the choice of a complication risk level could vary according to the supposed benefit of ATG. A high benefit of ATG may lead to accept a higher risk, whereas a slight benefit could lead to prefer a lower risk. Biomarkers, such as CD4⁺ T cell lymphopenia, may help to select ATG as an appropriate induction therapy. In the next part of this paragraph §2, we will discuss factors that may affect CD4⁺ T cell reconstitution after ATG-induced T cell depletion as well as factors that may explain the duration, intensity or variability of CD4⁺ T cell depletion among patients. In addition to ATG, Campath-1H, a humanized anti-CD52 monoclonal antibody called Alemtuzumab, can be used as induction immunosuppression causing T cell depletion (Kaufman et al., 2005; Cianco & Burke, 2008). Whether data obtained with ATG can be transposed to Alemtuzumab remains to be determined. Nevertheless, few clinical studies are available regarding the CD4⁺ T cell lymphopenia induced by Alemtuzumab administration (Scarsi et al., 2010) not always in the context of kidney transplantation (Cox et al., 2005).

2.1 A role for an altered immune reconstitution on persistent CD4⁺ T cell lymphopenia after anti-thymocyte globulin administration?

We will describe below factors identified as participating to CD4⁺ T cell reconstitution (*i.e.*, thymic function, homeostatic proliferation and cytokines involved in this latter process). Most of the works in this field were performed in the setting of hematopoietic cell transplantation. The identification of these factors in the setting of kidney transplantation will enable to use these factors as biomarkers to adapt immunosuppressive regimen and accelerate CD4⁺ T cell recovery in patients.

2.1.1 The role of the thymic activity on immune reconstitution after T cell depletion

Diseases (e.g., human immunodeficiency virus [HIV] infection), but also treatments (total body irradiation, high dose anti-cancer chemotherapy or depleting antibodies) may be

responsible for profound lymphopenia. Studying immune reconstitution after hematopoietic cell transplantation or following anti-HIV therapy has caught the attention of many teams (see below). Understanding factors involved in accelerated –or in contrast delayed– immune reconstitution may limit side effects of these therapies. Based on studies performed in animal models, Mackall and colleagues proposed several years ago that immune reconstitution after T cell depletion arises from two main pathways: thymopoiesis and homeostatic proliferation expansion of residual host lymphocytes or, in the context of hematopoietic cell transplantation, of graft-derived mature T cells (Fig. 1; Mackall et al., 1997). The latter pathway remains the major pathway early after hematopoietic cell transplantation, until donor-derived prothymocytes migrate to the recipient thymus, where they undergo maturation (Moss & Rickinson, 2005). Several evidences in human settings support today the hypothesis sustained by Mackall *et al.* (1997) due to the development of innovative tools allowing discrimination of recent thymic emigrants (RTE, a reflect of thymic activity/output) from other lymphopenia-induced expanded T cells (*i.e.*, naive or memory/activated). A significant improvement to assess thymic function was performed by Douek and colleagues in 1998, when they reported that circulating T cell excision circle (TREC) levels are a direct reflect of thymic function (Douek et al., 1998). These TREC correspond to the episomal DNA circles generated during the rearrangement of the VDJ genes of the TCR α and β chains. TREC are stably retained during cell division, but do not replicate, thus becoming diluted among the daughter cells. In addition to this initial study performed in HIV patients (Douek et al., 1998), circulating TREC level determination was performed in patients after allogeneic hematopoietic cell transplantation. In this setting, pre-transplant TREC levels were found to be a factor predicting T cell reconstitution both in adults and in pediatric patients (Chen et al., 2005; Clave et al., 2005). This assay was also a useful tool to identify RTE early after allogeneic hematopoietic cell transplantation (Douek et al., 2000; Hochberg et al., 2001; Hazenberg et al., 2002; Borghans et al., 2006). Moreover, TREC level determination was also used to assess T cell neogenesis in autologous hematopoietic cell transplantation (Farge et al., 2005). Recently, expression of surface markers –including CD45RA, CD31 or protein tyrosine kinase 7 (PTK7)– on CD4⁺ T cells has been shown to identify RTE and to attest to an efficient thymopoiesis (Haines et al., 2009; or for a recent review, Kohler & Thiel, 2009). In contrast, homeostatic proliferation expansion is characterized by T cells expressing the CD45RO isoform (Fig.1). Homeostatic proliferation of naive T cells induces the acquisition of a memory/activated phenotype (Fig.1).

A critical issue during T cell recovery is the reconstitution of a most diverse polyclonal T cell repertoire. While thymopoiesis generates “new” T cells with a polyclonal TCR repertoire, homeostatic proliferation expansion results in a very limited TCR repertoire diversity (Fig. 1). Thus, patients exhibiting impaired immune reconstitution due to altered thymic function are less equipped to respond to pathogens or even to control tumors than patients presenting an efficient T cell reconstitution with a fully diverse TCR repertoire (for a review, Williams et al., 2007).

A last concern is that the thymus involutes with age and injury, but keeps its capacity for renewal. This is well illustrated in clinical settings associated with T cell recovery (Dion et al., 2004) where the thymus expands and may become greater than the normal size with intense cellular density, as attested by computerized tomography (Williams et al., 2007). Radiographic measurement of thymus by computer tomographs correlates with circulating TREC levels (Harris et al., 2005). However, thymus renewal capacity declines with age (for a

review, Williams et al., 2007). In consequence, circulating TREC levels are inversely correlated with age (Gruver et al., 2007). Over the age of 45-50, thymic activity/output is reduced and naive T cell recovery may take until 5 years after severe iatrogenic lymphopenia (Williams et al., 2007).

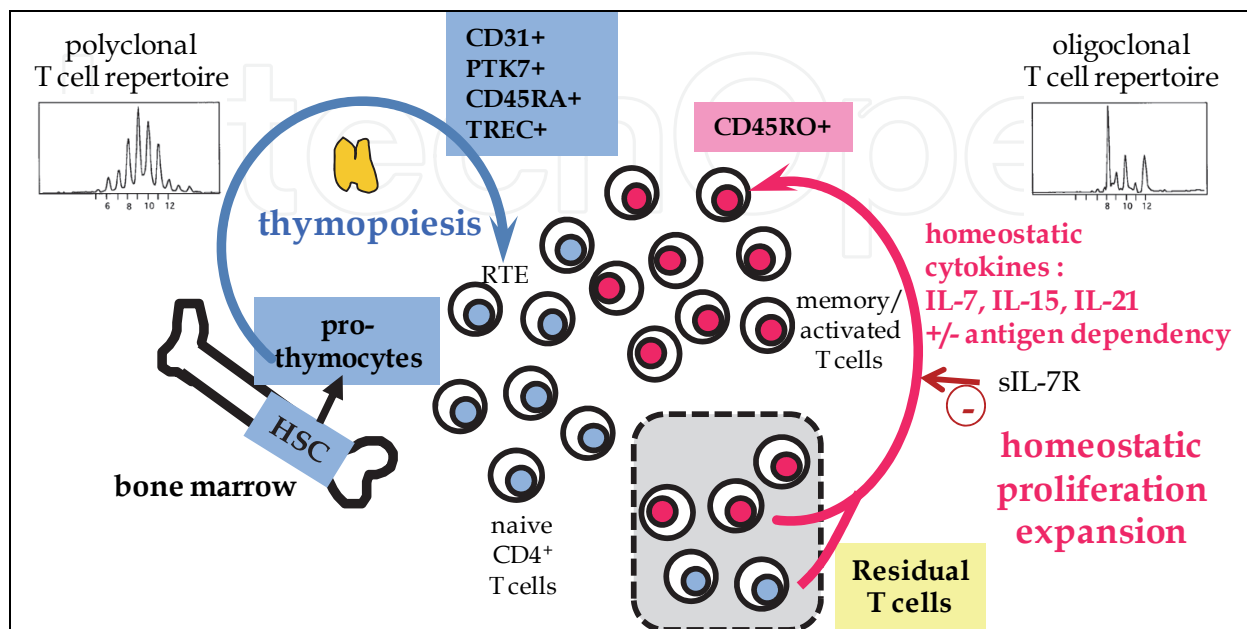


Fig. 1. The main pathways leading to immune reconstitution following CD4⁺ T cell depletion. The thymic pathway (thymopoiesis) depends on thymic activity. This activity has been shown to decline with age. This pathway generates new T cells, called RTE expressing the following markers: CD31⁺ CD45RA⁺ PTK7⁺ and not CD45RO. These RTE express CD127 (IL-7R α) and are sensitive to IL-7. Interleukin-7 participates to RTE expansion without inducing CD31 expression loss (Azevedo et al., 2009) or skewing T cell repertoire (Sportes et al., 2008). These RTE contribute to a diverse polyclonal T cell repertoire allowing patients to respond to multiple infectious and/or tumoral antigens. The homeostatic proliferation expansion depends on both residual T cells (*i.e.*, spared by ATG or depleting therapy) and homeostatic cytokine availability. These cytokines are IL-7, IL-15 and IL-21. Interleukin-7 is involved in CD4⁺ T cell expansion, whereas IL-15 and IL-21 are rather implicated in CD8⁺ T cell expansion (Boyman et al., 2009). Interleukin-7 activity may be neutralized by a soluble form of IL-7 receptor α (sIL-7R) (Rose et al., 2009). Although IL-7 expands RTE or naive T cells, memory phenotype cells express high levels of CD127, thus allowing them to respond to physiological levels of IL-7 for their survival and homeostatic proliferation. This pathway contributes to a limited T cell repertoire. Abbreviations used: HSC, hematopoietic stem cells; sIL-7R; soluble form of CD127 or IL-7R α ; RTE, recent thymic emigrants.

Few data are available to date concerning the human thymic function and CD4⁺ T cell recovery after kidney transplantation. Nickel *et al.* (2005) reported stable frequencies of RTE –assessed by CD31, CD45RA CD4 phenotype– 6 months after transplantation. These authors concluded that uremia due to past history of chronic renal dysfunction has no impact on thymic activity (Nickel et al., 2005). However, only 7 patients among 48 received depleting induction therapy (Nickel et al., 2005). This renders difficult to interpret the effects of thymic activity in the context of lymphopenia. In contrast, Scarsi *et al.* (2010) reported a

massive reduction of RTE one year post-transplantation after Campath-1H administration. This supports that naive CD4⁺ T cells –including RTE– may be highly sensitive to ATG (Louis et al., 2007; Gurkan et al., 2010)(see also below, paragraph §2.1.2) and that time is necessary for RTE “replenishment” after T cell depletion. The role of the thymic function at the time of kidney transplantation was not assessed in human. Several years ago, Monaco *et al* reported that thymectomy prior to ATG prolongs T cell lymphopenia in mice (Monaco et al., 1965). We recently identified the thymic activity (as assessed by circulating TREC levels) at the time of kidney transplantation as a major factor predicting CD4⁺ T cell immune reconstitution after ATG administration (Ducloux et al., 2010). We found a TREC value lower than 2'000 per 150'000 CD3⁺ cells at the time of transplantation to be the best threshold for the subsequent development of post-ATG CD4⁺ T cell lymphopenia (Ducloux et al., 2010). Renal transplant recipients with lower TREC levels at time of transplantation exhibited a higher morbidity and mortality risk due to cancers as well as cardiovascular diseases. Determination of circulating TREC levels at the time of transplantation may help to identify patients at high risk of persistent ATG-induced CD4⁺ T cell lymphopenia and post-transplant cancer occurrence (Ducloux et al., 2010). The strength/efficacy of this new biomarker could be a valuable tool to select the induction treatment (ATG *versus* non depleting anti-CD25 antibodies).

2.1.2 The role of homeostatic proliferation expansion and homeostatic cytokines on immune reconstitution after T cell depletion

The second pathway of immune reconstitution after induction therapy-induced lymphopenia is the homeostatic proliferation of residual T cells. This process, also called lymphopenia-induced proliferation, has been extensively studied in mice (for a review, Boyman et al., 2009). In murine models, this homeostatic proliferation expansion requires homeostatic cytokines (e.g., IL-7) and sometimes cognate antigen-driven interactions (Fig.1; Boyman et al., 2009). Several features with clinical consequences for lymphopenic patients are associated with homeostatic proliferation expansion: a limited TCR repertoire diversity, a shift from naive to memory/activated phenotype in the proliferating cells, a competition for limiting levels of homeostatic cytokines (increasing TCR repertoire skewing, hence decreasing the capacity of the host to respond to antigen challenge), a more delayed T cell recovery (Williams et al., 2007), a possibility to lose transplantation tolerance (Wu et al., 2004) or to favor autoimmunity by expanding autoreactive memory T cells (Monti et al., 2008).

Homeostatic proliferation expansion is the first pathway to be triggered when peripheral T cells decline acutely. This decrease in circulating T cell counts reduces IL-7 consumption, hence leads to enhanced levels of IL-7. This cytokine is then available for residual T cell expansion. High serum levels of IL-7 were found in allografted patients with severe lymphopenia after treatment depletion (Bolotin et al., 1999). However, IL-7 levels decrease rapidly with lymphocyte recovery (Bolotin et al., 1999). Interleukin-7 can be considered as a true regulator of the naive T cell pool size, driving homeostatic proliferation of CD4⁺ CD31⁺ RTE with sustained CD31 expression (Azevedo et al., 2009). Memory CD4⁺ T cells express high levels of CD127 (Boyman et al., 2009), then compete with RTE for IL-7. Dependency on IL-15 or IL-21 for homeostatic proliferation expansion is less marked for CD4⁺ T cells than CD8⁺ T cells. Thus, IL-7 levels after lymphopenia are a critical factor to be considered after depletion therapy. Cox *et al* have studied the IL-7 pathway (circulating IL-7 levels and CD127 expression on T cells) in lymphopenic multiple sclerosis patients receiving Campath-

1H treatment. No significant defect was observed (Cox et al., 2005). Data are needed to confirm this observation in the context of kidney transplantation. This is particularly interesting since recombinant human IL-7 has been used in clinical trials (Sportes et al., 2010). Interleukin-7 administration results in an expansion of both naive and memory CD4⁺ T cells and CD8 T⁺ cells with a tendency toward enhanced CD8 T⁺ cell expansion. Lymphopenic or normal older patients receiving IL-7 develop an expanded circulating T cell pool with increased T cell repertoire diversity. Moreover, recombinant human IL-7 administration exhibits a favorable toxicity profile, opening the perspective of potential future usage in renal transplant recipients with severe prolonged CD4⁺ T cell lymphopenia if this IL7 pathway will be found altered. Furthermore, IL-7 treatment of human thymus *-in vitro* or in a xenogeneic model– has been shown to increase thymic activity as attested by elevated TREC levels (Okamoto et al., 2002). Thus, IL-7 treatment may improve thymic activity after kidney transplantation.

2.2 CD4⁺ T cell subsets, sensitivity to anti-thymocyte globulin administration and immunosuppression-associated complications: the example of accelerated atherosclerosis

Anti-thymocyte globulins are a complex mixture of antibodies with multiple specificities directed against different molecules expressed by T cells, but also non T cells (Bonnefoy-Berard et al., 1991; Rebellato et al., 1994). Several authors believe that ATG exerts its effects through depletion as well as depletion-independent mechanisms. It has been reported that the different CD4⁺ T cell subsets were not equally sensitive to ATG-induced depletion. Initial works in mice showed that regulatory T cells (Treg) –playing a key role in the control and maintenance of tolerance (Fig.2)– were spared by anti-lymphocyte serum (ALS) (Minamimura et al., 2006), by a mechanism dependent of OX40 signaling pathway present in Treg with a memory phenotype (Kroemer et al., 2007). Moreover, in *in vitro* experiments, ATG has been reported to induce the conversion of Treg from naive CD25⁻ CD4⁺ T cells without acquisition of FoxP3 and CTLA-4 expression (Lopez et al., 2006). The source of ATG (from rabbit or horse) may impact Treg conversion with only rabbit-derived ATG allowing Treg conversion (Feng et al., 2008). An increase of Treg after rabbit ATG treatment has been reported *in vivo* in renal transplant recipients (Gurkan et al., 2010). Analysis of CD45RA, CD45RO, CD27 and CD31 marker expression on T cells from both adult and pediatric renal transplant recipients suggests that Treg comes from both RTE and peripheral expansion in adult patients, while they are mainly derived from thymus in children (Gurkan et al., 2010). Furthermore, ATG may also alter T cell migration (LaCorcia et al., 2009) and naive T cells have to home to secondary lymphoid organs in order to maintain a stable population size. A subset of stromal cells present in the secondary lymphoid organs, called fibroblastic reticular cells supports T cell survival (Link et al., 2007). Moreover, secondary lymphoid organs are an important source of IL-7 (Boyman et al., 2009), which participates to naive CD4⁺ T cell expansion after lymphopenia (see paragraph §2.1.2). Thus, altered T cell homing in the second lymphoid organs after ATG may participate to delayed immune reconstitution.

A thoroughly study in non human primates reported that ATG treatment induced a dose-dependent T cell depletion in the peripheral blood, the spleen and in the lymph nodes. T cell apoptosis in secondary lymphoid organs was identified as the main depletion mechanism (Preville et al., 2001). This supports that lymphocyte depletion is the major mechanism by which ATG preparation exerts its immunosuppressive effect. Another study in mice

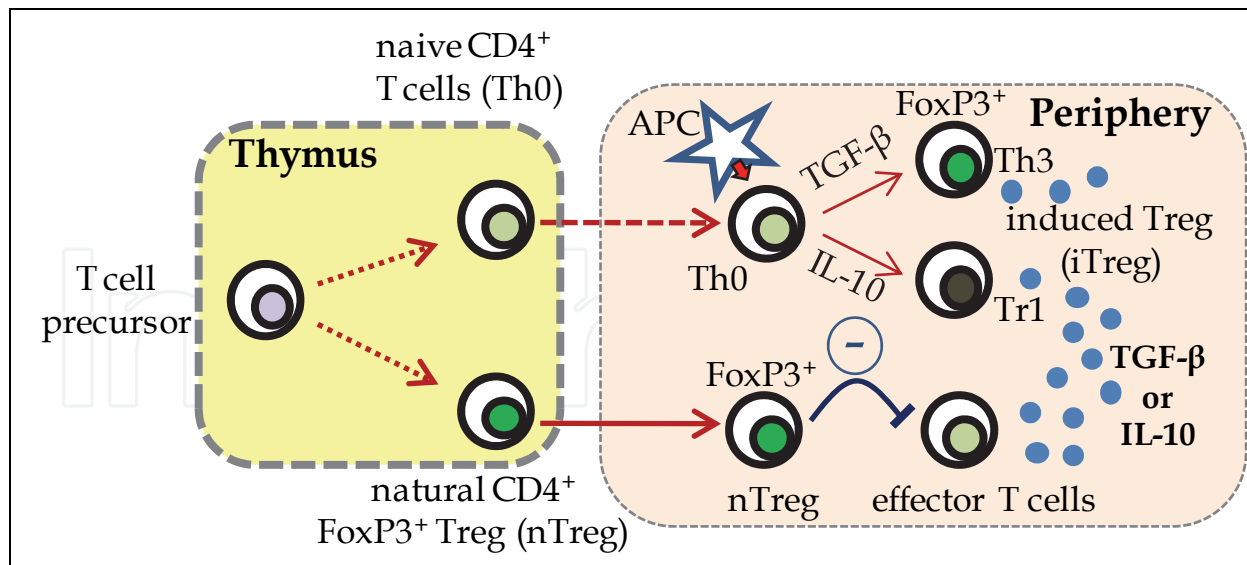


Fig. 2. The two main origins of CD25⁺ CD4⁺ regulatory T cells. The role of Treg is to control and maintain immune tolerance (Sakaguchi et al., 2010). These cells may be generated in the thymus and called natural Treg (nTreg). They express FoxP3 and exert their suppressive activity on effector T cells through cell contact, immunosuppressive cytokine secretion, and/or metabolic perturbations as well as by inhibiting antigen presenting cells (APC) (Vignali et al., 2008; Sakaguchi et al., 2010). Regulatory T cells may be also generated from conversion of naive CD25⁻ Th0 CD4⁺ T cells into induced Treg (iTreg) (see also, Fig.3). This conversion depends on cytokines present during T cell activation by APC. While IL-10 induces FoxP3^{neg} T regulatory 1 (Tr1) cells that produce IL-10 (Groux et al., 1997; Vieira et al., 2004), a TGF- β -rich microenvironment favors FoxP3⁺ Th3 that express membrane bound TGF- β and secrete high amount of TGF- β (Chen et al., 2003). Interleukin-10 and TGF- β inhibit effector T cell functions and also neutralize innate immune responses (see Fig.4).

reported that all CD4⁺ T cell subsets are equally sensitive to mouse ATG, but that naive T cells expand very quickly after homeostatic proliferation with the acquisition of a memory phenotype (Sener et al., 2009). This may explain why initial studies reported that memory phenotype T cells are more resistant to ATG-induced death (see above). The hypothesis of a different susceptibility to ATG-induced death or an imbalance in CD4⁺ T cell subset reconstitution is tantalizing to explain the relationship between CD4⁺ T cell lymphopenia and accelerated atherosclerosis after kidney transplantation. Depending on the cytokine microenvironment in which naive CD4⁺ T cells are primed, different effector CD4⁺ T helper cell (Th) subsets have been described (Fig.3). Whether ATG or immune recovery following ATG-induced lymphopenia may differently affect CD4⁺ Th subsets remains to be determined in renal transplant recipients. A study in renal transplant recipients suggested that Th2 subsets were less sensitive than Th1 subsets to ATG treatment (Weimer et al., 2005). However, other Th subsets –such as Th17 (Betteli et al., 2006; Mangan et al., 2006), or the putative Th9 (Dardahlon et al., 2008; Veldhoen et al., 2008) or Th22 (Duhon et al., 2009; Trifari et al., 2009) subsets (Fig.3)– have not been explored. Experimental mouse models of atherosclerosis using atherosclerosis prone apolipoprotein-E deficient or low density lipoprotein (LDL) receptor deficient mice permitted to distinguish pro-atherogenic from anti-atherogenic CD4⁺ T cell subsets (for recent reviews, Taleb et al., 2010a; Hansson & Hermansson, 2011; Fig.3). One may hypothesize that ATG-induced CD4⁺ T cell

lymphopenia may favor a preferential expansion of pro-atherogenic Th1 cells in detriment of anti-atherogenic Treg (*i.e.*, nTreg and iTreg subsets; Fig. 3). This remains to be determined in the future. Nevertheless, patients with end stage renal disease awaiting kidney transplantation exhibit an inflammatory state including high circulating levels of C reactive protein (CRP) (Ducloux et al., 2002b; Ducloux et al., 2004). Thus, immune reconstitution after depletion therapy occurs in the context of inflammation. One can speculate that pro-inflammatory and pro-atherogenic Th subsets are favored over anti-atherogenic T cells.

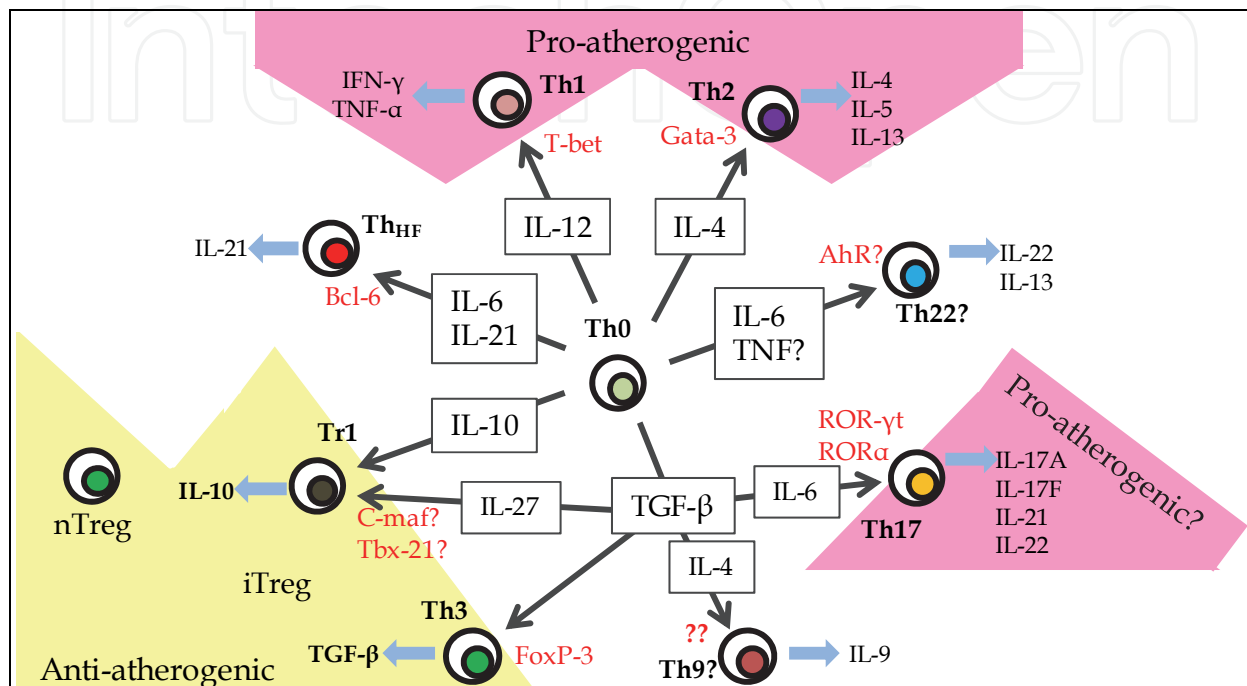


Fig. 3. CD4⁺ T cell subsets and their role in atherosclerosis. This figure summarizes cytokines involved in Th cell commitment, transcription factors necessary for this process as well as cytokines secreted by the different Th subsets. Transcription factors involved in Th commitment are indicated in red, while secreted cytokines are indicated after the blue arrow. According to cytokine microenvironment, distinct Th subsets can be generated: naive (Th0) T cell priming in the presence of IL-12 induces Th1 cells characterized by TNF- α and IFN- γ secretion and the transcription factor, t-bet. These Th1 cells are pro-atherogenic (in pink) and are found within atherosclerotic plaques (Taleb et al., 2010a). Th0 priming in the presence of IL-4 induces Th2 cells characterized by IL-4, IL-5 and IL-13 secretion and the transcription factor Gata-3. These Th2 cells favor atherosclerotic plaque disruption/instability (Taleb et al., 2010a), a late event in atherosclerosis (Hansson, 2005). Induced Treg (iTreg), already described in Fig.2, protect mice from atherosclerosis and thus are anti-atherogenic (in yellow) (Mallat et al., 2003). Natural Treg –directly produced in the thymus– exert the same anti-atherogenic effect (Ait-Oufella et al., 2006). Th0 priming in the presence of TGF- β and IL-6 leads to Th17 cells characterized by IL-17A, IL-22 and IL-21 secretion and the transcription factors ROR- γ t and ROR α . These Th17 cells seem to be pro-atherogenic (in pink) (Erbel et al., 2009; Gao et al., 2010; Ait-Oufella et al., 2010; for a recent commentary: Taleb et al., 2010b). The other Th subsets, namely the putative Th9 and Th22 or the helper follicular Th cells (Th_{HF} found in germinal centers and participating to B cell activation) have not been studied in the setting of atherosclerosis. Question mark indicates when data are not confirmed or not available.

As mentioned above, atherosclerosis is a chronic immune-mediated disease implicating both adaptive and innate immunity (Yan & Hansson, 2007; Woollard & Geismann, 2010; Hansson & Hermansson, 2011). In this review, we focused on CD4⁺ T cells to explain the increased incidence of atherosclerotic events associated with ATG administration. However, accelerated atherosclerosis is not only associated with induction therapy responsible for persistent CD4⁺ T cell lymphopenia, since cardiovascular diseases are observed in most renal transplant recipients (please see paragraph §1). This is why we also explore innate immune genetic factors to explain accelerated atherosclerosis. Most of the widely used immunosuppressive drugs target T cells and sometimes B cells (Halloran, 2004), while innate cells or factors are not always affected. For instance, calcineurin inhibitors may prevent Treg suppressive functions (Zeiser et al., 2006; Bonnefoy et al., 2008). Thus, regulatory functions are certainly unpaired in renal transplant recipients receiving calcineurin inhibitors. It was shown in mice that Treg dysfunction or blockade increases innate cell activation through Toll-like receptor (TLR) ligands (De Wilde et al., 2008). If this occurs in atherosclerotic plaques, this will favor atherosclerosis progression (Fig.4).

3. Recipient innate immune genetic factors as biomarkers of immunosuppression-associated complications

Inflammation plays a major role in atherosclerosis processes (Hansson, 2005). The atherosclerotic lesions contain large numbers of immune cells, particularly macrophages (Stary et al., 1995) and CD4⁺ T cells (Zhou et al., 1996). Macrophages are present in atherosclerotic lesions at early stages and play a critical role in lipid accumulation as well as in the plaque rupture (Hansson, 2005). The plaque rupture is responsible in coronary thrombosis (Hansson, 2005). Furthermore, atherosclerosis is associated with systemic immune responses and signs of inflammation. Histopathological and clinical investigations point at inflammatory activation of atherosclerotic plaques as a cause of acute coronary syndromes (Hansson, 2005), and sero-epidemiological studies have suggested links between atherosclerosis and microbial infections (Morre et al., 2000; Neumann et al., 2000). Moreover, several epidemiological studies and therapeutic trials have underlined the importance of inflammation in cardiovascular clinical end-points (Ridker, 2001; Ridker et al., 2009). The relevance of inflammation in atherosclerotic complications in humans is well illustrated by the JUPITER trial showing that achieving CRP levels under 2 mg/L with Rosuvastatin is associated with a 31% decrease in major cardiovascular events (Ridker et al., 2009).

In order to explore how inflammation and cells from the innate immunity may influence the complications associated with kidney transplantation, the analysis of different SNPs was performed in our laboratory. We followed the recommendations provided by *Nature Genetics* (1999) that are: a plausible/expected link between the analyzed protein or its gene promoter and the pathology, a functional characterization of the SNP, and a validation in independent cohorts. Moreover, the size of patient cohort has to be adapted to the frequency of mutated SNP. The following SNPs were analyzed in the settings of kidney transplantation outcome: TLR-4 (Ducloux et al., 2005b) and NOD2/CARD15 (Courivaud et al., 2006), as these two pattern recognition receptors (PRR) are involved in the recognition of pathogens and in the initiation of inflammatory immune responses (Fig.4). Sero-epidemiological studies have suggested a link between atherosclerosis and microbial infections (Morre et al., 2000; Neumann et al., 2000) and the atherosclerotic lesions contain large numbers of immune cells, particularly macrophages and dendritic cells (Woollard &

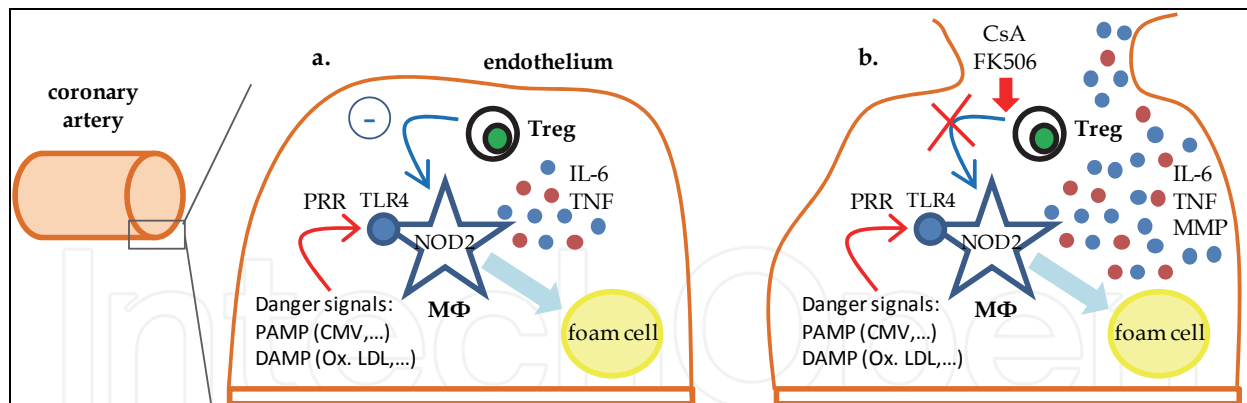


Fig. 4. Accelerated atherosclerosis in renal transplant recipients may result from a hyper-response of innate immune cells to Danger signals and a regulatory T cell deficiency in atherosclerotic lesions. Atherosclerotic lesions are asymmetric focal thickenings of the innermost layer of the artery, the intima. A view of the intima is shown with cells infiltrating this intima and lipid accumulation occurs *via* foam cells. (a) Treg controls the pro-inflammatory response and CPA activation. This limits atherosclerosis progression. (b) However, in case of Treg deficiency due to, for instance, calcineurin inhibitor (e.g., ciclosporin A, CsA or FK506) administration, pattern recognition receptor (PRR) stimulation by Danger signals induces an increased secretion of inflammatory cytokines, including IL-6 and TNF (De Wilde et al., 2008) as well as other factors involved in atherosclerosis progression such as matrix metalloproteinases (MMP; Hansson, 2005). This leads to atherosclerotic lesion progression and induces the activation and rupture of the plaque (b), thrombosis, and ischemia. Which innate immune cells are involved in plaque rupture? Macrophages ($M\Phi$) are present in atherosclerotic lesions at early stages (Stary et al., 1995). They differentiate in foam cells after lipid accumulation, but also increase local inflammatory responses when stimulated by Danger signals. According to Polly Matzinger (1994), these signals may correspond to pathogen-associated molecular patterns (PAMPs, linked to *Cytomegalovirus* [CMV] or *Chlamydia* infections both potentially implicated in atherosclerosis progression (Morre et al., 2000; Neumann et al., 2000) or to damage-associated molecular patterns (DAMPs, related to long history of end stage renal disease favoring hyaluronan accumulation or to increased oxidized LDL [Ox. LDL] production after lipid metabolism perturbations) that stimulate PRR, including TLR2 (Scheibner et al., 2006), TLR4 or NOD2/CARD15. DAMPs lead to sterile inflammatory responses that may favor auto-immune disease occurrence (Rock et al., 2010). For a recent review on Danger signals, please also refer to Kono & Rock (2008).

Geissmann, 2010; Fig.4). Thus, we hypothesized that an enhanced inflammatory response (including inflammatory cytokines, such as IL-6 or TNF- α) in the intima of the artery walls due to a "hyper-responsive" PRR (*i.e.*, TLR4 or NOD2/CARD15) may exert proatherogenic functions (Fig.4). We also studied other SNPs -that did not concern coding regions as for TLR4 and NOD2/CARD12- but rather the promoter gene region. In this setting, this promoter gene region regulates the levels of gene "production". For instance, we analyzed SNP in the *IL-6* or *COX-2* promoter gene (Bamoulid et al., 2006; Courivaud et al., 2009a; Courivaud et al., 2009b; Aubin et al., 2010). We correlated *IL-6* promoter gene SNP at position -174 with NODAT in overweight patients (Bamoulid et al., 2006). We reported, as already published in the general population (Fishman et al., 1998), that renal transplant

recipients carrying the G allele (GG or GC genotype carriers) produce higher levels of IL-6 and exhibit higher levels of CRP (Bamoulid et al., 2006). Diabetes is a traditional risk factor of cardiovascular diseases. Thus, NODAT may participate to accelerated atherosclerosis in renal transplant recipients. As previously reported in the general population (Kiechl et al., 2002), 2 TLR4 SNPs were also found associated with atherosclerotic events in renal transplant recipients (Ducloux et al., 2005b). In contrast, no association between NOD2/CARD15 polymorphisms (Courivaud et al., 2006) or COX-2 promoter gene SNP at position -765 (Courivaud et al., 2009a) and atherosclerotic events after kidney transplantation was observed. Data obtained in the former study (Courivaud et al., 2006) may rely on a minor role of NOD2/CARD15 in the atherosclerotic plaques. NOD2/CARD15 is preferentially located in the intestine (in crypts from the terminal ileum [Kobayashi et al., 2005] and in Paneth cells [Ogura et al., 2003]) and exerts mainly its function in the intestinal tract, as demonstrated in NOD2/CARD15 deficient mice (Kobayashi et al., 2005) and supported by the role of this PRR in gastrointestinal tract-associated pathologies (*i.e.*, Crohn's disease and intestinal graft-versus-host disease) (Hampe et al., 2002; Heliö et al., 2003; Holler et al., 2004). The latter study analyzing COX-2 promoter gene polymorphism (Courivaud et al., 2009a) is interesting, since an opposite result was obtained according to the analyzed transplant patient cohort. An increased risk of atherosclerotic events was observed in the first cohort, whereas in the second independent cohort the same SNP was associated with a protective effect on atherosclerotic event occurrence. This study (Courivaud et al., 2009a) illustrates perfectly the recommendations made by the editors of *Nature Genetics* concerning "genetic association studies" (1999). The current literature does not provide a clear landscape of SNP associated with complication outcome after kidney transplantation. Several causes may explain the discrepancy between the different studies, such as the cohort size and the functional validation of the SNP in the setting of immunosuppression. In order to increase the cohort size, most of the renal transplant recipients were included but they did not receive the same immunosuppressive regimen or alternatively the year of the graft was very different and thus clinical practices were difficult to compare. To limit these troubles, we are conducting a prospective study involving several renal transplantation centers to recruit a large cohort of patients in a limited time course. However, again, one may mention that clinical follow-up between different centers may be different. Thus, validation studies may be necessary to confirm or infirm SNP studies.

4. Conclusion

Overall, the aim of this review is to report our experience on the identification of biomarkers (CD4⁺ T cell lymphopenia after ATG, TREC levels at the time of transplantation, and innate immune genetic factors) predicting transplantation-related complications (mainly atherosclerosis and cancer occurrence), and to propose to the use these biomarkers in patient follow up and/or in immunosuppressive strategy design. Furthermore, we propose other "tracks" to improve the clinical relevance of these biomarkers as well as to understand their implications in the occurrence of immunosuppression-associated complications. The efficacy of these identified biomarkers should be tested and validated in prospective clinical trials in order to select the most appropriate immunosuppressive strategy. In the future, one could imagine that these biomarkers may help physicians to manage risks of cancers and cardiovascular diseases in renal transplant recipients. The management of these risks is of great interest as attested by recent reviews (Webster et al., 2008; Wang & Kasiske, 2010).

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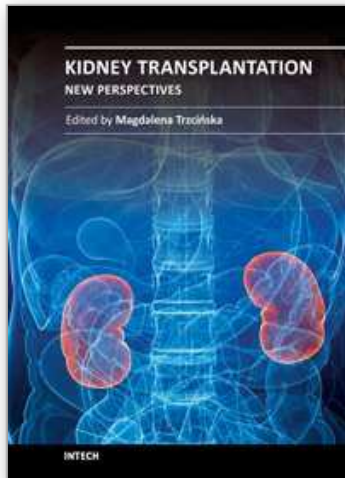
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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and that's why conscious 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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