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CD4 T Lymphopenia, Thymic Function, Homeostatic Proliferation and Late Complications Associated with Kidney Transplantation

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1. Introduction

Chronic kidney disease represents a public health problem worldwide. The prevalence of chronic kidney disease lies between 3 to 16% according to different epidemiological studies [1-5]. This high prevalence is observed in both developed and developing countries [1-5]. Chronic kidney disease is responsible for increased risk of cardiovascular diseases and end-stage renal failure. In the United States, for instance, the number of patients exhibiting end-stage renal failure was around 150 000 in 1995, 360 000 in 2003, and is estimated to reach 650 000 in 2015 [6]. This exponential growth of the end-stage renal disease population has relevant implications for health care systems. The treatment option for these patients is dialysis or kidney transplantation. The number of end-stage renal failure patients treated by either dialysis or transplantation was around 209 000 in 1991 and 472 000 in 2004 (data from the US Renal Data System 2006, reported in [3]). The costs of Medicare for end-stage renal failure treatment represents 5% of total budget, while it serves only 0.7% of patients [6]. The same observation is true for Europe with the proportion of the total health care budget dedicated to the end-stage renal disease population varying from 0.7% in the United Kingdom to 1.8% in Belgium in 1994, while this population is only 0.022% to 0.04% of the general population, respectively [6]. In France, the REIN (for *Réseau Epidémiologie et Information en Néphrologie*) program, hosted by the Agence de BioMédecine, is dedicated to assess the number of French patients suffering from end-stage renal failure and how these patients are treated (*i.e.*, dialysis

or transplantation). In 2009, 33 558 patients were dialyzed. This represents a frequency of 558 per million of inhabitants. At the same time, 29 181 patients received a kidney transplant (510 per million of inhabitants). During the last five years, the number of kidney transplantations per million of inhabitants in France was around 44. Currently, 8 397 patients with end-stage renal failure are awaiting transplantation among whom 4 043 are new patients. In 2010, only 2 893 kidney transplantations were performed in France (Agence de BioMédecine, REIN Annual Report 2010, [7]). Kidney transplantation has emerged as the best option for patients with end-stage renal failure, providing both a better quality of life and a better survival [8, 9]. Another advantage of renal transplantation over dialysis is its reduced cost. For instance, the 1-year cost per patient on maintenance hemodialysis exceeds US $52 000, whereas it is only a third (US $18 500) for kidney transplantation [6]. Overall, end-stage renal diseases are increasing worldwide. This corresponds to important expenses for health care systems that can be limited by preferentially selected kidney transplantation as therapeutic option. However, the severe lack of kidney transplant is a major obstacle preventing the full devel‐ opment of transplantation. This limits severely the number of end-stage renal disease patients who may benefit from this therapy. Moreover, this enforces the medical/scientific community involved in kidney transplantation to carefully select patients eligible for transplantation and to limit graft loss.

The use of nonspecific immunosuppressive drugs has significantly reduced the incidence of acute kidney graft rejection [10]. This led to a significant improvement in the first-year graft survival rates that are "almost close to perfect", as mentioned in [11]. However, the benefits of such immunosuppressive therapies on chronic rejection and overall long-term graft survival are uncertain [12, 13]. Long term graft survival remains unchanged over decades [13, 14]. Persistent excessive immunosuppression (also called over-immunosuppression) −related to these immunosuppressive drugs− exposes renal transplant recipients to long-term toxicities including: increased incidence of cancers, severe infectious complications and/or inflamma‐ tory "metabolic" diseases (for instance, diabetes, and accelerated atherosclerosis leading to cardiovascular diseases). The three major complications, cardiovascular diseases, infections and cancers, are reported to be the most common causes of patient death with functional graft. For instance, a recent study including 1 606 kidney transplant recipients reports that these three complications represent respectively 24%, 16%, and 12% of death with graft function [15]. Preventing these complications is a way to limit the loss of functional kidney graft and to ameliorate patient quality of life.

An enhanced risk of cancer after renal transplantation has been observed in the last decades [16-21], 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, involving 31 977 organ transplant recipients −among whom 97% have received a kidney graft− from Denmark, Finland, Sweden, Australia, and Canada illustrates perfectly the importance of malignancy occurrence after kidney transplantation. This study shows an increase in the incidence of

cancers related to viral infections implicating Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8), hepatitis viruses B and C (HBV and HCV), or related to *Helicobacter pylori* infections in renal transplant recipients when compared to the general population [16]. Nevertheless, increased incidence of cancers after transplantation is not restricted to virus-induced cancers, since other cancers such as kidney cancers, myeloma, leukemia, melanoma as well as bladder and thyroid cancers are more frequent in transplant recipients than in the general population [16]. Common epithelial cancers, such as breast and prostate cancers, occur at the same rate as for the general population [16]. But, despite similar incidence, a more aggressive course have been noticed in renal transplant recipients [22, 23]. Immunosuppression and its extent directly influence cancer occurrence after kidney transplantation [20, 24].

The incidence of cardiovascular diseases related to accelerated atherosclerosis associated with kidney transplantation [8, 25] is at least 3 to 5 times higher than in the general population [8]. Cardiovascular disease is reported to be the most common cause of death with functional graft ranging from 24% to 55% depending on the considered studies [8, 15, 26, 27]. Risk factors for cardiovascular diseases in renal transplant recipients are numerous including traditional and nontraditional factors. The main highly prevalent traditional risk factors of cardiovascular diseases are the following: tobacco use, physical inactivity, hypertension, diabetes, or dyslipidemia. Nontraditional cardiovascular risk factors related to a long history of end-stage renal failure, such as hyper-homocysteinemia, chronic inflammation or anemia, are also prevalent in renal transplant recipients [8, 15, 26, 28, 29]. Moreover, factors related to transplantation itself, including immunosuppression or rejection episodes as well as new-onset diabetes after transplant, impact on cardiovascular disease occurrence after kidney transplantation [8, 15, 26, 29, 30].

Altogether, it appears that over-immunosuppression is involved in both increased cancer occurrence and cardiovascular disease incidence observed after kidney transplantation. A greater understanding of risk factors leading to this excessive immunosuppression may help physicians in charge of end-stage renal failure patients 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 and patient selection. In this chapter, we will report the 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. For many years, we had been focusing on CD4$^+$ T cell lymphopenia −a consequence of anti-thymocyte globulin (ATG) administration− and T cell reconstitution after this severe T cell depletion. The analysis was performed on non-invasive blood samples (*i.e.*, serum and PBMC) from a Caucasian population receiving transplantation from deceased donors. Persistent CD4$^+$ T cell lymphopenia is a potent biomarker for over-immunosuppression-associated complications (see below, §2). But, this biomarker is not a predictive one, and thus, recent works in our laboratory have tried to identify predictive biomarkers linked to prolonged CD4$^+$ T cell lymphopenia. Pre-transplant thymic function, assessed by TREC levels, can be such a biomarker (see §4).

2. Persistent CD4$^+$ T cell lymphopenia, a biomarker for immunosuppression-associated complications

The first question to address is when CD4$^+$ T cell lymphopenia is encountered in renal transplant recipients. CD4$^+$ T cell lymphopenia in renal transplant recipients results mainly from ATG administration. CD4$^+$ T cell lymphopenia persists for several years in some transplanted patients [31, 32] despite a limited treatment duration (until 4 days). In addition to ATG, Campath-1H, a humanized anti-CD52 monoclonal antibody called Alemtuzumab, can be used as induction immunosuppression causing T cell depletion [33, 34].

Our group previously reported that persistent CD4$^+$ T cell lymphopenia after kidney transplantation is correlated with enhanced risks of cancers, including: skin cancers [35], monoclonal gammapathies [36], lymphomas as well as other non skin cancers, such as colon or lung cancers [37]. This persistent CD4$^+$ T cell depletion is also correlated with the increased incidence of opportunistic infections [38] and of atherosclerotic events [39]. On the opposite, CD4$^+$ T cell lymphopenia seems not to be associated with *de novo* genitourinary malignancies [40]. Recently, we associated prolonged CD4$^+$ T cell lymphopenia and renal transplant recipient mortality [41]. The two identified major causes of death in these patients were cancers and cardiovascular diseases [41]. Same data were observed by others in liver transplant recipients receiving ATG as induction therapy [42]. Overall, CD4$^+$ T cell lymphopenia represents an adequate biomarker for over-immunosuppression leading to immunosupression-associated complications, at least in patients receiving depletion therapy.

However, the limitations of using persistent CD4$^+$ T cell lymphopenia as a biomarker in clinical setting are the following: not all transplanted patients treated with ATG did develop a prolonged CD4$^+$ T cell lymphopenia [39, 41, 42] and this is not a predictive biomarker. Indeed, when a patient exhibits a prolonged CD4$^+$ T cell lymphopenia after ATG, how can physicians deal with it? Physicians can propose a more frequent clinical follow up in order, for instance, to detect earlier cancer occurrence. However, it will be difficult to prevent over-immunosuppression-associated complications. This is why 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 and to select the adequate immunosuppressive regimen. Indeed, ATG exerts a benefit over nondepleting induction therapy, especially for sensitized (high panel reactive antibodies, PRA) transplant patients. This is true not only for early acute graft rejection occurrence, but also for the preservation of allograft function [43, 44]. However, the ATG benefit is not similar for each patient [45, 46]. Thus, the choice of a complication risk level could vary according to the theoretical benefit of ATG. A high benefit of ATG may lead to accept a higher risk, whereas a slight benefit should lead to prefer a lower risk. Biomarkers, such as prolonged CD4$^+$ T cell lymphopenia, but rather those allowing us to predict this lymphopenia, may help to select ATG as an appropriate induction therapy. We imagine that these biomarkers identified in the setting of ATG can be transposed to other depleting therapies, such as Campath-1H/ Alemtuzumab. Indeed, clinical studies are available regarding the prolonged CD4$^+$ T cell

lymphopenia induced by Alemtuzumab administration [47], not always in the context of kidney transplantation [48, 49].

The identification of prolonged CD4$^+$ T cell lymphopenia was a critical step in our search for biomarkers associated with over-immunosuppression. However, we need to go further and to identify factors present at the time of transplantation responsible for the persistent lymphopenia. This could limit the complications associated with kidney transplantation. We reasoned that factors that affect the duration, intensity or variability of CD4$^+$ T cell reconstitution after ATG-induced T cell depletion can be useful biomarkers. Based on the literature, these factors can be the following: the thymic function/activity at time of transplantation and its capacity to regenerate, the capacity to respond to cytokines involved in homeostatic proliferation, and the variable sensitivity of CD4$^+$ T cell subsets to ATG-induced lymphopenia. This will be discussed in the next paragraphs of this review, but before that we will quickly summarize the different steps involved in T cell reconstitution after profound depletion.

Based on studies performed in animal models (mainly mouse models), Mackall and colleagues proposed several years ago that T cell reconstitution after profound T cell depletion in Human arises from two main pathways: thymopoiesis (*i.e.*, the capacity of producing new T cells from hematopoietic stem cells) and homeostatic proliferation expansion of residual host lymphocytes that resist to depletion [50]. 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 [51]. These two pathways are involved in T cell recovery after ATG-induced lymphopenia (see below, §3 and §4). Afterwards in this review, we will follow the chronological order of T cell reconstitution and list the factors involved in homeostatic proliferation and thymopoiesis that are critical for delayed or accelerated reconstitution. A third way of T cell reconstitution has been described in Human involving the extrathymic development, for instance in the tonsil [52]. This will not be discussed here. However, this is another interesting track to understand persistent CD4$^+$ T cell lymphopenia after ATG in renal transplant recipients in the future.

3. The role of homeostatic proliferation expansion after CD4$^+$ T cell depletion in the complications associated with over-immunosuppression

The first pathway of T cell reconstitution occurring after induction therapy-induced lymphopenia is the homeostatic proliferation of residual T cells, a compensatory process, also called lymphopenia-induced proliferation. We highly recommend a recent review on lymphodepletion and homeostatic proliferation [53]. How does this step influence T cell reconstitution after CD4$^+$ T cell depletion? First, it depends on the residual T cells that persist after ATG. In consequence, we will start with a paragraph dealing with data reporting sensitivity and resistance to ATG-induced T cell death. Second, the capacity of residual T cells to respond to homeostatic factors present in the microenvironment and competition for such factors may impact on T cell recovery. Here, we will restrict the discussion on CD4$^+$ T cells.

The CD4^{+} T cell pool is constituted by different CD4^{+} T cell subsets: naive CD4^{+} T cells expressing CD45RA that have not encountered their antigens called also T helper (Th) 0 cells and memory/activated CD4^{+} T cells expressing CD45RO^{+}. These cells can be divided into effector memory and central memory according to CD62L/CCR7 or CD62L/CD44 expression. Depending on the cytokine microenvironment in which naive CD4^{+} T cells are primed, different Th subsets have been described: Th1, Th2, and Th17 (for a general scheme of Th cell differentiation, please refer to [54]). Moreover, this CD4^{+} T cell pool contains regulatory T cells (Treg) that play a key role in the control and maintenance of tolerance [55, 56]. FoxP3^{+} natural Treg (nTreg) are produced in the thymus while induced Treg (iTreg) are generated in the periphery from naive CD45RA^{+} CD4^{+} T cells in the presence of immunosuppressive cytokines: IL-10 for FoxP3^{neg} T regulatory 1 (Tr1) cells [57] or TGF-β for FoxP3^{+} Th3 iTreg [58]. This CD4^{+} T cell pool may vary after T cell depletion and reconstitution may affect this pool. Modifications of the CD4^{+} T cell pool may have consequences on late complications associated with renal transplantation (see below, §3.3).

3.1. CD4^{+} T cell subsets and sensitivity to anti-thymocyte globulin administration

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 [59, 60]. A thorough study in non human primates reported that ATG treatment induced a dose-dependent T cell depletion in the peripheral blood, as well as in the spleen and in the lymph nodes. Massive T cell apoptosis in secondary lymphoid organs was identified as the main mechanism implicated in T cell lymphopenia [61]. This supports that lymphocyte depletion is the major mechanism by which ATG preparation exerts its immunosuppressive effect. However, when considering T cell reconstitution, one has to evoke other mechanisms: *i*) the relative resistance of some T cell subsets to ATG that has the advantage to expand in the lymphopenic environment; *ii*) depletion-independent mechanisms [62]; *iii)* the elimination of non T cells that may participate to homeostatic proliferation.

It has been reported that CD4^{+} T cells are more sensitive to ATG-induced depletion than CD8^{+} T cells [62] and that the different CD4^{+} T cell subsets are not equally sensitive to ATG-induced depletion [63, 64]. For instance, in a mouse model, Treg were spared by anti-lymphocyte serum (ALS) −an equivalent of ATG in mice− treatment [63]. This occurs by a mechanism dependent on OX40 signaling pathway present in Treg with a memory phenotype [65]. However, another study in mice 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 [66]. This may explain why initial studies reported that memory phenotype T cells are more resistant than naive T cells to ATG-induced death. The same is maybe true for CD8^{+} T cells that expand faster than CD4^{+} T cells (as discussed in [67]). 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, since some Th subsets are pro-atherogenic while other are anti-atherogenic (see §3.3). 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 [68]. However, other Th subsets −such as Th17, or the putative Th9 [69, 70] or Th22 [71, 72] subsets− have not been explored yet.

What are the arguments in favor of depletion-independent mechanisms that may influence CD4$^+$ T cell reconstitution after ATG-induced lymphopenia? The major mechanism is the induction of iTreg or the conversion of naive CD4$^+$ T cells into iTreg. In *in vitro* experiments, ATG has been reported to induce the conversion of iTreg from naive CD25$^-$ CD4$^+$ T cells [73]. The source of ATG (from rabbit or horse) may impact Treg conversion with only rabbit-derived ATG allowing Treg conversion [74]. An increase of Treg after rabbit ATG treatment has been reported *in vivo* in renal transplant recipients [75]. The same data were reported with mouse ATG in mice [64, 76]. ATG is constituted by a mixture of antibodies with multiple specificities (see below) and CD3-specific antibody has been shown to efficiently deplete T cells, and then in a second step, to favor conversion of residual naive CD4$^+$ T cells in iTreg *via* TGF-β [77, 78]. Whether CD3-specific antibodies present in ATG preparations are responsible for ATG-induced iTreg remains to be determined. In-depth analysis of Treg phenotype after ATG treatment using CD45RA, CD45RO, CD27 and CD31 markers suggests that Treg come from both thymus and peripheral expansion in adult renal transplant recipients, while they are mainly derived from thymus in pediatric patients [75]. Furthermore, ATG may also alter T cell migration [79] and naive T cells have to home to secondary lymphoid organs in order to maintain a stable population size [53]. A subset of stromal cells present in the secondary lymphoid organs, called fibroblastic reticular cells supports T cell survival *via* CCL19 [80]. Moreover, secondary lymphoid organs are an important source of IL-7 [80, 81], which participates to naive CD4$^+$ T cell expansion after lymphopenia (see below, §3.2). Thus, altered T cell homing in the secondary lymphoid organs after ATG may participate to delayed immune reconstitution. Transient CD3-specific antibody treatment resulting in T cell lymphopenia has been also shown to affect T cell homing by stimulating the accumulation of Th17 cells with regulatory functions in the small intestine [78]. This sustains the main role of "so-called" depletion-independent mechanisms after depleting antibody therapy in T cell homeostasis. We used the term "so-called", since these depletion independent-mechanisms may in fact correspond to bystander mechanisms related to depletion rather than really depletion-independent mechanisms.

3.2. CD4$^+$ T cell subsets and homeostatic proliferation after anti-thymocyte globulin administration

Lymphopenia-induced proliferation has been extensively studied in mice (for review [81]) and has been cleverly transposed to human setting [53]. T cell dynamics −including T cell replenishment by homeostatic proliferation or after thymopoiesis− are usually extrapolated from mice to humans and *vice versa*. These extrapolations are due to some common observations performed in both species. However, some major differences may exist, such as naive T cell lifespan: 7 to 11 weeks for mouse naive T cells *versus* 6 to 9 years for human naive T cells [82]. This will be also discussed later in this review when thymopoiesis will be evoked

(see below, §4.1). In murine models, homeostatic proliferation after T cell depletion uses different kinetics (fast and slow), requires homeostatic cytokines (e.g., IL-7) and sometimes cognate antigen-driven interactions (*i.e.*, peptide/major histocompatibility complex [MHC] presentation by antigen-presenting cells) [81]. The requirements of homeostatic cytokines and contact with host MHC molecules vary depending on whether residual naive or memory T cells are considered.

Homeostatic proliferation is the first pathway to be triggered when peripheral T cells decline acutely. It can follow a fast (~ one cell division per 6-8 hours) or a slow (~one division per 24-36 hours) kinetics [53]. The fast kinetics is an antigen-specific process, and thus, only a smaller subset of T cells (*i.e.*, antigen-specific T cells) is concerned. These antigens may be rather foreign antigens including, for instance, latent viruses such as EBV or commensal bacteria, such as gut flora that favors homeostatic expansion of residual T cells in the gut [83]. Recent fascinating reports have described how commensal bacteria are involved in the regulation of the immune system in the gastro-intestinal tract [84, 85]. Interestingly, limited clinical manifestations involving the gastro-intestinal tract have been reported in renal transplant recipients. The slow homeostatic proliferation occurs in response to T cell depletion, can be self-antigen driven and implicates IL-7 [53]. Interleukin-7 is produced at a relatively constant level and a decrease in circulating T cell counts reduces IL-7 consumption, hence leading to enhanced levels of IL-7. This cytokine become then available for residual T cell expansion. High serum levels of IL-7 were found in transplanted patients with severe lymphopenia after treatment-induced depletion [86]. However, IL-7 levels decrease rapidly with lymphocyte recovery [86]. It was recently proposed that levels of IL-7 receptor (CD127) expression on reconstituting T cells rather than the absolute number of T cells may be responsible for the IL-7 availability [87]. Down-regulation of CD127 by increased levels of IL-7 causes termination of homeostatic proliferation [88]. Thus, IL-7 can be considered as a true regulator of the naive T cell pool size, driving homeostatic proliferation of CD31+ CD4+ recent thymic emigrants (RTE, see below, §4) with sustained CD31 expression [89]. Memory CD4+ T cells –the dominant T cell subset following antibody-mediated T cell depletion [90]– express high levels of CD127 [81], and then compete with RTE for IL-7. Moreover, memory CD4+ T cells expand more quickly during lymphopenia [53, 90]. While Treg are characterized by a low CD127 expression [91, 92], Treg may express high levels of CD127 upon activation [93] and may respond to IL-7 driven homeostatic proliferation [94]. To finish with the role of IL-7 in homeostatic proliferation, one has to mention that this cytokine is particularly available in secondary lymphoid organs attached to extracellular matrix after being synthesized by fibroblastic reticular cells [53, 80, 81]. This highlights the role of an adequate T cell homing to achieve an efficient T cell reconstitution. In addition, the strength of T cell receptor (TCR) affinity for peptide/MHC regulates homeostatic proliferation mediated by IL-7: the stronger is the TCR affinity, the less IL-7 concentration is necessary [95, 96]. Dependency on other cytokines (e.g., IL-15 or IL-21) for homeostatic proliferation expansion is less marked for CD4+ T cells than for CD8+ T cells. Thus, IL-7 levels after lymphopenia are a critical factor to be considered after depletion therapy, and competition of the different T cell subsets that resist to this therapy may occur. All these subsets do not expand with the same kinetics (see next paragraph). Cox *et al* [48] have studied the IL-7 pathway (circulating IL-7 levels and CD127 expression on T cells) in lymphopenic

multiple sclerosis patients receiving Campath-1H/Alemtuzumab treatment. No significant defect was observed [48]. 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 [97] (see below, §4.3).

The kinetics of reconstitution after lymphopenia are dependent on the considered T cell subsets, with memory T cells expanding more rapidly than naive T cells and naive CD8$^+$ T cells undergoing faster proliferation rates than naive CD4$^+$ T cells [53, 62]. Furthermore, Th1 cell expansion is favored by homeostatic proliferation [98]. This sustains that the subsets of T cells that resist to depleting therapy play a major role in reconstitution. Antigen persistence such as latent viruses may favor T cell exhaustion [67], and the loss of T cell specificity participating to immunodeficiency. The picture is more complicated for Treg [53]. Initial works reported that in lymphopenic environment, Treg expand quickly and massively by homeostatic proliferation [98], as a mechanism to prevent unwanted autoimmune responses. "Spontaneous" conversion of naive CD4$^+$ T cells into iTreg in the lymphopenic environment [99] may also participate to this increase of Treg. Moreover, the sites (gut *versus* secondary lymphoid organs) may influence the speed (fast or slow) of recovery [53] and the T cell subset implicated in homeostatic proliferation [78]. A recent editorial suggests harnessing this homeostatic proliferation to favor transplantation tolerance [67].

3.3. Clinical implications of altered homeostatic proliferation in the setting of CD4$^+$ T cell lymphopenia

How can altered homeostatic proliferation after severe CD4$^+$ T cell depletion participate in increased cancer occurrence or accelerated atherosclerosis? Several features with clinical consequences for lymphopenic patients are associated with the preferential homeostatic proliferation of limited T cells: *i)* a limited TCR repertoire diversity leading to reduced immune responses against oncogenic virus or maybe tumor antigens explaining the increased incidence of cancers, *ii)* a shift from naive to memory/activated phenotype in the proliferating cells, *iii)* a competition for limiting levels of homeostatic cytokines (increasing TCR repertoire skewing, hence decreasing the capacity of the host to respond to antigen challenge), *iv)* a more delayed T cell recovery [100], a possibility to lose transplantation tolerance [101], to favor autoimmunity by expanding autoreactive memory T cells [102], or T cell exhaustion [67]. Presence of latent infectious antigens, such as cytomegalovirus CMV, may participate in T cell exhaustion and subsequent cancer occurrence [103]. Thus, homeostatic proliferation favors over-immunosuppression and the overall immunodeficiency leading to enhanced cancer incidence.

Homeostatic proliferation may also be implicated in accelerated atherosclerosis. Indeed, experiments performed in atherosclerosis prone apolipoprotein-E deficient or low density lipoprotein receptor deficient mice have distinguished pro-atherogenic from anti-atherogenic CD4$^+$ T cell subsets (for reviews, [104, 105]). 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). 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)

[106, 107]. Thus, immune reconstitution after depletion therapy occurs in the context of inflammation and may favor Th1 subsets. In lymphopenic setting, Th1 have been reported to expand massively [98]. One can speculate that pro-inflammatory and pro-atherogenic Th subsets are favored over anti-atherogenic T cells in renal transplantation recipients receiving ATG treatment leading to increased incidence of cardiovascular diseases.

4. The role of thymic activity after CD4+ T cell depletion in the complications associated with over-immunosuppression

The thymus participates more lately than homeostatic proliferation to immune reconstitution after profound T cell depletion. The role of the thymic function on immune reconstitution after profound T cell depletion has been studied in different clinical settings such as human immunodeficiency virus (HIV) infection or hematopoietic cell transplantation (for recent review [108]).

Different tools are available to discriminate recent thymic emigrants (RTE, reflecting thymic activity/output) from other lymphopenia-induced expanded T cells (*i.e.*, naive or memory/activated). Douek and colleagues reported that circulating T cell excision circle (TREC) levels are a direct reflect of thymic function [109]. 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. It is possible to distinguish sjTREC and βTREC generated during recombination of the TCR α-chain and β-chain, respectively. The proliferative ability of thymic progenitors within the thymus can be assessed by sjTREC/βTREC ratio due to the sequential recombination of TCR β-chain, and then, of TCR α-chain after several divisions (for further explanations, please refer to a complete review on TREC [108]). Expression of surface markers −including CD45RA, CD31 or protein tyrosine kinase 7 (PTK7)− on circulating CD4+ T cells has been shown to identify RTE and to attest to an efficient thymopoiesis [110, 111]. CD31+ CD4+ T cells contain higher sjTREC levels than their CD31^{neg} counterpart [89]. However, maintenance of CD31 expression on CD4+ T cells during IL-7-driven homeostatic proliferation can be observed [89]. This renders CD31 expression analysis as a less pertinent marker to interpret thymic activity.

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 [112] where the thymus expands and may become greater than the normal size with intense cellular density, as attested by computerized tomography [100]. Radiographic measurement of thymus by computer tomographs correlates with circulating TREC levels [113]. However, thymus renewal capacity declines with age (for a review [100]). In consequence, circulating TREC levels are inversely correlated with age [114]. 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 [100]. Overall, tools are available to study the part of thymic output in T cell reconstitution after ATG-induced lymphopenia.

4.1. Altered thymic activity, a predictive biomarker of persistent CD4⁺ T cell lymphopenia after anti-thymocyte globulins

Few data are available to date concerning the human thymic function and CD4⁺ T cell recovery after kidney transplantation. Several years ago, Monaco *et al* reported that thymectomy prior to ATG prolongs T cell lymphopenia in mice [115], attesting for the role of thymus in T cell reconstitution after ATG. Stable frequencies of RTE –assessed by CD31, CD45RA CD4 phenotype– have been reported in renal transplant recipients 6 months after transplantation [116]. These authors concluded that uremia due to past history of end-stage renal failure has no impact on thymic activity [116]. Only 7 patients among the 48 analyzed have received depleting induction therapy [116]. This renders difficult to interpret the role of thymic activity in the context of lymphopenia. In contrast, Scarsi et al [47] reported a massive reduction of RTE one year post-transplantation after Campath-1H/Alemtuzumab administration. Prolonged selective CD4⁺ T cell lymphopenia suggests that naive CD4⁺ T cells –including RTE– are highly sensitive to ATG [31, 75] and that time is necessary for RTE "replenishment" after T cell depletion. Analysis of thymic function in a cohort of rheumatoid arthritis patients receiving Alemtuzumab 12 years before shows that circulating TREC levels are independent on patient age but correlate with CD4⁺ T cell counts (*i.e.*, patients with lower TREC are still lymphopenic) and patients with normal CD4⁺ T cell counts exhibit the same TREC levels than age-matched controls [49]. Thus, TREC and CD31 expression analysis can be used to monitor thymic function in the setting of kidney transplantation.

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 [41, 117]. In a first patient cohort, 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 prediction of persistent post-ATG CD4⁺ T cell lymphopenia [41]. Renal transplant recipients with lower TREC levels at the 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 [41]. Moreover, in a second cohort of patients, the levels of TREC at the time of transplantation is predictive of cancer occurrence in renal transplantation recipients and correlate with naive CD45RA⁺ CD4⁺ T cell recovery 1-5 years after transplantation [117]. Thus, TREC analysis at the time of transplantation can be a useful predictive biomarker for over-immunosuppression-associated complications. This new biomarker could be a valuable tool to select induction treatment (ATG *versus* non depleting anti-CD25 antibodies). Renal transplant recipients with lower TREC levels at the time of transplantation should not be eligible for ATG treatment. This needs to be validated in prospective trials.

The maintenance of naive T cell pool appears critical to avoid complications associated with over-immunosuppression after kidney transplantation. A recent interesting study challenges

some "dogma" on the role of thymic output in the maintenance of human naive T cell pool [118]. While thymic output is stable even with age in mice, in humans peripheral T cell proliferation may be the major mechanism contributing to the maintenance of naive T cell pool. Indeed, when the authors normalized the TREC content of peripheral CD4+ T cells by the TREC content of single positive CD4+ thymocytes (obtained from 45 children who underwent cardiac surgery), they observed that, in individuals older than 20, only around 10% of circulating naive T cells come from thymus while the majority are formed from peripheral naive T cell proliferation. The same data were obtained using *in vivo* kinetic labeling using deuterated water and mathematical modeling. This confirms that T cell dynamics differ in mice and humans (see above, §3.2) and challenges the data obtained with TREC analysis. However, a potential limitation of this work is that analyses have been performed in healthy volunteers (in steady state) [118] and not in lymphopenic patients. As mentioned before, the human thymus keeps the capacity for renewal [100], especially in case of profound T cell depletion. Nevertheless, this works reinforces the idea that thymic function in lymphopenic renal transplant recipients should be further explored using, for instance, more sophisticated approaches such as *in vivo* labeling using deuterated water.

4.2. Clinical implications of altered thymic function in the setting of CD4+ T cell lymphopenia

How can altered thymic output after severe CD4+ T cell depletion participate in increased cancer occurrence or accelerated atherosclerosis? A major role of thymus during T cell recovery is the reconstitution of a most diverse polyclonal T cell repertoire. Thus, renal transplant recipients with an impaired thymic function exhibiting a skewed T cell repertoire and are less equipped to respond to pathogens (including oncogenic viruses) or even to control tumors than patients presenting an efficient T cell reconstitution with a fully diverse TCR repertoire (for a review [100]). This may explained the increased occurrence of cancers in renal transplant recipients.

In patients with altered thymic function, homeostatic proliferation becomes the main contributor to T cell recovery, and thus, duration of lymphopenia is extended with uncontrolled pro-atherogenic CD4+ T cell subset expansion leading to accelerated atherosclerosis (see above). Moreover, impaired thymic function and uncontrolled homeostatic proliferation may lead to immune exhaustion that aggravates immunodeficiency. In addition, impaired thymic output by limiting naive T cell production impacts highly on homeostatic proliferation. This explains why pre-transplant thymic function is a good and sensitive biomarker.

4.3. Perspectives: Toward a restoration of thymic function?

We recently identified impaired thymic function as a biomarker for increased occurrence of cancers and accelerated atherosclerosis related to persistent CD4+ T cell lymphopenia [41, 117]. It remains interesting to localize the defect more accurately in order to propose a therapeutic restoration of this function. One hypothesis is that the defect is localized before the thymus for instance, in CD34+ lymphoid precursors, as proposed for HIV [119]. This is a
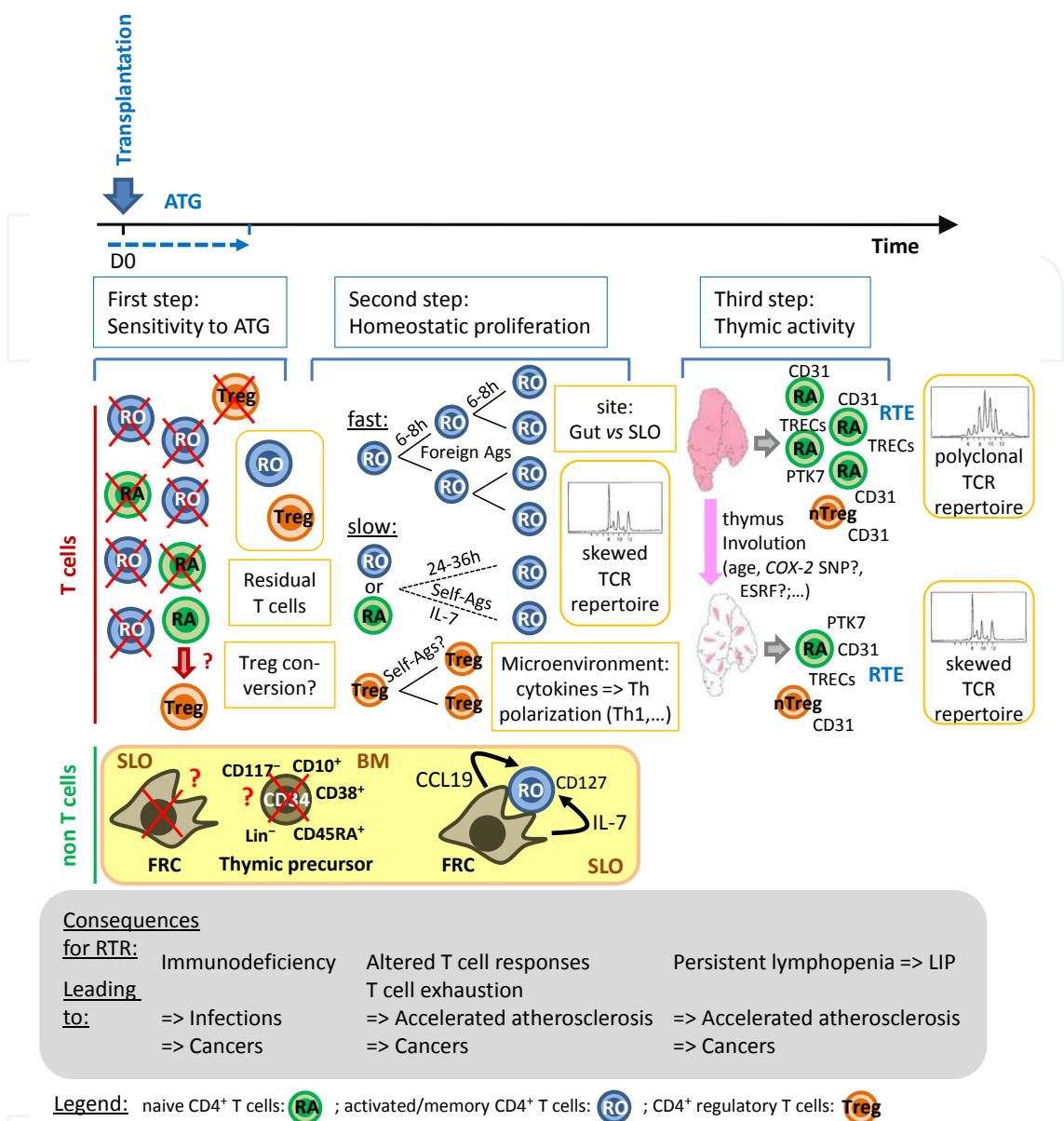
Figure 1. CD4+ T cell recovery after anti-thymoglobulin (ATG)-induced depletion in renal transplant recipient (RTR) is dependent on three steps/stages: *i)* sensitivity to ATG; *ii)* cytokine and/or antigen-dependent homeostatic proliferation, a process called also lymphopenia-induced proliferation (LIP); *iii)* thymic activity. This figure identifies for each step critical parameters that may influence CD4+ T cell recovery. Sensitivity to ATG depends on the considered CD4+ T cell subsets. ATG may affect non T cells (lymphoid precursors or fibroblastic reticular cells [FRC] that in turn impact on T cell reconstitution). Non depletion mechanisms are illustrated by conversion of naive CD4+ T cells into Treg. T cell recovery after depletion implicates first LIP. Kinetics of T cell proliferation depends on: the type of antigen (self antigens [Self-Ags] may induce a slow kinetic, whereas foreign antigens [Foreign Ags], including: EBV, CMV or commensal bacteria] may rather induce a fast kinetic – the average division time is given). The microenvironment and the site may also play a role. Cytokines such as IL-7 may participate in LIP, but also in helper T cell (Th) polarization. Finally, complete CD4+ T cell recovery involves the thymus with production of new CD4+ T cells (called recent thymic emigrants [RTE]) allowing the reconstitution of a polyclonal TCR repertoire. Thymic function can be impacted by patient age, end stage renal failure (ESRF) duration, or maybe also by *COX-2* gene promoter single nucleotide polymorphisms (SNP). A dysfunction in each step may lead to complications in RTR (summarized in the gray box). *Other abbreviations used*: BM, bone marrow; D0, day 0 (*i.e.*, the day of transplantation); h, hour; SLO, secondary lymphoid organs; Th, T helper cells. The question mark represents a potential mechanism. For more details, please refer to the text.

possibility since ATG contains a mixture of antibodies with multiple specificities [59, 60], and thus, ATG may affect circulating thymic precursors. With this assumption in mind, we hypothesize that the capacity to regenerate hematopoiesis may impact thymic function. The *cyclo-oxygenase-2* (*COX-2*) gene promoter polymorphism at position -765 is responsible for the control of prostaglandin-E2 (PGE-2) synthesis and PGE-2 has been reported to be involved in lymphocyte reconstitution following depletion [120-122]. Indeed, COX-2 is expressed by thymic stroma [121], participates not only in thymocyte development [122], but also in accelerated hematopoiesis following myelotoxic injury [120]. We found that the *COX-2* gene promoter polymorphism at position -765 is associated with a higher risk of ATG-induced persistent CD4 T-cell lymphopenia. Pre-transplant TREC levels were higher in GG patients than in C carriers who have lower serum PGE-2 levels [123]. The possibility of selecting patients with low or high risk of immune reconstitution impairment through the *COX-2* gene promoter polymorphism could offer the opportunity to use ATG more safely. This suggests that ATG may affect T cell reconstitution before thymus.

Significant advances have been performed in the comprehension of endogenous thymus regeneration and several factors have been shown to increase thymic activity (for a recent review [108], see also Ref.[124] for IL-22). This is particularly interesting since recombinant human IL-7 has been used in clinical trials [97]. Administration of IL-7 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 [97]. Lymphopenic or normal older hosts receiving IL-7 develop an expanded circulating T cell pool with increased T cell repertoire diversity [100]. Moreover, IL-7 administration exhibits a favorable toxicity profile [97], opening the perspective of potential future use in renal transplant recipients with severe prolonged CD4$^+$ T cell lymphopenia in case that this IL7 pathway is 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 [125]. Thus, IL-7 treatment may improve thymic activity after kidney transplantation.

5. Conclusion

We summarize in a Figure the different factors and critical steps involved in CD4$^+$ T cell reconstitution after depletion by ATG (Figure 1). Overall, the aim of this review was to report our experience on the identification of biomarkers (CD4$^+$ T cell lymphopenia after ATG and TREC levels at the time of transplantation) predicting transplantation-related complications (mainly atherosclerosis and cancer occurrence), and to propose to 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 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.

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