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MINIREVIEWS

T-cell ageing in end-stage renal disease patients: Assessment and clinical relevance

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Abstract

End-stage renal disease (ESRD) patients have a defective T-cell-mediated immune system which is related to excessive premature ageing of the T-cell compartment. This is likely to be caused by the uremia-associated pro-inflammatory milieu, created by loss of renal function. Therefore, ESRD patients are highly susceptible for infections, have an increased risk for virus-associated cancers, respond poorly to vaccination and have an increased risk for atherosclerotic diseases. Three ageing parameters can be used to assess an immunological T-cell age. First, thymic output can be determined by assessing the T-cell receptor excision circles-content together with CD31 expression within the naïve T cells. Second, the telomere length of T cells and third the T-cell differentiation status are also indicators of T-cell ageing. Analyses based on these parameters in ESRD patients revealed that the immunological T-cell age is increased by on average 20 years compared to the chronological age. After kidney transplantation (KTx) the aged T-cell phenotype persists although the pro-inflammatory milieu is diminished. This might be explained by epigenetic modifications at hematopoietic stem cells level. Assessment of an immunological T-cell age could be an important tool to identify KTx recipients who are at risk for allograft rejection or to prevent over-immunosuppression.

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Key words: End-stage renal disease patients; Kidney transplantation; T-cell ageing; T-cell differentiation; Uremia

Core tip: The uremia-induced inflammatory environment in end-stage renal disease (ESRD) patients is associated with a prematurely aged T-cell compartment, resulting in defective T-cell-mediated immunity. ESRD patients are highly susceptible for infections, have an increased risk for virus-associated cancers, respond poorly to vaccination and have an increased risk for atherosclerotic diseases. Adequate renal replacement therapy in the form of kidney transplantation is able to diminish the uremic pro-inflammatory environment but unsuccessfully reverses the aged T-cell system. Assessment of T-cell ageing might be a tool to facilitate individualization of immunosuppressive regimes and prevent over-immunosuppression and its associated clinical complications in kidney transplant recipients.

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INTRODUCTION

Loss of renal function is strongly associated with a defective immune system which is known as uremia-associated immune deficiency[1-3]. Retention of uremic molecules and cytokines in end-stage renal disease (ESRD) patients are key mechanisms in generating oxidative stress and inflammation[2,4,5]. This creates a pro-

inflammatory environment in which both the innate (first line of defense, a-specific)[3,6-8] as well as the adaptive (specific) immune system are affected (Figure 1)[3,9,10].

T cells, members of the adaptive immune system, are the best-studied immune cells in ESRD patients and in the field of transplantation they are the main target of immunosuppressive medication[11]. The uremia-associated pro-inflammatory milieu causes T-cell defects associated with premature T-cell ageing when compared to healthy age-matched individuals (Figure 1)[12]. Analysis of the T-cell compartment in ESRD patients revealed that the immunological age of T cells is increased by 20 years compared to their chronological age (Figure 1)[12].

The dysfunctional immune system of ESRD patients has a substantial clinical impact on both the morbidity and mortality of ESRD patients. Patients are highly susceptible for infections[13,14], have an increased risk for virus-associated cancers[15], respond poorly to vaccination[16] and have an increased risk for atherosclerotic diseases[17,18].

In this review, the concept of uremia-associated age-related changes of T cells is highlighted focusing on the assessment of an immunological T-cell age, clinical implications and possible therapeutic options for ESRD patients.

CONCEPT OF T-CELL AGEING

With normal healthy ageing, the T-cell immune system ages as well[19]. Hematopoietic stem cells (HSCs), generated in the bone marrow, give rise to myeloid as well as lymphoid progenitor cells[20]. T cells are generated from the latter. With increasing age, HSCs are skewed towards myeloid-generating subsets at the expense of lymphoid-generating HSCs, resulting in a lower number of progenitor T cells. These progenitor T cells are further "educated" in the thymus in which naïve T cells will form specific receptors on their cell surface known as T-cell receptors (TCRs). With increasing age, the thymus involutes[21,22]. This process involves a decrease in tissue in combination with a loss of tissue organization with the net outcome that numbers of naïve T cells leaving the thymus, known as recent thymic emigrants (RTEs) are reduced. Involution of the thymus starts at birth and is accelerated during adolescence[23].

This explains the lymphopenic number in naive T cells with increasing age. Despite the fact that the naïve T-cell pool can also be maintained by homeostatic proliferation in which TCR triggering in combination with the cytokines Interleukin (IL)-7 and IL-15 expand T cells[24], the net effect is a diminished number of naïve T cells and the number of memory T cells in the peripheral blood of elderly individuals is preserved[25]. A relatively expanded number of naïve T cells by homeostatic proliferation results in a T-cell pool with a restricted TCR repertoire[24,26]. A diverse TCR repertoire is a necessary prerequisite for an adequate and effective T-cell response towards newly encountered antigens[27].

After encountering and activation by an antigen, a naïve T cell will proliferate and become a memory T cell. During physiological ageing the population of antigen-experienced memory T cells will increase and the majority of these cells will become highly differentiated. These cells are known to have an increase in pro-apoptotic markers[28] and loss in co-stimulatory molecule CD28[29,30]. CD28 plays an important role in the activation of T cells and a loss of CD28 can result in insufficient activation, shorter replicative lifespan and a higher toxicity[29]. Furthermore, highly differentiated cells are known to have a reduction in their telomere length[31].

A telomere is a region of repetitive nucleotides which is located at the end of each chromosome and prevents chromosomal instability. Loss of telomere length has been linked to an increased risk for tumor development and to T-cell ageing[32,33].

ASSESSING AN IMMUNOLOGICAL T-CELL AGE

A global assessment of the immunological age of the T-cell system can be performed by the analysis of three ageing parameters. During the formation of the T-cell receptor (TCR) in the thymus, DNA sequences in the TCR loci are deleted and circularized into episomal DNA molecules, so called single joint TCR excision circles (TREC), a process known as TCR rearrangement[34]. This TREC remains in the newly formed naïve T cells leaving the thymus. Upon replication of these cells in the periphery, the TREC is only transferred to one daughter cell resulting in a reduction of TRECs in the naïve daughter T cells. With an increasing age, the number of RTEs containing a TREC declines log linearity due to a lower thymic output of RTEs and an increase in proliferation of naïve T cells. The TREC content can be determined using a quantitative polymerase chain reaction (qPCR) method normalized to the single-copy albumin gene[34,35]. Next to the TREC content, these RTEs can be detected by measuring the expression of CD31 within the naïve T-cell pool[36,37]. In addition to the thymic output of T cells, the diversity of the TCR repertoire can be analyzed by sequencing in order to determine the loss of TCR specificities within the T-cell population and to assess the percentage of oligoclonal T cells[27,38]. Recently, a novel TREC assay in which the TCR diversity was combined with the TREC content to get quantitative insight into intra-thymic and post-thymic proliferative capacity of T cells and its alterations upon ageing[39].

As a second parameter for the assessment of an immunological T-cell age, the T-cell telomere length can be determined as a measurement for the proliferative history of a T-cell population[40]. A decline in telomere length is highly associated with an increased proliferative history. A commonly used method to assess a relative telomere length (RTL) is the fluorescent *in situ* hybridization (FISH) method[41,42]. During this procedure a labeled

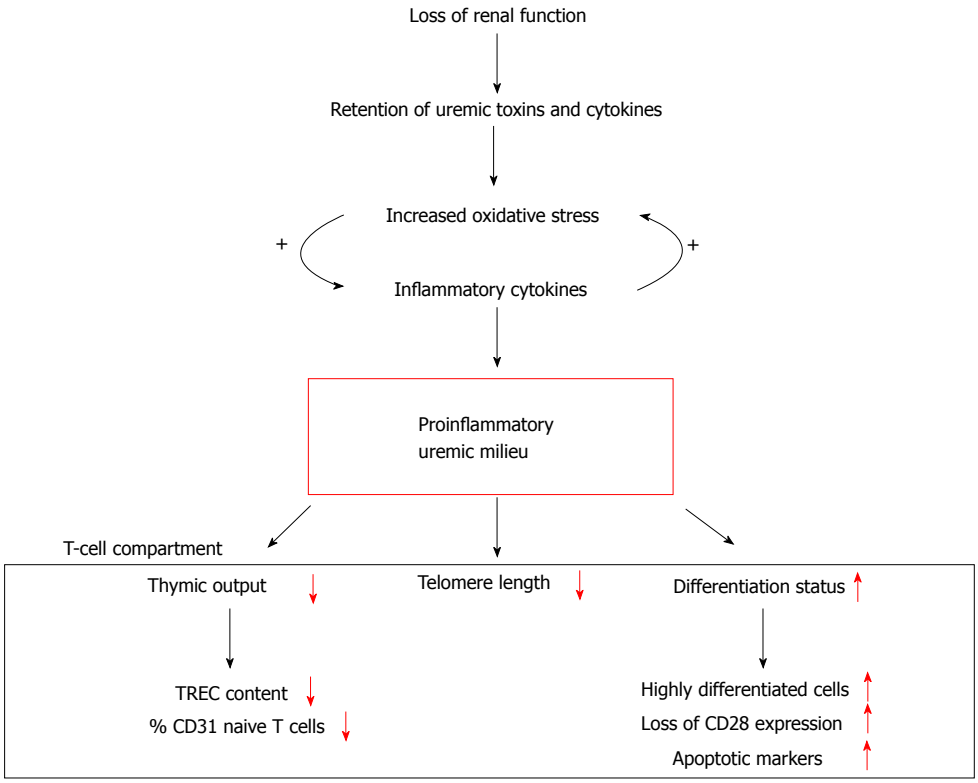

Figure 1 Schematic overview of the effects on the T-cell compartment caused by the uremia-induced pro-inflammatory milieu in end-stage renal disease patients. Loss in renal function creates a pro-inflammatory milieu by the retention of uremic toxins and cytokines which increases oxidative stress and the production of inflammatory cytokines. This pro-inflammatory uremic milieu is associated with premature T-cell ageing, which results in defective T-cell immunity. End-stage renal disease (ESRD) patients have a lower thymic output of naïve T cells which can be measured by the TCR excision circles (TREC) content and the percentage of CD31-expressing naïve T cells. Furthermore, ESRD patients have an expanded population of highly differentiated T cells with a loss in CD28 expression and an increase in apoptotic markers. Moreover, these expanded T cells have a high proliferative history causing a decline in telomere length which can be measured by the relative telomere length analysis.

peptide nucleic acid (PNA) probe binds to the telomere repeats which can be read-out by fluorescent microscopy or by fluorescence measurements using a flow cytometry (flow FISH). The RTL can be calculated by relating the intensity of the bound PNA probe to that of a T-cell lymphoblastic leukemia (1301 CCRF-CEM) cell-line, known for its long telomeres, as an internal control[41]. Inclusion of antibodies in this method makes it possible to analyze the telomere length in different T-cell populations (*i.e.,* $CD4^+$ and $CD8^+$ T cells)[2,41]. A limitation of this assay is the temperature (82 ℃) which is required for DNA annealing which makes the use of stable fluorochromes necessary[41,42]. Quantum dots (nanoparticles) were found to be highly fluorescent, bind to antibodies and have much better temperature stability. Quantum dots conjugated with antibodies directed to T-cell antigens were found to retain most of their fluorescence following the annealing step. The use of quantum dots can be a solution for the limitations in antibody use in the flow-FISH procedure and allows to assess a telomere length in different T-cell subsets within one assay[42].

In addition to the telomere length, the activity of the telomerase can be measured. Telomerase is responsible for maintaining telomere length and the cellular replicative potential and an impaired activity of telomerase results attrition of telomeres[19]. Measuring the activity of telomerase gives additional information on the telomere shortening. This assay is based on the capacity of a test sample to amplify a telomere template[43].

The differentiation status of the T-cell compartment can be used as a third parameter to assess an immunological age. The increase in highly differentiated memory cells with increasing age can be determined by analysis of the phenotype of circulating T-cells using multicolor flowcytometry. Based on the expression of the chemokine (C-C motif) receptor 7 (CCR7), enabling cells to migrate to secondary lymphoid organs, and CD45RO, an isoform of the leukocyte common antigen expressed on memory T cells, a distinction within the memory T-cell compartment can be made. The different memory T cell subsets include Central Memory (CM) ($CCR7^+$ and $CD45RO^+$), able to home to secondary lymph nodes and producing mainly IL-2 which is necessary for the proliferation of T cells, Effector Memory (EM) ($CCR7^-$ and $CD45RO^+$), able to migrate to peripheral tissues exerting direct effector functions and terminally differentiated effector memory $CD45RA^+$ (EMRA) ($CCR7^-$ and $CD45RO^-$), which exert cytotoxic activities and are highly susceptibility to apoptosis[44]. Moreover, these terminally differentiated cells often lose the expression CD28 which makes them less dependent on co-stimulation to become activated[45]. In addition, CD57 can be measured

as a marker for highly differentiated memory T cells[12,46]. CD95 (FAS) and CD279 (known as programmed death receptor-1 (PD-1)) are both commonly used as pro-apoptotic markers[12,28,47].

AGED T-CELL SYSTEM IN ESRD PATIENTS

Based on the analyses of the T-cell ageing parameters, *i.e.*, assessment of TREC- content, relative telomere length and differentiation status we showed that the immunological age of ESRD patients is advanced by 20 years compared to their calendar age[12]. As compared to an age-matched healthy control, ESRD patients had a lower thymic output of naïve T cells, a decline in the T-cell telomere length and an increase in the differentiation status towards the terminally differentiated memory phenotype with a large number of CD28-negative (or CD28null) T cells (Figure 1)[12]. Progressive loss of renal function was highly correlated with a lack of IL-7, a loss of naïve T cells and an increase in terminally differentiated $CD8^+$ T cells[48]. The effects of renal replacement therapy (RRT) on the T-cell ageing parameters seemed to be small and were limited to the $CD8^+$ T-cell compartment of young ESRD patients[2]. The type of RRT did not influence the ageing parameters since both hemodialysis (HD) and peritoneal dialysis (PD) patients showed signs of an aged T-cell compartment[2]. Moreover, the duration of dialysis did not seem to influence the ageing parameters[49]. Furthermore, the type of underlying kidney disease was not related to any parameter of immunological ageing[2] indicating that the loss of renal function is the dominant factor for a decreased thymic output of naïve T cells and increased differentiation/proliferation of memory T cells.

Cytomegalovirus (CMV) is known to affect the T-cell compartment which closely resembles ageing[46,50-52]. Infection with the virus results in chronic latency and the effects of CMV on the T-cell compartment are relevant, since approximately 70% of the ESRD patients is infected with CMV[50]. In these patients, CMV was associated with an increased number of highly differentiated $CD4^+$ and $CD8^+$ T cells and a relatively small decline in $CD8^+$ T-cell telomere length[46,50,53]. The effects were restricted to the memory T-cell compartment since the thymic output of T cells was not affected. Therefore we concluded that CMV only affects the differentiation status of circulating T cells[46,50,53].

CLINICAL IMPLICATIONS OF AN AGED T-CELL COMPARTMENT

The uremia-associated prematurely aged T-cell immune system has a substantial clinical impact leading to an increased morbidity and mortality. ESRD patients are highly susceptible for infections which might further contribute to the pro-inflammatory milieu. For instance periodontitis, which is common in patients with chronic kidney disease (CKD), often leads to inflammation[54].

T cells of ESRD patients have an impaired production of IL-2 and the inadequate T-cell proliferative capacity results insufficient T-cell responses[55-57]. This in combination with low numbers of T cells results into inadequate T-cell responses directed to viruses and a decreased tumor surveillance which significantly increases the risk for virus-associated tumors[15,58]. Next to IL-2, in hemodialysis (HD) patients it was found that activated T cells have impaired responses to tumor necrosis factor (TNF)-α, implying a state of tachyphylaxis[59].

Following vaccination against hepatitis B, the formation of antigen-specific $CD4^+$ EM T cells is severely impaired in ESRD patients[56]. The poor development of IL-2 producing $CD4^+$ EM T cells in patients with ESRD was strongly associated with a low generation of antibodies towards hepatitis B antigens[56]. The inability to maintain protective antibody titers after T-cell dependent vaccinations[60,61] or after a natural infection[62,63] might be caused by a loss of antigen-specific T cells as a result of their increased susceptibility for apoptosis[12,47].

Furthermore, the loss in TCR diversity of naïve T cells due to a lower number of RTEs but an increase in proliferated naïve T cells is linked to a decreased efficiency of vaccination but also to an increased susceptibility for infections and cancers[26,64].

$CD4^+$ T cells lacking CD28 expression, are found to be highly cytotoxic as they produce large amounts of interferon (IFN)-γ and TNF-α and release granzyme-B and perforin upon activation. In several studies[17,65] it is shown that these cytotoxic cells are present in unstable atherosclerotic plaques and are associated with an increased risk for recurrence of both acute coronary events and ischemic stroke resulting in a higher mortality rate[66]. As confirmed in ESRD patients, high numbers $CD4^+$CD28null T cells is strongly associated with a history of cardiovascular diseases[17,18,65,67].

$CD8^+$CD28null T cells contain a subpopulation of cells possessing immunosuppressive capacities[68,69] and has therefore been linked to a decreased vaccination responsiveness of healthy individuals[70]. These immunosuppressive capacities also suggest that these cells could be important in preventing allograft rejection after kidney transplantation (KTx). Indeed, we recently demonstrated that patients with an expanded population of highly differentiated (EMRA) $CD8^+$CD28null T cells had a lower risk for allograft rejection after KTx[71]. Another explanations might be that $CD8^+$CD28null T cells represents clonal expansions of particular antigen-specific $CD8^+$ T cells that compete for immunologic space which is associated with reduction of T-cell diversity[72]. This might affect the diversity of alloreactive T-cells as well. Next to these highly differentiated $CD8^+$ T cells in KTx recipients, a high proportion of highly differentiated $CD4^+$ T cells was also linked to a lower risk for allograft rejection[73].

PREMATURE T-CELL AGEING AND KIDNEY TRANSPLANTATION

After KTx, the levels of pro-inflammatory proteins and oxidative stress decrease rapidly to levels that are comparable to healthy individuals[74]. Despite this, the uremia-associated prematurely aged T-cell immune system existed after KTx. (Meijers et al, 2014 submitted)

Immunosuppressive treatment affected the number of highly differentiated cells directly post-KTx. However after tapering the immunosuppressive medication, these highly differentiated T-cell numbers were restored to pre-KTx values. Furthermore, the telomere length of the T-cell compartment did not change and thymic function was not improved the first year post-KTx (Meijers *et al* 2014 submitted). Even after T-cell depleting immunosuppressive therapy [*i.e.*, rabbit antithymocyte globulin (rATG)] T cells are repopulating by homeostatic proliferation instead of a higher thymic output of naïve T cells[75,76]. Therefore, the uremia-associated immunological ageing seems stably imprinted in the T-cell system and not reversible by KTx.

Normal ageing is associated with, epigenetic changes in HSCs resulting in a shift in the balance towards myeloid precursors at the expense of the lymphoid ones[77,78]. Healthy ageing results in genetic alterations affecting T cells at developmental stages leading to phenotypic as well as functional changes[79]. In ESRD patients, uremia is able to cause epigenetic changes[80]. Young *et al*[81] 2012 found that methylation of the KLOTHO gene is initiated by oxidative stress in ESRD patients. KLOTHO deficient mice created a syndrome that resembles human ageing[82]. Although KTx reverses the uremic proinflammatory environment[74] it is unable to induce changes at the epigenetic level. The persistence of the aged T-cell phenotype post-KTx has several clinical implications as it may increase the risk for infections, malignancies and cardiovascular diseases in KTx recipients. T-cell lymphopenia has been associated with a high risk for infections and malignancies post-KTx[83,84].

Due to ageing of the T-cell compartment, elderly patients are more vulnerable for drugs toxicity, infections and malignancies caused by over-immunosuppression. In these patients, the incidence of virus-associated cancers is even higher post-KTx as it is pre-KTx[58,85]. Over-immunosuppression might be prevented after mapping the T-cell immune system of the transplant recipient[73,86] as T cells are the main target of immunosuppressive medication[11]. A study of Ducloux *et al*[87] in 2010 showed that prolonged $CD4^+$ T-cell lymphopenia after severe T-cell depletion by rATG is associated with an increased risk for infections and mortality post-KTx. High TREC values implying for a "younger" T-cell compartment pre-KTx, is associated with a better reconstitution of T-cell numbers after rATG and lower risk for infections and cancer post-KTx[87].

THERAPEUTIC OPTIONS TO REVERSE T-CELL AGEING

As mentioned earlier, RRT did not reduce T-cell ageing since no major differences between patients on dialysis and predialysis patients with respect to the T-cell ageing parameters were observed[2]. Adequately targeting the presence of the pro-inflammatory environment in ESRD patients by KTx[74] did not successfully reverse the aged T-cell immune system.

Another method to reduce the level of oxidative stress and inflammation in ESRD patients is targeting the transcription factor Nuclear factor-erythroid-2-related factor 2 (Nrf2) which is an important regulator of genes encoding antioxidant and detoxifying molecules[88]. Treatment with bardoxolone methyl, which is an activator of Nrf2 may attenuate T-cell ageing in ESRD patients[88]. However, treatment is restricted due to the increased risk of cardiovascular diseases after treatment with bardoxolone[89].

Another therapeutic option that might be able to improve T-cell function in ESRD patient is treatment with IL-7, a key cytokine for homeostatic proliferation of naïve T cells, that is reduced in patients causing a depletion of naïve T-cell pool[48,90]. The first human studies, in which IL-7 was administered, are promising since an increased naïve T-cell pool with a broader TCR repertoire diversity was found[38,91]. At present, IL-7 administration has not been tested in patients with ESRD.

CONCLUSION

Progressive loss of renal function creates a pro-inflammatory milieu which is highly associated with a dysfunctional immune system. This is a logical explanation for the increased vulnerability for infections, poor vaccination responses, high risk for malignancies and high risk for atherosclerotic diseases. Analysis of the T-cell system showed that ESRD patients have a prematurely aged T-cell compartment resulting in an impaired function. ESRD patients have a lower thymic output of naïve T cells, T cells have shorter telomeres and the T-cell compartment is shifted towards more differentiated T cells.

Therapeutic options to minimize morbidity and decrease mortality by improving or even fully reversing the aged T-cell phenotype are warranted. Although improvement of renal function by adequate renal replacement therapy in the form of KTx, which drastically decreases the uremia-associated pro-inflammatory milieu, the prematurely aged T-cell phenotype appeared to be irreversible. Therefore the aged T-cell immune system remains an important determinant of the dysfunctional immune system post-KTx. More research is necessary to fully understand the uremia-associated premature T-cell ageing phenomenon, also at earlier developmental stages of T-cells, to be able to successfully intervene and increase the life-span of ESRD patients.

Until today, all KTx recipients receive the same standard immunosuppressive therapy to prevent allograft rejection. Recently it was shown that the effect of calcineurin-inhibitors and rapamycin on peripheral blood mononuclear cells (PBMCs) was different between young and elderly individuals[92]. Assessing an immunological T-cell age using T-cell ageing parameters as described in this review, may guide clinicians in decision-making with respect to transplanting an ESRD patient or not, adjusting immunosuppression following KTx to minimize its long-term-associated adverse events.

REFERENCES

1 **Betjes MG**, Meijers RW, Litjens NH. Loss of renal function causes premature aging of the immune system. *Blood Purif* 2013; **36**: 173-178 [PMID: 24496187 DOI: 10.1159/000356084]
2 **Meijers RW**, Litjens NH, de Wit EA, Langerak AW, van der Spek A, Baan CC, Weimar W, Betjes MG. Uremia causes premature ageing of the T cell compartment in end-stage renal disease patients. *Immun Ageing* 2012; **9**: 19 [PMID: 22971545 DOI: 10.1186/1742-4933-9-19]
3 **Betjes MG**. Immune cell dysfunction and inflammation in end-stage renal disease. *Nat Rev Nephrol* 2013; **9**: 255-265 [PMID: 23507826 DOI: 10.1038/nrneph.2013.44]
4 **Vaziri ND**. Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin Nephrol* 2004; **24**: 469-473 [PMID: 15490413]
5 **Pecoits-Filho R**, Heimbürger O, Bárány P, Suliman M, Fehrman-Ekholm I, Lindholm B, Stenvinkel P. Associations between circulating inflammatory markers and residual renal function in CRF patients. *Am J Kidney Dis* 2003; **41**: 1212-1218 [PMID: 12776273 DOI: 10.1016/S0272-6386(03)00353-6]
6 **Ando M**, Lundkvist I, Bergström J, Lindholm B. Enhanced scavenger receptor expression in monocyte-macrophages in dialysis patients. *Kidney Int* 1996; **49**: 773-780 [PMID: 8648919 DOI: 10.1038/ki.1996.107]
7 **Lim WH**, Kireta S, Leedham E, Russ GR, Coates PT. Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. *Kidney Int* 2007; **72**: 1138-1148 [PMID: 17728708]
8 **Verkade MA**, van Druningen CJ, Vaessen LM, Hesselink DA, Weimar W, Betjes MG. Functional impairment of monocyte-derived dendritic cells in patients with severe chronic kidney disease. *Nephrol Dial Transplant* 2007; **22**: 128-138 [PMID: 17005525]
9 **Fernández-Fresnedo G**, Ramos MA, González-Pardo MC, de Francisco AL, López-Hoyos M, Arias M. B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. *Nephrol Dial Transplant* 2000; **15**: 502-510 [PMID: 10727545 DOI: 10.1093/ndt/15.4.502]
10 **Pahl MV**, Gollapudi S, Sepassi L, Gollapudi P, Elahimehr R, Vaziri ND. Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. *Nephrol Dial Transplant* 2010; **25**: 205-212 [PMID: 19684120 DOI: 10.1093/ndt/gfp397]
11 **Halloran PF**. Immunosuppressive drugs for kidney transplantation. *N Engl J Med* 2004; **351**: 2715-2729 [PMID: 15616206 DOI: 10.1056/NEJMra033540]
12 **Betjes MG**, Langerak AW, van der Spek A, de Wit EA, Litjens NH. Premature aging of circulating T cells in patients with end-stage renal disease. *Kidney Int* 2011; **80**: 208-217 [PMID: 21525849 DOI: 10.1038/ki.2011.110]
13 **Hoen B**, Kessler M, Hestin D, Mayeux D. Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey. *Nephrol Dial Transplant* 1995; **10**: 377-381 [PMID: 7792034]
14 **Sarnak MJ**, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int* 2000; **58**: 1758-1764 [PMID: 11012910 DOI: 10.1111/j.1523-1755.2000.00337.x]
15 **Stewart JH**, Vajdic CM, van Leeuwen MT, Amin J, Webster AC, Chapman JR, McDonald SP, Grulich AE, McCredie MR. The pattern of excess cancer in dialysis and transplantation. *Nephrol Dial Transplant* 2009; **24**: 3225-3231 [PMID: 19589786 DOI: 10.1093/ndt/gfp331]
16 **Verkade MA**, van de Wetering J, Klepper M, Vaessen LM, Weimar W, Betjes MG. Peripheral blood dendritic cells and GM-CSF as an adjuvant for hepatitis B vaccination in hemodialysis patients. *Kidney Int* 2004; **66**: 614-621 [PMID: 15253714 DOI: 10.1111/j.1523-1755.2004.00781.x]
17 **Betjes MG**, de Wit EE, Weimar W, Litjens NH. Circulating pro-inflammatory CD4posCD28null T cells are independently associated with cardiovascular disease in ESRD patients. *Nephrol Dial Transplant* 2010; **25**: 3640-3646 [PMID: 20400452 DOI: 10.1155/2013/841430]
18 **Betjes MG**, Meijers RW, de Wit LE, Litjens NH. A killer on the road: circulating CD4(+)CD28null T cells as cardiovascular risk factor in ESRD patients. *J Nephrol* 2012; **25**: 183-191 [PMID: 22135034 DOI: 10.5301/jn.5000057]
19 **Chou JP**, Effros RB. T cell replicative senescence in human aging. *Curr Pharm Des* 2013; **19**: 1680-1698 [PMID: 23061726 DOI: 10.2174/1381612811319090016]
20 **Kondo M**, Scherer DC, King AG, Manz MG, Weissman IL. Lymphocyte development from hematopoietic stem cells. *Curr Opin Genet Dev* 2001; **11**: 520-526 [PMID: 11532393 DOI: 10.1016/S0959-437X(00)00227-6]
21 **Palmer DB**. The effect of age on thymic function. *Front Immunol* 2013; **4**: 316 [PMID: 24109481 DOI: 10.3389/fimmu.2013.00316]
22 **Linton PJ**, Dorshkind K. Age-related changes in lymphocyte development and function. *Nat Immunol* 2004; **5**: 133-139 [PMID: 14749784 DOI: 10.1038/ni1033]
23 **Naylor K**, Li G, Vallejo AN, Lee WW, Koetz K, Bryl E, Witkowski J, Fulbright J, Weyand CM, Goronzy JJ. The influence of age on T cell generation and TCR diversity. *J Immunol* 2005; **174**: 7446-7452 [PMID: 15905594 DOI: 10.4049/jimmunol.174.11.7446]
24 **Williams KM**, Hakim FT, Gress RE. T cell immune reconstitution following lymphodepletion. *Semin Immunol* 2007; **19**: 318-330 [PMID: 18023361 DOI: 10.1016/j.smim.2007.10.004]
25 **Czesnikiewicz-Guzik M**, Lee WW, Cui D, Hiruma Y, Lamar DL, Yang ZZ, Ouslander JG, Weyand CM, Goronzy JJ. T cell subset-specific susceptibility to aging. *Clin Immunol* 2008; **127**: 107-118 [PMID: 18222733 DOI: 10.1016/j.clim.2007.12.002]
26 **Kohler S**, Wagner U, Pierer M, Kimmig S, Oppmann B, Möwes B, Jülke K, Romagnani C, Thiel A. Post-thymic in vivo proliferation of naive CD4+ T cells constrains the TCR repertoire in healthy human adults. *Eur J Immunol* 2005; **35**: 1987-1994 [PMID: 15909312 DOI: 10.1002/eji.200526181]
27 **Britanova OV**, Putintseva EV, Shugay M, Merzlyak EM, Turchaninova MA, Staroverov DB, Bolotin DA, Lukyanov S, Bogdanova EA, Mamedov IZ, Lebedev YB, Chudakov DM. Age-related decrease in TCR repertoire diversity measured with deep and normalized sequence profiling. *J Immunol* 2014; **192**: 2689-2698 [PMID: 24510963 DOI: 10.4049/jimmunol.1302064]
28 **Gupta S**, Gollapudi S. CD95-mediated apoptosis in naïve, central and effector memory subsets of CD4+ and CD8+ T cells in aged humans. *Exp Gerontol* 2008; **43**: 266-274 [PMID: 18215485 DOI: 10.1016/j.exger.2007.12.006]
29 **Weng NP**, Akbar AN, Goronzy J. CD28(-) T cells: their role in the age-associated decline of immune function. *Trends Immunol* 2009; **30**: 306-312 [PMID: 19540809 DOI: 10.1016/j.it.2009.03.013]
30 **Wikby A**, Maxson P, Olsson J, Johansson B, Ferguson FG.

Changes in CD8 and CD4 lymphocyte subsets, T cell proliferation responses and non-survival in the very old: the Swedish longitudinal OCTO-immune study. *Mech Ageing Dev* 1998; **102**: 187-198 [PMID: 9720651 DOI: 10.1016/S0047-6374(97)00151-6]

31 **Monteiro J**, Batliwalla F, Ostrer H, Gregersen PK. Shortened telomeres in clonally expanded CD28-CD8+ T cells imply a replicative history that is distinct from their CD28+CD8+ counterparts. *J Immunol* 1996; **156**: 3587-3590 [PMID: 8621891]

32 **Verdun RE**, Karlseder J. Replication and protection of telomeres. *Nature* 2007; **447**: 924-931 [PMID: 17581575 DOI: 10.1038/nature05976]

33 **Blackburn EH**. Switching and signaling at the telomere. *Cell* 2001; **106**: 661-673 [PMID: 11572773 DOI: 10.1016/S0092-8674(01)00492-5]

34 **Zubakov D**, Liu F, van Zelm MC, Vermeulen J, Oostra BA, van Duijn CM, Driessen GJ, van Dongen JJ, Kayser M, Langerak AW. Estimating human age from T-cell DNA rearrangements. *Curr Biol* 2010; **20**: R970-R971 [PMID: 21093786 DOI: 10.1016/j.cub.2010.10.022]

35 **Douek DC**, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, Picker LJ, Koup RA. Changes in thymic function with age and during the treatment of HIV infection. *Nature* 1998; **396**: 690-695 [PMID: 9872319 DOI: 10.1038/25374]

36 **Kimmig S**, Przybylski GK, Schmidt CA, Laurisch K, Möwes B, Radbruch A, Thiel A. Two subsets of naive T helper cells with distinct T cell receptor excision circle content in human adult peripheral blood. *J Exp Med* 2002; **195**: 789-794 [PMID: 11901204 DOI: 10.1084/jem.20011756]

37 **Kohler S**, Thiel A. Life after the thymus: CD31+ and CD31- human naive CD4+ T-cell subsets. *Blood* 2009; **113**: 769-774 [PMID: 18583570 DOI: 10.1182/blood-2008-02-139154]

38 **Qi Q**, Zhang DW, Weyand CM, Goronzy JJ. Mechanisms shaping the naïve T cell repertoire in the elderly - thymic involution or peripheral homeostatic proliferation? *Exp Gerontol* 2014; **54**: 71-74 [PMID: 24440389 DOI: 10.1016/j.exger.2014.01.005]

39 **van der Weerd K**, Dik WA, Schrijver B, Bogers AJ, Maat AP, van Nederveen FH, van Hagen PM, van Dongen JJ, Langerak AW, Staal FJ. Combined TCRG and TCRA TREC analysis reveals increased peripheral T-lymphocyte but constant intra-thymic proliferative history upon ageing. *Mol Immunol* 2013; **53**: 302-312 [PMID: 23000520 DOI: 10.1016/j.molimm.2012.08.019]

40 **Weng NP**, Levine BL, June CH, Hodes RJ. Human naive and memory T lymphocytes differ in telomeric length and replicative potential. *Proc Natl Acad Sci USA* 1995; **92**: 11091-11094 [PMID: 7479943 DOI: 10.1073/pnas.92.24.11091]

41 **Baerlocher GM**, Vulto I, de Jong G, Lansdorp PM. Flow cytometry and FISH to measure the average length of telomeres (flow FISH). *Nat Protoc* 2006; **1**: 2365-2376 [PMID: 17406480 DOI: 10.1038/nprot.2006.263]

42 **Kapoor V**, Hakim FT, Rehman N, Gress RE, Telford WG. Quantum dots thermal stability improves simultaneous phenotype-specific telomere length measurement by FISH-flow cytometry. *J Immunol Methods* 2009; **344**: 6-14 [PMID: 19268672 DOI: 10.1016/j.jim.2009.02.004]

43 **Fajkus J**. Detection of telomerase activity by the TRAP assay and its variants and alternatives. *Clin Chim Acta* 2006; **371**: 25-31 [PMID: 16616059 DOI: 10.1016/j.cca.2006.02.039]

44 **Sallusto F**, Lenig D, Förster R, Lipp M, Lanzavecchia A. Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. *Nature* 1999; **401**: 708-712 [PMID: 10537110 DOI: 10.1038/44385]

45 **Dubey C**, Croft M, Swain SL. Naive and effector CD4 T cells differ in their requirements for T cell receptor versus costimulatory signals. *J Immunol* 1996; **157**: 3280-3289 [PMID: 8871622]

46 **Meijers RW**, Litjens NH, de Wit EA, Langerak AW, van der Spek A, Baan CC, Weimar W, Betjes MG. Cytomegalovirus contributes partly to uraemia-associated premature immunological ageing of the T cell compartment. *Clin Exp Immunol* 2013; **174**: 424-432 [PMID: 23962178 DOI: 10.1111/cei.12188]

47 **Meier P**, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. *J Am Soc Nephrol* 2002; **13**: 204-212 [PMID: 11752039]

48 **Litjens NH**, van Druningen CJ, Betjes MG. Progressive loss of renal function is associated with activation and depletion of naive T lymphocytes. *Clin Immunol* 2006; **118**: 83-91 [PMID: 16257266 DOI: 10.1016/j.clim.2005.09.007]

49 **Boxall MC**, Goodship TH, Brown AL, Ward MC, von Zglinicki T. Telomere shortening and haemodialysis. *Blood Purif* 2006; **24**: 185-189 [PMID: 16373996 DOI: 10.1159/000090517]

50 **Litjens NH**, de Wit EA, Betjes MG. Differential effects of age, cytomegalovirus-seropositivity and end-stage renal disease (ESRD) on circulating T lymphocyte subsets. *Immun Ageing* 2011; **8**: 2 [PMID: 21214947 DOI: 10.1186/1742-4933-8-2]

51 **Derhovanessian E**, Larbi A, Pawelec G. Biomarkers of human immunosenescence: impact of Cytomegalovirus infection. *Curr Opin Immunol* 2009; **21**: 440-445 [PMID: 19535233 DOI: 10.1016/j.coi.2009.05.012]

52 **Khan N**, Shariff N, Cobbold M, Bruton R, Ainsworth JA, Sinclair AJ, Nayak L, Moss PA. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. *J Immunol* 2002; **169**: 1984-1992 [PMID: 12165524 DOI: 10.4049/jimmunol.169.4.1984]

53 **Betjes MG**, Huisman M, Weimar W, Litjens NH. Expansion of cytolytic CD4+CD28- T cells in end-stage renal disease. *Kidney Int* 2008; **74**: 760-767 [PMID: 18615000 DOI: 10.1038/ki.2008.301]

54 **Ismail G**, Dumitriu HT, Dumitriu AS, Ismail FB. Periodontal disease: a covert source of inflammation in chronic kidney disease patients. *Int J Nephrol* 2013; **2013**: 515796 [PMID: 23840952 DOI: 10.1155/2013/515796]

55 **Litjens NH**, Huisman M, Hijdra D, Lambrecht BM, Stittelaar KJ, Betjes MG. IL-2 producing memory CD4+ T lymphocytes are closely associated with the generation of IgG-secreting plasma cells. *J Immunol* 2008; **181**: 3665-3673 [PMID: 18714042 DOI: 10.4049/jimmunol.181.5.3665]

56 **Litjens NH**, Huisman M, van den Dorpel M, Betjes MG. Impaired immune responses and antigen-specific memory CD4+ T cells in hemodialysis patients. *J Am Soc Nephrol* 2008; **19**: 1483-1490 [PMID: 18480314 DOI: 10.1681/ASN.2007090971]

57 **Meier P**, Dayer E, Ronco P, Blanc E. Dysregulation of IL-2/IL-2R system alters proliferation of early activated CD4+ T cell subset in patients with end-stage renal failure. *Clin Nephrol* 2005; **63**: 8-21 [PMID: 15678692 DOI: 10.5414/CNP63008]

58 **Vajdic CM**, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor JM, Grulich AE. Cancer incidence before and after kidney transplantation. *JAMA* 2006; **296**: 2823-2831 [PMID: 17179459 DOI: 10.1001/jama.296.23.2823]

59 **van Riemsdijk IC**, Baan CC, Loonen EH, Knoop CJ, Navarro Betonico G, Niesters HG, Zietse R, Weimar W. T cells activate the tumor necrosis factor-alpha system during hemodialysis, resulting in tachyphylaxis. *Kidney Int* 2001; **59**: 883-892 [PMID: 11231343 DOI: 10.1046/j.1523-1755.2001.00571.x]

60 **Girndt M**, Pietsch M, Köhler H. Tetanus immunization and its association to hepatitis B vaccination in patients with chronic renal failure. *Am J Kidney Dis* 1995; **26**: 454-460 [PMID: 7645553 DOI: 10.1016/0272-6386(95)90491-3]

61 **Krüger S**, Müller-Steinhardt M, Kirchner H, Kreft B. A 5-year follow-up on antibody response after diphtheria and tetanus vaccination in hemodialysis patients. *Am J Kidney Dis* 2001; **38**: 1264-1270 [PMID: 11728959 DOI: 10.1053/

ajkd.2001.29223]
62 **Charest AF**, Grand'Maison A, McDougall J, Goldstein MB. Evolution of naturally acquired hepatitis B immunity in the long-term hemodialysis population. *Am J Kidney Dis* 2003; **42**: 1193-1199 [PMID: 14655191 DOI: 10.1053/j.ajkd.2003.08.020]
63 **Tsouchnikas I**, Dounousi E, Xanthopoulou K, Papakonstantinou S, Thomoglou V, Tsakiris D. Loss of hepatitis B immunity in hemodialysis patients acquired either naturally or after vaccination. *Clin Nephrol* 2007; **68**: 228-234 [PMID: 17969490 DOI: 10.5414/CNP68228]
64 **Cicin-Sain L**, Smyk-Pearson S, Currier N, Byrd L, Koudelka C, Robinson T, Swarbrick G, Tackitt S, Legasse A, Fischer M, Nikolich-Zugich D, Park B, Hobbs T, Doane CJ, Mori M, Axthelm MK, Lewinsohn DA, Nikolich-Zugich J. Loss of naive T cells and repertoire constriction predict poor response to vaccination in old primates. *J Immunol* 2010; **184**: 6739-6745 [PMID: 20483749 DOI: 10.4049/jimmunol.0904193]
65 **Yadav AK**, Jha V. CD4+CD28null cells are expanded and exhibit a cytolytic profile in end-stage renal disease patients on peritoneal dialysis. *Nephrol Dial Transplant* 2011; **26**: 1689-1694 [PMID: 21382991 DOI: 10.1093/ndt/gfr010]
66 **Nadareishvili ZG**, Li H, Wright V, Maric D, Warach S, Hallenbeck JM, Dambrosia J, Barker JL, Baird AE. Elevated pro-inflammatory CD4+CD28- lymphocytes and stroke recurrence and death. *Neurology* 2004; **63**: 1446-1451 [PMID: 15505163 DOI: 10.1212/01.WNL.0000142260.61443.7C]
67 **Betjes MG**, Weimar W, Litjens NH. Circulating CD4(+)CD28null T Cells May Increase the Risk of an Atherosclerotic Vascular Event Shortly after Kidney Transplantation. *J Transplant* 2013; **2013**: 841430 [PMID: 24288592]
68 **Filaci G**, Fravega M, Negrini S, Procopio F, Fenoglio D, Rizzi M, Brenci S, Contini P, Olive D, Ghio M, Setti M, Accolla RS, Puppo F, Indiveri F. Nonantigen specific CD8+ T suppressor lymphocytes originate from CD8+CD28- T cells and inhibit both T-cell proliferation and CTL function. *Hum Immunol* 2004; **65**: 142-156 [PMID: 14969769 DOI: 10.1016/j.humimm.2003.12.001]
69 **Simone R**, Zicca A, Saverino D. The frequency of regulatory CD3+CD8+CD28- CD25+ T lymphocytes in human peripheral blood increases with age. *J Leukoc Biol* 2008; **84**: 1454-1461 [PMID: 18780874 DOI: 10.1189/jlb.0907627]
70 **Goronzy JJ**, Fulbright JW, Crowson CS, Poland GA, O'Fallon WM, Weyand CM. Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. *J Virol* 2001; **75**: 12182-12187 [PMID: 11711609 DOI: 10.1128/JVI.75.24.12182-12187.2001]
71 **Betjes MG**, Meijers RW, de Wit EA, Weimar W, Litjens NH. Terminally differentiated CD8+ Temra cells are associated with the risk for acute kidney allograft rejection. *Transplantation* 2012; **94**: 63-69 [PMID: 22691956 DOI: 10.1097/TP.0b013e31825306ff]
72 **Franceschi C**, Bonafè M, Valensin S. Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. *Vaccine* 2000; **18**: 1717-1720 [PMID: 10689155 DOI: 10.1016/S0264-410X(99)00513-7]
73 **Trzonkowski P**, Debska-Slizień A, Jankowska M, Wardowska A, Carvalho-Gaspar M, Hak Ł, Moszkowska G, Bzoma B, Mills N, Wood KJ, Myśliwska J, Rutkowski B. Immunosenescence increases the rate of acceptance of kidney allotransplants in elderly recipients through exhaustion of CD4+ T-cells. *Mech Ageing Dev* 2010; **131**: 96-104 [PMID: 20060852 DOI: 10.1016/j.mad.2009.12.006]
74 **Simmons EM**, Langone A, Sezer MT, Vella JP, Recupero P, Morrow JD, Ikizler TA, Himmelfarb J. Effect of renal transplantation on biomarkers of inflammation and oxidative stress in end-stage renal disease patients. *Transplantation* 2005; **79**: 914-919 [PMID: 15849543 DOI: 10.1097/01.TP.0000157773.96534.29]
75 **Bouvy AP**, Kho MM, Klepper M, Litjens NH, Betjes MG, Weimar W, Baan CC. Kinetics of homeostatic proliferation and thymopoiesis after rATG induction therapy in kidney transplant patients. *Transplantation* 2013; **96**: 904-913 [PMID: 23985721 DOI: 10.1097/TP.0b013e3182a203e4]
76 **Nickel P**, Kreutzer S, Bold G, Friebe A, Schmolke K, Meisel C, Jurgensen JS, Thiel A, Wernecke KD, Reinke P, Volk HD. CD31+ naïve Th cells are stable during six months following kidney transplantation: implications for post-transplant thymic function. *Am J Transplant* 2005; **5**: 1764-1771 [PMID: 15943637 DOI: 10.1111/j.1600-6143.2005.00924.x]
77 **Cho RH**, Sieburg HB, Muller-Sieburg CE. A new mechanism for the aging of hematopoietic stem cells: aging changes the clonal composition of the stem cell compartment but not individual stem cells. *Blood* 2008; **111**: 5553-5561 [PMID: 18413859 DOI: 10.1182/blood-2007-11-123547]
78 **Roeder I**, Horn K, Sieburg HB, Cho R, Muller-Sieburg C, Loeffler M. Characterization and quantification of clonal heterogeneity among hematopoietic stem cells: a model-based approach. *Blood* 2008; **112**: 4874-4883 [PMID: 18809760 DOI: 10.1182/blood-2008-05-155374]
79 **Chen G**, Lustig A, Weng NP. T cell aging: a review of the transcriptional changes determined from genome-wide analysis. *Front Immunol* 2013; **4**: 121 [PMID: 23730304 DOI: 10.3389/fimmu.2013.00121]
80 **Zawada AM**, Rogacev KS, Hummel B, Grün OS, Friedrich A, Rotter B, Winter P, Geisel J, Fliser D, Heine GH. SuperTAG methylation-specific digital karyotyping reveals uremia-induced epigenetic dysregulation of atherosclerosis-related genes. *Circ Cardiovasc Genet* 2012; **5**: 611-620 [PMID: 23074332 DOI: 0.1161/CIRCGENETICS.112.963207]
81 **Young GH**, Wu VC. KLOTHO methylation is linked to uremic toxins and chronic kidney disease. *Kidney Int* 2012; **81**: 611-612 [PMID: 22419041 DOI: 10.1038/ki.2011.461]
82 **Kuro-o M**, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997; **390**: 45-51 [PMID: 9363890 DOI: 10.1038/36285]
83 **Calarota SA**, Zelini P, De Silvestri A, Chiesa A, Comolli G, Sarchi E, Migotto C, Pellegrini C, Esposito P, Minoli L, Tinelli C, Marone P, Baldanti F. Kinetics of T-lymphocyte subsets and posttransplant opportunistic infections in heart and kidney transplant recipients. *Transplantation* 2012; **93**: 112-119 [PMID: 22134368 DOI: 10.1097/TP.0b013e318239e90c]
84 **Ducloux D**, Carron PL, Rebibou JM, Aubin F, Fournier V, Bresson-Vautrin C, Blanc D, Humbert P, Chalopin JM. CD4 lymphocytopenia as a risk factor for skin cancers in renal transplant recipients. *Transplantation* 1998; **65**: 1270-1272 [PMID: 9603180 DOI: 10.1097/00007890-199805150-00022]
85 **van de Wetering J**, Roodnat JI, Hemke AC, Hoitsma AJ, Weimar W. Patient survival after the diagnosis of cancer in renal transplant recipients: a nested case-control study. *Transplantation* 2010; **90**: 1542-1546 [PMID: 21076383 DOI: 10.1097/TP.0b013e3181ff1458]
86 **Bradley BA**. Rejection and recipient age. *Transpl Immunol* 2002; **10**: 125-132 [PMID: 12216942 DOI: 10.1016/S0966-3274(02)00058-8]
87 **Ducloux D**, Courivaud C, Bamoulid J, Vivet B, Chabroux A, Deschamps M, Rebibou JM, Ferrand C, Chalopin JM, Tiberghien P, Saas P. Prolonged CD4 T cell lymphopenia increases morbidity and mortality after renal transplantation. *J Am Soc Nephrol* 2010; **21**: 868-875 [PMID: 20203160 DOI: 10.1681/ASN.2009090976]
88 **Ruiz S**, Pergola PE, Zager RA, Vaziri ND. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. *Kidney Int* 2013; **83**: 1029-1041 [PMID: 23325084 DOI: 10.1038/ki.2012.439]
89 **Lambers Heerspink HJ**, Chertow GM, Akizawa T, Audhya P, Bakris GL, Goldsberry A, Krauth M, Linde P, McMurray JJ,

Meyer CJ, Parving HH, Remuzzi G, Christ-Schmidt H, Toto RD, Vaziri ND, Wanner C, Wittes J, Wrolstad D, de Zeeuw D. Baseline characteristics in the Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes mellitus: the Occurrence of renal eveNts (BEACON) trial. *Nephrol Dial Transplant* 2013; **28**: 2841-2850 [PMID: 24169612 DOI: 10.1093/ndt/gft445]

90 **Schluns KS**, Kieper WC, Jameson SC, Lefrançois L. Interleukin-7 mediates the homeostasis of naïve and memory CD8 T cells in vivo. *Nat Immunol* 2000; **1**: 426-432 [PMID: 11062503 DOI: 10.1038/80868]

91 **Sportès C**, Hakim FT, Memon SA, Zhang H, Chua KS, Brown MR, Fleisher TA, Krumlauf MC, Babb RR, Chow CK, Fry TJ, Engels J, Buffet R, Morre M, Amato RJ, Venzon DJ, Korngold R, Pecora A, Gress RE, Mackall CL. Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. *J Exp Med* 2008; **205**: 1701-1714 [PMID: 18573906 DOI: 10.1084/jem.20071681]

92 **Welzl K**, Kern G, Mayer G, Weinberger B, Säemann MD, Sturm G, Grubeck-Loebenstein B, Koppelstaetter C. Effect of different immunosuppressive drugs on immune cells from young and old healthy persons. *Gerontology* 2014; **60**: 229-238 [PMID: 24434865 DOI: 10.1159/000356020]

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