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Immunosenescence and organ transplantation

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Abstract

Increasing numbers of elderly transplant recipients and a growing demand for organs from older donors impose pressing challenges on transplantation medicine. Continuous and complex modifications of the immune system in parallel to aging have a major impact on transplant outcome and organ quality. Both, altered alloimmune responses and increased immunogenicity of organs present risk factors for inferior patient and graft survival. Moreover, a growing body of knowledge on age-dependent modifications of allorecognition and alloimmune responses may require age-adapted immunosuppression and organ allocation.

Here, we summarize relevant aspects of immunosenescence and their possible clinical impact on organ transplantation.

Keywords

immunosenescence; aging; innate immunity; adaptive immunity; organ transplantation; transplant outcome; immunosuppression; organ allocation

Introduction

Improved longevity linked to medical progress and demographic changes have dramatically increased the amount of older patients developing end-stage organ disease. While only 7.6 percent of new patients with end-stage renal disease (ESRD) were older than 75 years in 1980, more than 20% of patients with ESRD were ≥ 75 years in 2004 [1]. Consequently, the majority of those in need for organ transplantation are currently older than 50 years [2]. In an attempt to meet the rapidly increasing demand, organs from so-called expanded criteria donors (ECD) have been used more frequently. In fact, more than half of all currently transplanted kidneys are from donors >50 years [2]. Clearly, changing demographics and an increasing longevity are likely to contribute to a further increase of the elderly in need for medical care including organ transplantation.

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Immunosenescence can affect all immune compartments and does not necessarily represent a uniform compromise of immunological efficacy but rather individual shifts in function and regulation. Clinical implications of immunosenescence include increased risks of infections, malignancies, autoimmune disorders, atherosclerosis and neuro-degenerative changes. Consequences of immunosenescence have broad implications in organ transplantation and may require an adapted immunosuppression when treating older recipients or when utilizing organs from older donors.

Of note, age criteria are only inconsistently applied in studies on immunosenescence, thus contributing to conflicting data in aging research [3].

Clinical implications of advanced recipient age

Elderly individuals with end-stage renal disease undergoing transplantation have shown better long-term survival than matched controls staying on dialysis [4]. Improved life expectancies were observed although older recipients are more likely to receive older and functionally compromised organs [5]. At the same time it has to be noted that older recipients represent a highly selected patient population [4,6] Graft survival censored for death with a functioning graft improves with age. Of note, older recipients have an overall higher mortality [7,8] and almost 50% of graft losses in old recipients are related to death with a functioning graft [9]. Moreover, more than 50% of all mortalities in older recipients have been linked to cardiovascular disease, infections or malignancies – complications that are all exacerbated by immunosuppressive therapy and age [10].

Clinical trials have confirmed reduced rates of acute rejections in older recipients receiving corneal, kidney, cardiac, liver and lung transplantation [5,11–16]. In renal transplantation, <25% of graft failures in old recipients have been attributed to rejections compared with 50% in recipients <45 years [17]. Acute rejections occurring in older recipients seem more detrimental and have a more pronounced impact on patient and graft survival [18]. Both, organ quality and age may be of importance in this context as old recipients are more likely to receive organs from older donors [5].

Furthermore, recipient age has been identified as an independent risk factor for chronic allograft failure in clinical studies and experimental models [7,19,20]. Both, organ age and an increased susceptibility to calcineurin inhibitor (CNI) -related nephrotoxicity may be of importance in this context (Fig. 1).

Principles of immunosenescence and alloimmune responses

Hematopoietic stem cells

Cellular components of the immune system are mostly short-lived and require continuous replenishment. Hematopoietic stem cells (HSC) are long-lived and comprise only 0.01% of the bone marrow population. At any given cell division, HSC have the potential to give rise to all blood cell types of the myeloid and lymphoid lineages. Alternatively, they may self-renew to produce more HSCs. Despite their extensive proliferative and regenerative capacity, a growing body of evidence suggests that these cells show signs of aging with important functional implications [21,22] (Fig. 2).

Reconstitution potential

Both, clinical and experimental data support a measurable and successive functional decline of the reconstitution capacity of old purified HSCs [23–25].

An age-dependent accumulation of damaged genomic and mitochondrial DNA subsequent to oxidative stress might be the most important factor driving the functional decline [26,27]. Old HSCs seem to have compromised abilities to repair DNA damages, impacting cell cycle regulation. Of note, the cell-cycle inhibitor p16INK4a increases with age in HSCs [28].

Stem cell niches formed by stromal cells in the bone marrow maintain regulatory interactions with HSCs. Since stromal cells are exposed to comparable environmental damages and stress, a modified support provided by these niches might also be of relevance for the observed age-related changes [29].

Quantitative changes

The functional compromise of the immune response with aging is in part compensated by increased frequencies and an enhanced expansion of old HSCs [30,31]. Despite the prevailing view that the frequency of HSCs diminishes in parallel to a compromised cellularity in the bone marrow of the elderly [32], more recent data have suggested an increase in the frequency of human HSCs with aging [22,33].

Lineage potentials

Murine HSCs have shown changes in lineage potential with aging resulting in an attenuated lymphoid and preserved or even increased myeloid lineage output [34]. A more robust self-renewal potential [35] and a differential response to the aging cytokine milieu [36] have been proposed for the progressive predominance of myeloid-biased HSC clones. These changes are accompanied by the down-regulation of genes mediating lymphoid specification and function. At the same time, an up-regulation of genes involved in myeloid specification and function is observed [37]. Interestingly, pediatric leukemias tend to involve lymphoid lineages while leukemias in the adult population tend to involve myeloid leukemias [38,39].

Modifications of T cell compartments during immunosenescence

T cell generation: After entering the thymus, T-cell progenitors originating from the bone marrow interact with stromal cells, macrophages and dendritic cells to undergo a number of proliferative and differentiation events that lead to the emigration of mature and functional T cells into the peripheral T cell pool.

Clinically, thymic involution starts at the age of one year and advances rapidly with puberty [40]. Thymic involution has been shown to correlate with an enlargement of the perivascular space possibly as a consequence to the loss of thymocytes, thymic stroma and thymic epithelial space, all areas in which thymopoiesis takes place [41].

The aging thymus retains its capacity to produce naïve T cells despite a significant atrophy. More reliable measurements of changes in thymic output with the so called signal joint T cell receptor excision circle (sjTREC) assay have recently revealed that the output of T cells declines as a function of thymopoietic tissue [42].

Several hypotheses have been brought forward to explain thymic involution, including a decline in supply of bone marrow progenitors, alterations in the productive rearrangement of TCRs, loss of cells in the thymic microenvironment and alterations in circulating (GH, GnRH) or intrathymic (IL-7, neurotrophins, thymic hormones) hormones, cytokines, and growth factors [43]. The infiltrating adipose tissue replacing the thymus may also be a contributing factor, either directly or through the release of soluble factors [44].

T cell receptor repertoire: The loss in thymic output with age does not result in significant modifications of the total number of peripheral T cells [45]. Indeed, the total number of

peripheral T-cells seems to be regulated via a compensatory process of thymus-independent expansion of mature T cells following low-affinity interactions with self-peptide/MHC complexes [46,47]. Moreover, aging is linked to a significantly limited TCR repertoire with T-cell diversity dropping 1000-fold in individuals >70 years [48,49]. Changes in the TCR repertoire are also expected to impact mechanisms of allorecognition [50].

CD28^{-} T cells: CD28 is a co-stimulatory receptor that plays a pivotal role in antigen-dependent activation, proliferation and survival of T cells. By age 80, 10-15% of peripheral blood $CD4^{+}$ T cells and 50-60% of $CD8^{+}$ T cells lack the expression of CD28. In contrast, at birth, virtually all human T cells express CD28 [51]. As these cells are frequently expanding oligoclonally, their T cell receptors display reduced diversity [52]. Of note, $CD28^{-}$ T cells show an altered expression of additional co-stimulatory receptors [53] and a gain in cytolytic functions [54]. $CD28^{-}$ T cells also acquire expression of NK cell receptors such as killer immunoglobulin-like receptors (KIRs) [55] which fundamentally influences signal recognition as ligands for these receptors are not limited to APCs.

Loss of CD28 expression in T cells with age has been attributed to repeated antigenic stimulation, a process that can also be observed in-vitro [56]. $CD28^{-}$ T cells have shorter telomeres than their $CD28^{+}$ counterparts within the same clonal population and might have already reached their limit of proliferative potential [57]. In addition, the presence of type I interferons during TCR activation increases the proportion of $CD28^{-}$ T cells in culture [58], suggesting an important role for a pro-inflammatory environment during immunosenescence. Some evidence is also suggesting that the generation of $CD28^{-}$ T cells might be driven or accelerated by chronic viral stimulation, most prominently linked to herpes viridae such as CMV [59].

Of note, an efficient CMV immunosurveillance can be maintained with increased age. In immunocompromised patients such as transplant recipients this balance, however, can be disturbed, accelerating the clonality of $CD8^{+}$ T cells which may potentially contribute to a higher level of chronic subclinical inflammation [60]. Of interest, transfer of these T cells from old into young mice led to reduced resistance to viral challenge [61].

Memory T cells: The proportion of memory T cells increases with age, possibly as a consequence to a cumulative exposure to pathogens and environmental antigens [62]. Selected changes in lymphocyte turnover, particularly in the memory $CD8^{+}$ T cell compartment, have been reported in mice. Human and murine $CD8^{+}$ memory T cells were also found to have a longer half-life than other T cell subsets [63,64]. Furthermore, memory cells derived from old naïve cells seem to proliferate less well, produce reduced levels of cytokines and provide less cognate helper function [65]. Although old mice displayed a larger number of memory T cells prior to transplantation, these cells did not exhibit enhanced alloreactivity compared with young memory T cells [66].

Proliferative Response: T cells enter a state of reduced proliferative capacity when telomeres are reduced to a critical length after a certain number of cell divisions known as the ‘Hayflick’ limit [67,68]. The loss of CD28 expression has been associated with loss of proliferative capacity of T cells during repeated cycles of replication, a process termed ‘replicative senescence’ [69]. $CD28^{-}$ T cells show irreversible cell-cycle arrest in addition to apoptosis resistance and reduced proliferative responses [70]. Previous studies had established limited proliferative responses of old T cells to antigenic and mitotic stimuli [71,72].

In line with these observations, adoptively transferred old T-cells proliferated less well in response to their specific antigen [73] and young T cell-deficient mice reconstituted with old

T cells demonstrated a delayed rejection of allogeneic skin allografts, illustrating an overall decline in T cell-mediated alloresponses with increasing age [74].

T cell signaling: Old $CD4^+$ T cells stimulated ex vivo with irradiated donor spleen cells manifested impaired allospecific IL-2 and IFN-γ responses [74]. Those observations are in line with previous reports showing limited capacities of old T cells to produce and respond to IL-2 upon stimulation with antigen [75]. This process has also been linked to an age-dependent and limited activation of the transcription factors AP-1 and NF-AT [76].

The two classical signals required for T cell activation (TCR ligation and co-stimulation) are affected by aging. Old murine $CD4^+$ T cells are less efficient in forming TCR synapses with APCs [77] and show a limited expression of several activation and differentiation markers such as CD40L/CD154, CD25 and CD28 [78,79]. Additional changes in the signaling cascades of old T cells include impairments in calcium metabolism, tyrosine kinase phosphorylation and protein kinase C translocation [80] as wells as alterations in cell membrane lipid rafts [81].

Cytokine responses: A number of studies suggest an imbalance between Th1 and Th2 responses in aging and some, but not all reports have linked aging to a decreased Th1/Th2 ratio [82–84]. The overall frequency of type 1 and type 2 cytokine-producing cells seems to increase with age, potentially influenced by higher frequencies of memory T cells which have less strict requirements for stimulation while producing a broader set of cytokines [85,86]. High levels of lymphocyte function-associated antigen 1 (LFA-1) on $CD28^-$ T cells also reduce the activation threshold of these cells [87].

The role of Th17 immune responses in aging is still unclear, although some have reported on a shift in cytokine expression towards augmented IL-17 alloimmune responses [88,89].

Migration: Recent observations indicate that the expression of selected pro-inflammatory chemokines and receptors are modified in old human and murine T cells, possibly influencing T cell migration patterns. Changes in the expression of CCR7 and CD62L were linked to a defective homing of T-cells to secondary lymphoid organs [90].

Regulatory T cells: Regulatory T cells (Tregs) mediate suppressive functions through various mechanisms [91]. Autoimmune diseases, chronic inflammation and cancer have been linked to quantitative and qualitative defects of Tregs. As some of these disorders have a higher incidence in older individuals, age-related changes in this subset have been of interest [92].

As an alternative to the declining thymic output, Tregs can be generated through a peripheral mechanism [93]. Although most studies have not seen a correlation between numbers of Tregs and aging, few selected studies have shown an increase in the frequency of Tregs with age [94]. These differences might in part be due to different phenotypic definitions, since some studies used only CD25 and other studies used CD25 and Foxp3 as markers for Tregs. In a recent experimental study, we were able to show that Treg functions in old recipient mice remained intact with age [73]. Those findings have also been confirmed clinically [95,96].

Apoptosis and T cell survival: Aging affects major signaling pathways of T cell apoptosis [97]. Clinical studies have shown that both, old naïve and memory T cells have an increased CD95/Fas expression [98] and an decreased expression of Bcl-2, both correlating with enhanced apoptosis [99]. The functional relevance of these findings is still being debated

[100]. Successive shortening of telomeric DNA, as described for T cells with advancing age, is an additional independent factor for increased apoptosis [101].

B cell compartment

B cell generation: The production of B cells wanes with increasing age [102]. Both, early B cell progenitors and the expression of critical transcriptional regulators including E2A gene products such as E47 are reduced with aging [103,104]. In line with these changes, the expression of recombination activating gene (RAG) enzymes, which are crucial for the passage through the pro- and pre-B cell stages, is diminished in old individuals [105]. A limited expression of downstream products of E2A has also been demonstrated in peripheral B cells from old mice [106]. Moreover, in-vivo labeling has revealed that production rates in pro-, pre- and immature bone marrow B cell pools diminish with age [107]. Thus, maintaining the number of peripheral B cells despite decreased output seems to be facilitated trough a decreased turnover of mature B cells [108].

Aging may also impact the balance between B1 and B2 cells: As B2 production wanes with age, the proportional contribution of B1 cells may increase [109]. B1 cells characterized by polyspecificity and low-affinity self-reactivity are a self-renewing pool predominantly found in peritoneal and pleural cavities [110].

B cell receptor diversity and specificity: A significant and age-dependent loss in diversity of the B cell receptor (BCR) has been correlated with poor health and compromised survival [111]. In addition to a reduced output of naïve B cells and intrinsic repertoire differences in B cells generated from old HSCs, some truncation of the repertoire might reflect expanded clones of memory B cells [112].

These changes may also lead to a shift in antibody specificity. In most inbred mouse strains, the spontaneous appearance of autoreactive antibodies is linked to increasing age. Moreover, a compromised selection of newly formed B cells may increase the likelihood of autoreactive B cells to survive. BLyS/BAFF, a B lymphocyte stimulator regulating survival pathways via BLyS receptor 3 [113] provides a limited survival resource during aging for which newly formed and mature B cells compete [114]. Expanded clones of memory B cells might also lead to increased autoantibody titers since some of these were initially expanded and selected by cross-reactive antigens or self-antigens.

B cell responses: Germinal center (GC) formation and kinetics are impaired in older mice [115]. Correspondingly, B cell expansion, antibody affinity maturation and memory B cell differentiation are compromised while amounts of long-lived plasma cells in the bone marrow decline [116,117]. Reduced CD40L/CD154 expression by T cells and a modified cytokine environment [78] may explain the age-dependent limited formation of GCs [112]. Furthermore, follicular dendritic cells as organizers of the lymphoid microarchitecture in GCs have been found to be less effective in trapping and dispersing antigen, correlating with fewer and smaller GCs [118]. The generation of high affinity antibodies is also compromised by intrinsic class switching defects secondary to decreased induction of E47 and activation-induced cytidine deaminase [119].

Aging affects innate immune responses and graft immunogenicity

Innate immune cells express a variety of pattern recognition receptors (PRR) that recognize conserved pathogen-associated patterns (PAMP) and damage-associated molecular patterns (DAMPs) [120]. They also express additional receptors for complement factors, antibodies, and receptors that can sense “self” and “missing self” [121]. This wide array of receptors

allows them to critically impact transplant outcome by influencing the initiation, duration and the overall character of alloimmune responses [122].

Surgery, tissue trauma, consequences of ischemia/reperfusion injury, vascular dysfunctions, and graft preservation are all inevitably linked to graft damage. In response to inflammatory cytokines/chemokines and complement products, IRI mobilizes intragraft DCs and causes a rapid and massive cellular infiltration of various immune cells including monocytes/macrophages, neutrophils, NK cells, DCs, T and B cells [123]. Stimulation of PRRs by DAMPS on damaged graft cells initiate the induction of additional inflammatory cytokines. APCs mature in response to these signals to induce adaptive immune responses [124] and graft cells expressing markers of cellular stress become the target of NK-mediated killing [125].

Dendritic cells

In remains debated if numbers and phenotype of DCs remain unchanged during aging [126–128], or if peripheral human myeloid DCs (mDCs) decline with age [129]. A higher frequency of mature phenotypes with an increased expression of co-stimulatory molecules CD86 and CD83 has been observed in old DCs [129]. Various numerical and phenotypic age-dependent changes in DCs have been described for skin [130], mucosal immune system [131], thymus [132] and brain [133], implying that the impact of aging on DCs might vary depending on specific subsets and the tissue of residence.

Age-dependent effects on antigen sensing and activation of DCs are discussed controversial. Several clinical studies have reported comparable levels of TLR-induced activation and cytokine secretion by monocyte-derived DCs [127,128] while others found a compromised cytokine secretion upon TLR-dependent stimulation [126]. Impaired migration of DCs to draining lymph nodes has been observed both, experimentally and clinically[134,135]. Intrinsic defects of DCs and the aging microenvironment may be of relevance in this context. Data on the capacity of old DCs to prime and activate T cells have been inconsistent [136–138].

Macrophages

A significant decrease in macrophage precursors and macrophages was found in the bone marrow of old individuals [32]. Both, aging human and rodent macrophages seem to express less MHC class II molecules [139,140].

Several reports using murine models indicate a decline in phagocytosis, opsonization, and tumor cell killing by old murine peritoneal macrophages [141,142]. Macrophages from old rats also demonstrated a decrease in the ability to produce superoxide anion upon incubation with IFN-γ or opsonized zymosan [143]. An abrogation in the mitogen-activated protein kinase (MAPK) pathway may be of additional importance in this context [144]. Both, decreased [145] as well as increased [146] amounts of inducible nitric oxide synthase (iNOS) mRNA have been reported in old murine macrophages. Recently, age-specific nitrite-production patterns based on the dose of IFN-γ used for stimulation have been demonstrated [147].

Age has also been associated with an increased production of PGE_2 by macrophages [148]. PGE_2 has been linked to DC functions by altering the secretion of IL-12, IL-10, IL-2 and by decreasing the expression of MHC class II, all impacting proliferative responses in T cells and the Th1/Th2 cytokine balance [149–151].

It has been discussed whether macrophages are the source of elevated levels of pro-inflammatory cytokines found in the elderly [152]. Several recent reports suggested a

decrease in the production of pro-inflammatory cytokines by both, human and murine macrophages [153,154].

In wound healing, macrophages promote angiogenesis and help clearing the wound bed from infections. Clinical wound healing studies demonstrated a delay in monocyte and macrophage infiltration with age associated with a decreased expression of adhesion molecules [155]. Peritoneal macrophages from old mice also produced less VEGF upon stimulation [156].

Natural killer cells

NK cells of old individuals in the SENIEUR protocol demonstrated preserved [157] or even enhanced [158] cytotoxicity. In other studies, age-specific compromises in NK cell cytotoxicity have been correlated with an impaired turnover of inositol triphosphate [159–161]. Interestingly, antibody-dependent cell-mediated cytotoxicity does seem to be preserved with aging [162] and changes in intracellular signaling were not observed in this pathway [161].

An age-related relative increase of human NK cells has been reported [163] and may represent a compensatory mechanism during immunosenescence [164]. These changes were also associated with a phenotypic and functional shift towards highly cytotoxic $CD56^{dim}$ populations [165]. Both, human and murine NK cells have shown a decreased proliferative response following IL-2 stimulation, associated with a decrease in Ca^{2+} mobilization [165]. Moreover, IL2-induced production of IFN-γ and other chemokines was decreased in NK cells from old individuals [165,166], possibly compromising adaptive immune responses driven by NK cells.

Neutrophil granulocytes

Numbers of circulating neutrophils and their capacity to migrate to the site of inflammation do not seem to be compromised with age [167–170]. In-vitro studies have confirmed an unimpaired adhesion of neutrophils to vascular endothelial cells [171]; chemotaxis, however, was found to be impaired [172,173] in the elderly.

There seems to be an age-dependent loss of microbiocidal capacity of neutrophils [174]. Impaired phagocytosis of opsonized bacteria or yeast by neutrophils in the elderly have been observed [175,176] and Fc receptor-mediated production of reactive oxygen species (ROS) was found to be significantly decreased in elderly individuals [177,178].

Mechanistically, decreased intracellular Ca^{2+} levels in stimulated neutrophils [179] and diminished actin polymerization [180] seem to be playing a role. Old neutrophils also showed impaired anti-apoptotic responses to pro-inflammatory signals like IL-2, LPS or GM-CSF, associated with compromised lipid raft function [181,182].

The impact of aging on organ quality and immunogenicity

A large retrospective study demonstrated that kidneys from old donors failed earlier: the projected graft half-life was reduced to 5 years if the donor was older than 60 years, compared with 10.2 years when kidneys from young donors were transplanted [183]. Of note, an adverse effect of donor age was not observed in living donor transplants, indicating that unspecific injuries have a more pronounced affect in older organs [184,185].

Intrinsic functional impairments of old organs may play a role. In fact, autopsy studies showed a decline in kidney weight, number of glomeruli and mean glomerular volume with increasing age [186]. Moreover, longitudinal studies have shown a diminished renal reserve

with aging, accompanied by functional deficits [187], potentially leading to more detrimental injuries subsequent to unspecific injuries and cellular distress. It is unclear whether those effects are related to aging itself or if they represent an accumulation of injuries subsequent to undetected or minimal renal disease.

A retrospective clinical analysis showed an increased need for postoperative dialysis when transplanting old kidneys [183] and donor age has been identified as an independent risk factor for DGF [18]. DGF, in turn, has been linked to increased rates of acute rejection episodes [188].

Several studies have demonstrated an increased susceptibility for IRI with increasing age. In heart transplantation, an increased release of mitochondrial reactive oxygen species has been linked to the observed age-related differences [189]. Augmented age-related IR injuries have also been shown in experimental and clinical liver [190], kidney [191,192] and musculoskeletal studies [193,194].

Tissue injury induces a stereotypic injury response that promotes immune recognition and subsequent injury [195]. This pattern can then, at least in theory, initiate a vicious cycle of repeated injury and injury responses [196] leading to higher immunogenicity of older grafts [197].

An increased immunogenicity of old donor organs may also be mediated by intragraft DCs. Enhanced antigen-presenting capacities of DCs have been reported previously [198–200]. In our own experimental work, we observed that old murine DCs induced more potent alloimmune responses in-vitro (unpublished observations). Clinically, older monocyte-derived DCs (MDDCs) have shown impaired capacities of phagocytosis and pinocytosis [201] in addition to an impaired phagocytosis of apoptotic cells. The latter might potentially lead to an accumulation of necrotic cells which subsequently activate DCs and enhance antigen presentation and secretion of pro-inflammatory cytokines [202]. Inflamm-aging presents a more integrated concept of how donor age may impact graft immunogenicity. Aging is associated with a compromised competence and integrity of epithelial barriers [203]. Subclinical infections may thus increase the accumulation of antigenic burden and represent a persisting challenge to the innate immune system, which – together with deficiencies in adaptive immunity and compromised HSCs – may gain importance in preserving immunologic protection [204]. This shift may lead to the reported elevated levels of pro-inflammatory cytokines in the elderly [205] and may also increase the overall pro-inflammatory state of organs for transplantation. In keeping with this concept, hearts from old mice contained significantly elevated frequencies of donor-derived leukocytes prior to transplantation [73].

The augmented immunogenicity of older organs may also lead to a more vigorous immune response. In fact, an increased incidence of acute rejection episodes after transplantation of old kidneys has been noted [18,206,207]. The Eurotransplant Senior Program reported higher rejection rates. Of note, this program aims for brief ischemic times regardless of HLA matching [208]. In a recent large retrospective analysis of the UNOS database, we found that increased donor age was associated with higher frequencies of acute rejection episodes [5,16].

Experimentally, transplantation of old organs was associated with more potent early immune responses [209,210] and recipients of old grafts demonstrated higher frequencies of effector/memory T-cells and increased in-vitro alloreactivity [211]. Following an acute rejection, old organs may have a compromised capacity to repair. Clinically, increased rates of graft losses were observed for kidneys from old donors after DGF [212]. Fewer functioning nephrons may accelerate the consequences of specific and unspecific injuries in old kidneys and

consequences of multiple injuries may also contribute to premature senescence limiting efficient repair mechanisms in older organs [213] (Fig. 3).

Clinical implications

Organ allocation

The transplantation of older kidneys into older recipients has been proposed in an effort to translate consequences of organ and recipient age into optimized allocation systems [17]. This approach is based, at least in part, on the principle that a kidney from an older donor might be sufficient to meet the metabolic demands of older recipients while allowing an optimized utilization of older organs [214]. The less vigorous alloresponse of old recipients may also counterbalance the increased immunogenicity of old organs.

The Eurotransplant Senior Program (ESP) has implemented these concepts by allocating kidneys from donors >65 years of age regardless of HLA matching to non-sensitized local recipients ≥65 years of age [215]. In a 5-year follow-up study, waiting times had decreased significantly and allocation to local recipients led to reduced cold ischemic times and less frequent DGF [208]. While a slightly higher rate of acute rejection episodes occurred, patient and graft survival were comparable to the standard allocation scheme. A detailed risk-benefit analysis for particular age cohorts with respect to comorbidities, however, has not been established and seems of great clinical relevance.

Age-adapted immunosuppression

Age-related changes in the immune system may be of particular relevance for the management of immunosuppression in the elderly. Lower doses or different drug combinations may be able to provide an appropriate level of immunosuppression while minimizing side effects. In parallel to recipient age, risks for infections increase and mortality rates related to infections in renal allograft recipients >65 years approach that of wait-listed patients [216,217]. Recipient age has also been identified as a strong predictor of post-transplant malignancies [218] and a fivefold increase has been identified in recipients ≥65 years compared with recipients 18-34 years of age [219].

Many age-related factors may influence the pharmacology of immunosuppressive drugs in the elderly. In addition to age-intrinsic effect on pharmacodyamics, pharmacokinetics may be also altered by reduced gastric emptying, decreased splanchnic blood flow, in addition to changes in cytochrome isoenyzmes, P-glycoprotein and compromised protein binding [220]. Decreased hepatic blood flow and decreased renal clearance may also augment organ-specific toxicities [221]. Cyclosporine is highly lipophilic and as fat content increases with age its volume of distribution may increase [220]. Numerous co-morbid conditions in the elderly and drug-drug interactions caused by medication may augment side-effects of immunosuppressive drugs furthermore.

Prospective randomized trials evaluating adapted immunosuppressive protocols for old transplant recipients are so far not available. The elderly are in fact often excluded from clinical trials, possibly because of co-morbid conditions, altered drug pharmacokinetics, and higher rates of adverse effects.

The augmented immunogenicity of older organs may require a more potent early immunosuppression. The preferred induction immunosuppressive agent in the elderly, however, is unclear. With a reduced risk for infections and malignancies compared with antilymphocytic agents, interleukin 2 receptor antagonists (IL2RA) may be preferable in older recipients.[222,223]

Clinical studies on the utilization of azathioprine over mycophenolate mofetil (MMF) are conflicting. In a retrospective study, elderly renal transplant recipients receiving mycophenolate mofetil (MMF)/cyclosporine/prednisone were compared with those on azathioprine/ cyclosporine/prednisone. Older patients treated with azathioprine had a lower rate of opportunistic infection, reduced mortality and improved graft survival [224]. In contrast, Meier-Kriesche et al found MMF in the elderly to be associated with improved patient and graft survival and lower rates of acute rejection compared with azathioprine [225].

Protocols designed for the minimization of maintenance immunosuppression in the elderly have mainly focused on CNI avoidance or withdrawal. In two studies with MMF and steroid maintenance following induction with basiliximab, patient and allograft survival as well as graft function were comparable to standard protocols [226,227]. Furthermore, a retrospective cohort study recently reported that reduced doses of MMF and tacrolimus in renal transplant recipients over 60 years of age were associated with improved graft and patient survival without increased risks for AR [228].

The role of mammalian target of rapamycin (mTOR) inhibitors in immunosuppressive protocols for the elderly is still controversial. An improvement in renal function [227] and a reduced incidence of post-transplant malignancies [229] have been reported in mTOR based calcineurin inhibitor (CNI) free immunosuppressive protocols. At the same time, abnormal lipid metabolism, pulmonary infections and impaired wound healing have been linked to treatment with mTOR inhibitors [230]. Similarly, the benefit of newly established co-stimulatory blockade approaches in older renal transplant recipients remains unclear, especially with clinical reports on altered expression of CTLA4 on T cells from aged individuals [231,232]. In a recent experimental study, co-stimulatory blockade-based treatment failed to extend allograft survival in older mice to the same extent as in younger recipients [66].

Conclusions

Aging as a non-directional process based on numerous extrinsic and intrinsic factors affects the immune system in a global and complex way. While many functions seem to deteriorate with age, regulatory shifts may eventually lead to misbalanced or overzealous immune responses. Understanding the consequences of immunosenescence and organ age on alloimmune responses will be critical as the age of transplant recipients is continually increasing and there is a growing demand for organs from aged donors.

Advanced donor and advanced recipient age are both risk factors for poorer transplant outcome. Organs from old donors are more immunogenic and have shown impaired repair mechanisms and compromised functional reserves. Elderly organ transplant recipients mount dysfunctional alloimmune responses with an increased risk of chronic allograft failure and a more detrimental impact of acute rejection episodes on transplant outcome. However, immunosenescence may not be necessarily conceptualized as a less vigorous but rather as a fundamentally modified immune response. Changes in organ quality and alloimmune responses with aging demand adapted organ allocation concepts and modified immunosuppressive protocols for which more clinical studies are in need. From an immunological and utilitarian view, older organs may be do best in older recipients.

With much of the experimental data on immunosenescence gained outside of transplantation, further investigations into understanding the impact of age on function and balance of pathways of allospecific and organ age-specific immune responses is warranted.

Clinical implications of immunosenescence are far reaching beyond organ transplantation and it is expected that research in this area will allow us to better understand age-impacted processes such as autoimmunity, tolerance induction, vaccination, and wound healing [233–238].

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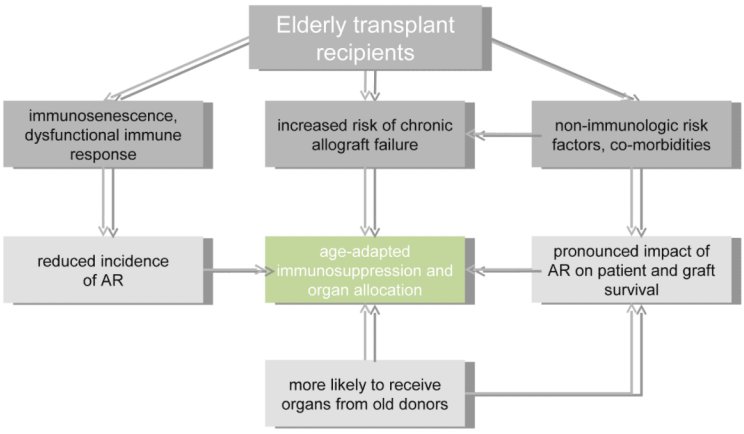

Figure 1. Clinical implications of immunosenescence for the elderly transplant recipient

Modified immune responses subsequent to immunosenescence are clinically characterized by higher rates of chronic allograft failure and less frequent, however more detrimental acute rejections, implicating age-adapted immunosuppression and organ allocation. AR, acute rejection.

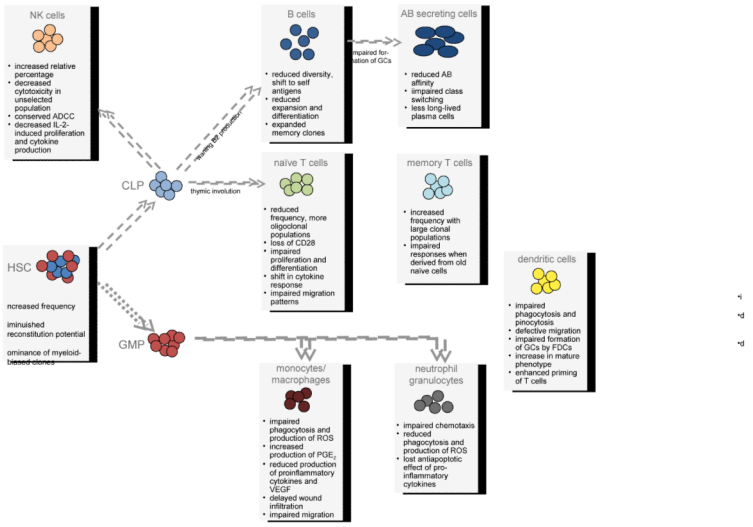

Figure 2. Cellular substrates of the aging immune system

Immunosenescence impacts innate and adaptive immune responses on all levels. HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; ADCC, antibody-dependent cell-mediated cytotoxicity; GC, germinal center; AB, antibody; FDC, follicular dendritic cell; GMP, granulocyte-macrophage progenitor; ROS, reactive oxygen species; PGE2, Prostaglandin E2; VEGF, vascular endothelial growth factor.

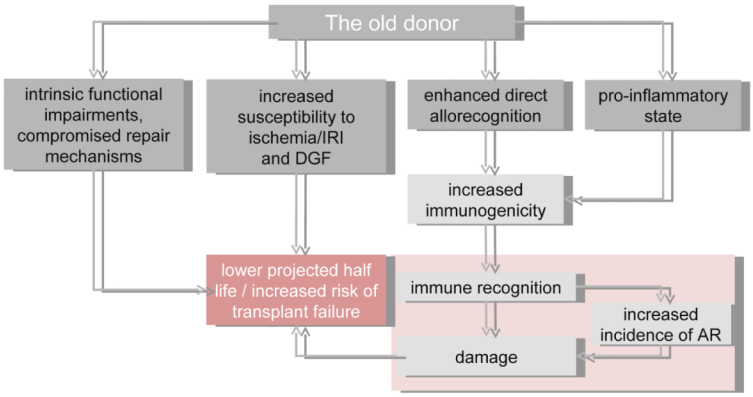

Figure 3. Increasing donor age as a risk factor for inferior transplant outcome

Intrinsic functional impairments, susceptibility to IRI and DGF, enhanced direct allorecognition, and a more pro-inflammatory state of organs from old donors contribute to a cycle of damage, modified immune recognition and compromised repair that ultimately translates into increased risk of transplant failure and inferior transplant outcome. AR, acute rejection.