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REVIEW

Impact of immunosenescence on transplant outcome

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Summary

Aging affects all compartments of the immune response and has a major impact on transplant outcome and organ quality. Although clinical trials in the aging transplant population remain rare, our current understanding of immunosenescence provides a basis for an age-adapted immunosuppression and organ allocation with the goal to optimize utilization and to improve outcomes in older recipients. From a more general perspective, understanding the mechanisms and consequences of immunosenescence will have a broad impact on immune therapies in and beyond transplantation.

Introduction

The prevalence of end-stage organ diseases among older patients is imposing growing challenges on organ transplantation. The proportion of patients over the age of 75 years developing end-stage renal disease (ESRD), for example, has almost tripled from 7.6% to over 20% during the last three decades [1]. As renal transplantation is the treatment of choice for many of these patients [2], the majority of those on waiting lists for kidney transplants are now older than 50 years [3]. To meet this rapidly increasing demand, more than half of all currently transplanted kidneys are from donors older than 50 years [3]. Improved longevity linked to medical progress and ongoing demographic changes will likely aggravate the necessity of care for the elderly and the aging transplant population in particular.

Aging affects all compartments of innate and adaptive immunity. It is important to note that immunosenescence should not be conceptualized as a uniform deterioration, but rather as a plethora of complex modifications of immunologic functions and regulations with broad consequences on alloimmune responses. Clinical implications of immunosenescence for organ transplantation may include an adaptation and selection of immunosuppression for older patients or recipients of older organs, but are also far reaching beyond the field of organ transplantation with increased risks of infections, malignancies, autoimmune disorders, atherosclerosis, and neurodegenerative changes.

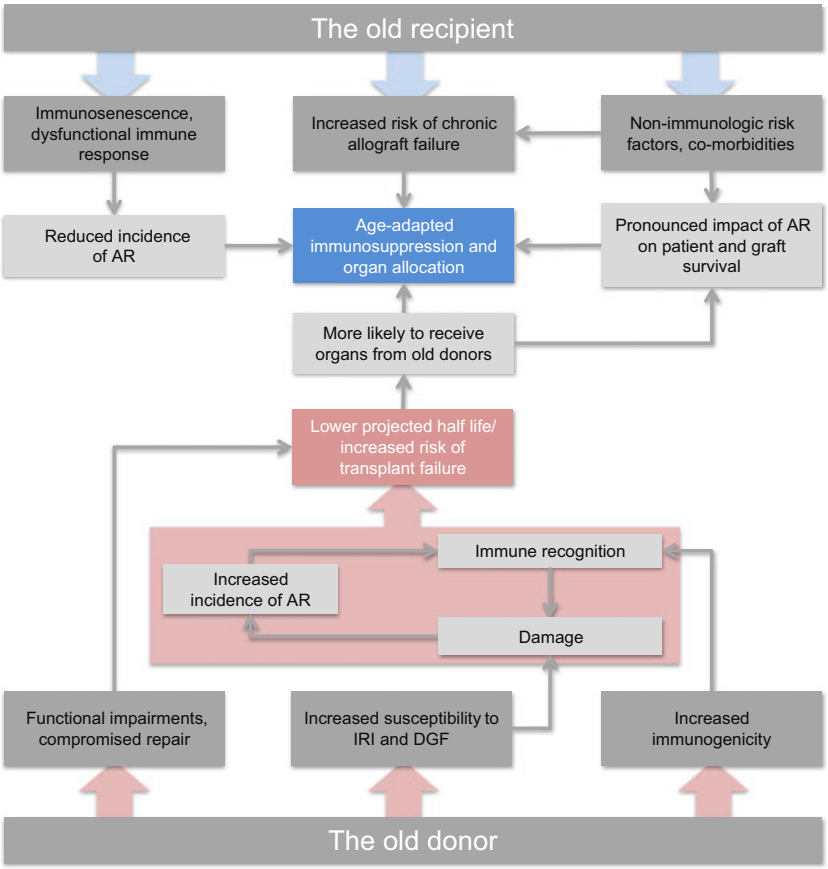

Figure 1 Clinically, modified immune responses of older transplant recipients have been linked to higher rates of chronic allograft failure and less frequent, but more detrimental acute rejections. Old recipients are also more likely to receive organs from old donors, which may ultimately translate into inferior transplant outcome as a result of intrinsic functional impairments, increased susceptibility to IRI, and an augmented immunogenicity of organs from old donors all contributing to modified immune recognition and compromised repair. AR, acute rejection; IRI, ischemia/reperfusion injury; DGF, delayed graft function.

Clinical outcomes

Older renal transplant recipients have an overall higher mortality [4] and almost 50% of graft losses in old recipients are related to death with a functioning graft compared with 15% in young recipients [5]. Of note, older recipients demonstrate improved long-term graft survival when censored for death with a functioning graft [6]. Interestingly, more than 50% of all mortalities in older recipients have been linked to complications that are exacerbated by immunosuppressive therapy and age such as cardiovascular disease, infections, or malignancies [7].

Immunosenescence has been linked to lower rates of acute rejection episodes in clinical trials with corneal, kidney, heart, liver, and lung transplantation [8–12]. In renal transplantation, less than 25% of graft failures in old recipients have been attributed to rejections compared with 50% in recipients <45 years [13]. Acute rejections in the elderly, however, exert more pronounced detrimental effects on patient and graft survival [14]. Intrinsic organ age-related effects and aspects of immunogenicity may be of relevance in this context [6] as older recipients are more likely to receive organs from old donors.

Advanced recipient age has also been identified as an independent clinical risk factor for chronic allograft failure [15], which might be explained by the dysfunctional immune responses in the elderly, further aggravated by organ age-related impairments, an increased susceptibility to calcineurin inhibitor (CNI)-related nephrotoxicity, and a more pro-inflammatory environment in older organs. The detrimental effects of advanced recipient age on chronic allograft nephropathy have also been reported in experimental models [16,17].

Projected life expectancies, nevertheless, almost doubled from 6 to 10 years in renal transplant recipients older than 65 years compared with age-matched con-

trols staying on dialysis [18], although older recipients are more likely to receive older and functionally compromised organs [6]. At the same time, it has to be noted that older recipients represent a highly selected patient population [2].

Thus, clinical studies assessing both transplant and patient survival are in need for the implementation of age-adapted immunosuppressive protocols.

Consequences of advanced donor age

Organs from donors older than 60 years show a significantly reduced projected half-life of 5 years compared with 10.2 years when kidneys from young donors were transplanted [19]. Unspecific injuries may have a more pronounced effect in older organs as adverse effects of donor age were not observed in living donor transplants [20].

Intrinsic functional impairments of old organs such as a decrease in kidney weight, number of glomeruli, and mean glomerular volume may play an additional role [21]. Furthermore, aging seems to lead to functional deficits in the ability to respond to challenges of fluid excess or deficit [22].

Advanced donor age has also been associated with increased risks of delayed graft function (DGF) and pronounced detrimental consequences subsequent to ischemia/reperfusion injury (IRI). Donor age per se has been identified as an independent risk factor for DGF [14] and a retrospective clinical analysis showed an increased need for postoperative dialysis when older kidneys were transplanted [19]. DGF, in turn, has lead to increased rates of acute rejection episodes in some studies [23].

An increased susceptibility for IRI with advancing age has been demonstrated in several experimental models, potentially linked to an augmented release of mitochondrial reactive oxygen species [24–27].

Tissue injury, in turn, promotes a stereotyped immune response that facilitates immune recognition and subsequent injury leading to an augmented immunogenicity of old donor organs [28–30].

Inflamm-aging is a more general concept explaining the impact of donor age on immunogenicity. Subclinical infections in the elderly, at least in part related to a compromised integrity of epithelial barriers, present a persisting challenge to the innate immune system, which – also because of deficiencies in adaptive immunity and compromised hematopoietic stem cells – may gain importance in preserving immunologic protection [31,32]. This shift may lead to elevated levels of pro-inflammatory cytokines in the elderly [33] and impact the immunogenicity of older organs utilized for transplantation. In line with this concept, we were able to demonstrate elevated frequencies of donor-derived leukocytes in hearts from old mice prior to transplantation [34].

The increased incidence of acute rejection episodes after transplantation of old kidneys [14,35–37] may be explained by the augmented immunogenicity of older donor organs. Experimentally, engraftment of old organs has been linked to more potent early immune responses [38,39], higher frequencies of effector/memory T cells, and an augmented alloreactivity *in vitro* [40].

Old organs may also have a compromised capacity to repair and increased rates of graft losses after acute rejection episodes have been observed clinically for kidneys from old donors [41]. The consequences of specific and unspecific injuries in old kidneys may be furthermore exacerbated by a reduced reserve of functioning nephrons. Moreover, repeated injuries may also contribute to premature senescence of stromal and parenchymal cells [42].

Cellular consequences of immunosenescence on alloimmune responses

Consequences of aging on hematopoietic stem cells

Hematopoietic stem cells (HSCs) are long-lived and give rise to all blood cell types of the myeloid and lymphoid lineages to replenish the cellular components of the immune system. Despite their extensive proliferative and regenerative capacity, a growing body of evidence suggests that these cells show signs of aging [43,44]. Both, clinical and experimental data support a measurable and successive functional decline in the reconstitution capacity of old purified HSCs [45,46]. This functional compromise is in part compensated by an enhanced expansion potential [47,48] and some recent data have also suggested an increase in the frequency of human HSCs with aging [44,49]. Murine HSCs furthermore show changes in lineage potential with aging, resulting in attenuated lymphoid lineage output and preserved or even increased myeloid lineage output [50,51]. Interestingly, pediatric leukemias tend to involve lymphoid lineages, while leukemias in the adult population tend to involve myeloid leukemias [52].

Aging broadly affects T cell responses to alloantigens

Thymic involution as a hallmark of immunosenescence starts at the age of 1 year and advances rapidly with puberty [53]. Measurements of changes in thymic output with the signal joint T cell receptor excision circle assay revealed that T cell output declines as a function of thymopoietic tissue, with a retained residual capacity to produce naive T cells [54].

While the loss in thymic output with age does not result in significant changes in the total amount of peripheral T cells [55] as this number seems to be regulated via a thymus-independent expansion of mature T cells [56], the

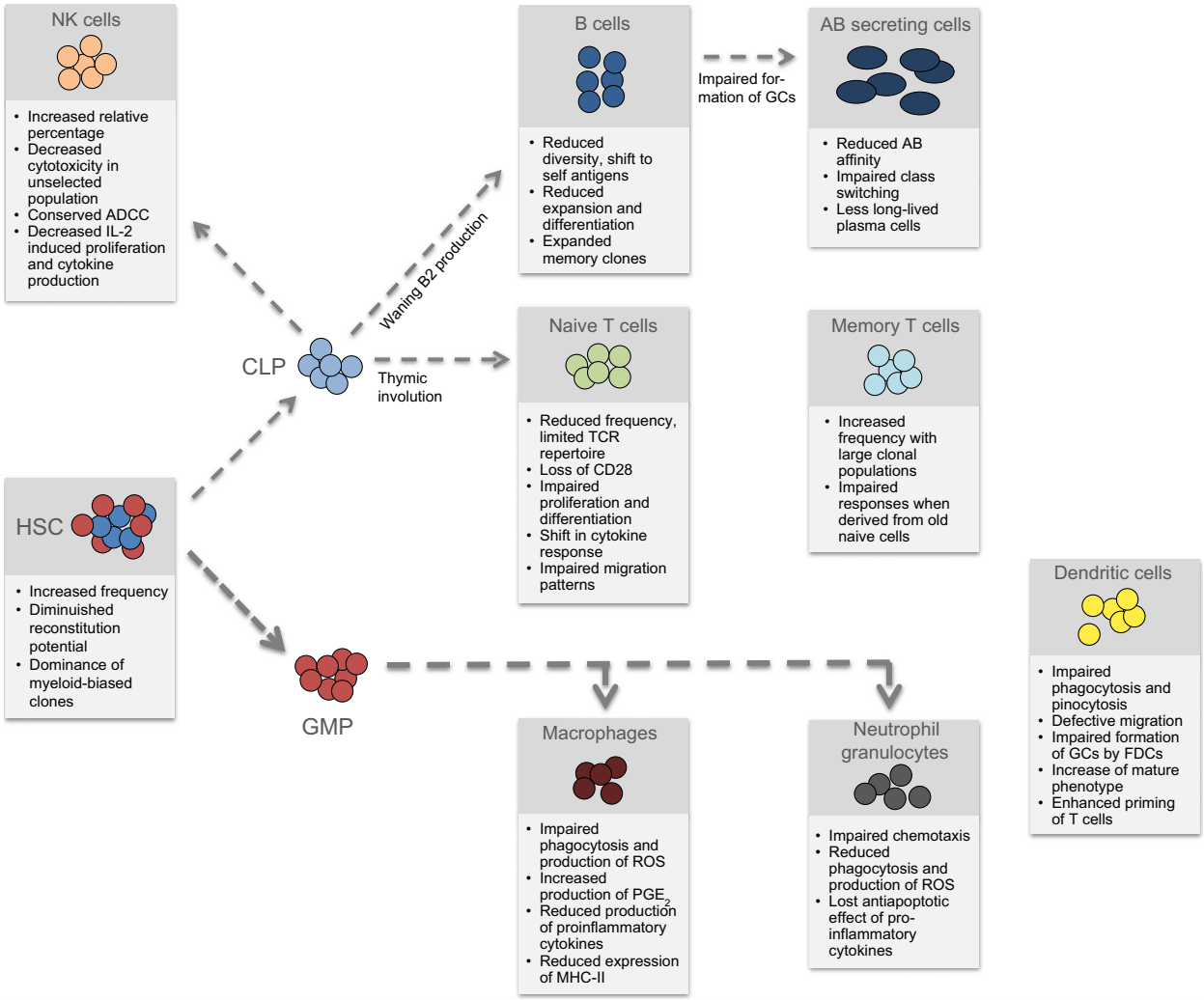

Figure 2 Aging is linked to changes of all innate and adaptive immune compartments. HSC, hematopoietic stem cell; CLP, common lymphoid progenitor; ADCC, antibody-dependent cell-mediated cytotoxicity; GC, germinal center; AB, antibody; FDC, follicular dendritic cell; TCR, T cell receptor; GMP, granulocyte-macrophage progenitor; ROS, reactive oxygen species; PGE_2, Prostaglandin E_2.

decreased amount of naive T cells and their peripheral expansion, however, results in a significantly limited TCR repertoire with the diversity of TCR-β chains dropping 1000-fold in individuals older than 70 years [57]. Changes of the T cell repertoire with aging are also expected to impact allorecognition [58].

An age-related increase in the frequency of $CD8^+$ T cells lacking the expression of CD28 has been described [59]. As a consequence of oligoclonal expansion, TCRs of $CD28^-$ T cells display reduced diversity [60], a finding that may also contribute to the overall limitation of the TCR repertoire [61]. Moreover, $CD28^-$ T cells show an altered expression of co-stimulatory receptors [62] and a gain in cytolytic functions [63]. They also acquire the expression of NK cell receptors such as killer immunoglobulin like receptors (KIRs) [64].

Loss of CD28 expression in T cells with age has been attributed to repeated antigenic stimulation [65] and shortened telomeres with depleted proliferative potential [66]. In addition, the presence of a pro-inflammatory environment with type I interferons during TCR activation increases the proportion of $CD28^-$ T cells *in vitro* [67]. Chronic viral stimulation representing a repeated antigenic stimulus and an inflammatory environment might thus drive the generation of $CD28^-$ T cells [68].

Loss of CD28 expression has also been associated with reduced proliferative capacity during repeated cycles of replication ('replicative senescence') [69,70], besides a reduced proliferative response of old T cells to antigenic as well as mitotic stimuli [71,72]. In keeping with this, adoptively transferred old T cells proliferate less well in response to their specific antigen [34] and young T cell deficient mice

reconstituted with old T cells demonstrate a delayed rejection, illustrating an overall compromise of T cell-mediated alloresponses with increasing age [73].

When old $CD4^+$ T cells were stimulated ex vivo with irradiated donor spleen cells, they manifested impaired allospecific IL-2 and IFN-γ responses [73], a finding that is in line with previously reported decreased capacities of old naive T cells to produce and respond to IL-2 upon stimulation with antigen [74,75]. A number of reports have also linked aging to a decrease in the Th1/Th2 cytokine ratio [76,77], whereas the overall frequency of type 1 and type 2 cytokine-producing T cells seems to increase with age. This may be linked to higher frequencies of memory T cells [78] and high levels of lymphocyte function-associated antigen 1 on $CD28^-$ T cells that reduce their activation threshold [79]. Of additional importance seem cytokine expression shifts toward an IL-17 repertoire or augmented IL-17 alloimmune responses with aging [80,81]. Recently, a potential role for γδ T cell-derived IL-17 in acute allograft rejection has been proposed [82].

The two classical signals required for T cell activation (TCR ligation and co-stimulation) seem to be affected by aging as old murine $CD4^+$ T cells are less efficient in forming TCR synapses with APCs [83] and show a limited expression of several activation and differentiation markers such as CD40L/CD154, CD25, and CD28 [84,85]. In addition, adoptively transferred antigen-specific $CD8^+$ T cells showed a decreased expression of CD62L in young recipients compared with old recipients [73], a finding that together with other recent observations indicates that both human and murine T cells may show age-dependent modifications in migration patterns because of altered expression of selected pro-inflammatory chemokines and receptors [86].

Potentially linked to the cumulative exposure to pathogens and environmental antigens paralleled by a decreased output of naive T cells [87], a number of studies found increased relative numbers of memory T cells in the elderly. While old mice with larger numbers of memory T cells prior to transplantation exhibited comparable *in vitro* alloreactivity [88], memory T cells derived from old naive cells showed compromised proliferative responses and cognate helper functions as well as reduced levels of cytokine production [89]. Higher frequencies of human regulatory T cells (Tregs) with age were also reported [90] and in a recent experimental study, we were able to show that Treg functions in old recipient mice remained intact [34], findings that have also been confirmed clinically [91,92].

Effects of aging on B cells

Production rates in pro-, pre-, and immature bone marrow B cell pools [93,94] and expression of critical transcriptional regulators as well as of the recombination activating gene enzymes all diminish with age [95–97]. The number of peripheral B cells, however, seems to be maintained through a decreased turnover of mature B cells [98]. The entailing significant loss in diversity of the B cell receptor (BCR) with aging has been correlated with poor health and compromised survival [99]. In addition to a reduced output of naive B cells and intrinsic repertoire differences of old HSCs, some truncation of the repertoire might reflect expanded clones of memory B cells [100]. Moreover, aging may impact the balance between B1 and B2 cells [101] as the proportional contribution of B1 cells increases with the waning production of B2 cells.

Age-dependent limited formation of germinal centers (GCs) and altered T cell-dependent responses impair B cell expansion, antibody affinity maturation and memory B cell differentiation [102,103], and are possibly linked to intrinsic class switching defects [104], modified cytokine secretion by T cells as well as reduced CD40L/CD154 expression by T cells and subsequently impaired cognate interactions between T and B cells [84,100]. 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 [105].

Aging impacts innate immune responses and augments the immunogenicity of older organs

Depletion of interstitial dendritic cells (DCs) in kidneys of CD11c-DTR reporter mice reduced tubular cell necrosis and renal dysfunction after IRI [106]. Mice lacking specific toll-like receptors or intracellular proteins required for subsequent signaling showed significantly reduced tissue damage after IRI [107], linked to prolonged allograft survival [108].

Interstitial intragraft DCs may mediate the aforementioned increased immunogenicity of old donor organs. Enhanced antigen-presenting capacities of DCs have been reported previously [109–111] and in own experimental studies, we observed that old murine DCs induced more potent alloimmune responses *in vitro* (unpublished observations). Clinically, older monocyte-derived DCs (MDDCs) have shown impaired capacity of phagocytosis and pinocytosis [112] including impaired phagocytosis of apoptotic cells [113]. Apoptotic cells may accumulate and become necrotic, thus inducing maturation of DCs with subsequently enhanced antigen presentation and increased secretion of pro-inflammatory cytokines [113].

Various numerical and phenotypic age-dependent changes in DCs have been described for specific subsets and tissues of residence [114–117], while data on the capacity of old DCs to prime and activate T cells have

been inconsistent [118–120]. In addition, some clinical studies have reported comparable levels of TLR-induced activation and cytokine secretion by MDDCs [121,122] and an impaired migration of DCs to draining lymph nodes has been observed in experimental and clinical settings [123,124].

A significant decrease in macrophage precursors and mature macrophages has been observed clinically in parallel to aging [125]. Aging human and rodent macrophages seem to have reduced levels of MHC class II expression [126], which may contribute to poorer T cells responses [127]. Increased production of PGE_2 by macrophages may be of additional importance for modified T cell responses with aging [128] as PGE_2 critically influences DC functions by altering the secretion of IL-12, IL-10, IL-2 and by decreasing the expression of MHC class II, thus impacting proliferative responses in T cells and the Th1/Th2 cytokine balance [129–131].

It has been discussed whether macrophages are the source of elevated levels of pro-inflammatory cytokines found in the elderly ('inflamm-aging') [132]. Although several recent reports have suggested a decrease in the production of pro-inflammatory cytokines by both, human and murine macrophages [133,134], chronic inflammatory diseases and poor nutrition might also be of relevance in this context [135,136].

Both, human and murine natural killer (NK) cells have shown a decreased proliferative response following stimulation with IL-2 [137] and IL-2-induced production of IFN-γ was decreased in NK cells from old individuals [137,138], possibly compromising immune responses driven by NK cells. An age-related relative increase in human NK cells has been reported [139] that may represent a compensatory mechanism [140]. These changes were accompanied by an increase in the more mature, highly cytotoxic $CD56^{dim}$ population [137] and unaltered [141] or even enhanced [142] cytotoxicity. Antibody-dependent cell-mediated cytotoxicity does also seem to be preserved with aging [143].

A recent study identified neutrophils as an important link between innate and adaptive immunity as they stimulated donor DCs in a contact-dependent fashion to augment their production of IL-12 and expand alloantigen-specific T cells [144]. Chemotaxis of neutrophils was found to be impaired in the elderly [145,146] and there seems to be an age-dependent loss of microbiocidal capacity [147]. Impaired phagocytosis of opsonized bacteria and yeast by neutrophils has been observed [148,149] and Fc receptor-mediated production of reactive oxygen species was found to be significantly decreased in the elderly [150]. Old neutrophils also showed limited anti-apoptotic responses to pro-inflammatory signals like IL-2, LPS, or GM-CSF [151,152].

Clinical consequences of immunosenescence

Analyses of clinical outcomes after transplantation of old recipients and allocation of old donor organs show independent deleterious effects of advanced donor and recipient age. The multifaceted modifications in adaptive and innate alloresponses linked to immunosenescence may justify both reduced and adapted immunosuppressive maintenance therapy in old recipients. The augmented immunogenicity of older organs, at the same time, may require a potent early immunosuppression. Moreover, some allocation systems such as the Eurotransplant Senior Program have already implemented the clinical reality of an aging donor and recipient population, whereas other allocation systems are currently in the process of being modified to implement the consequences of aging.

Organ allocation

The transplantation of older kidneys into older recipients has been proposed to optimize outcome as the less vigorous alloresponses of old recipients may counterbalance the increased immunogenicity of old organs [13]. Moreover, organs from older donors might be sufficient to meet the metabolic demands of older recipients while allowing a more efficient utilization of older organs [153].

The Eurotransplant Senior Program (ESP) is allocating kidneys from donors >65 years of age regardless of HLA matching to nonsensitized local recipients ≥ 65 years of age [154]. In a 5-year follow-up study, waiting times had decreased significantly and allocation to local recipients had led to reduced cold ischemic time and reduced incidence of DGF [155]. Patient and graft survival were comparable to standard allocation policies, although a slightly higher rate of acute rejection episodes was noted.

Immunosuppression

While minimizing side effects such as opportunistic infections and post-transplant malignancies, lower doses or different combinations of immunosuppressive agents might be able to provide an appropriate level of immunosuppression for the elderly transplant recipient.

Prospective randomized trials evaluating adapted immunosuppressive protocols for old transplant recipients are so far not available, possibly because of comorbid conditions, altered drug pharmacokinetics, and higher rates of adverse effects leading to frequent exclusions of the elderly from clinical trials.

Pharmacokinetics of immunosuppressive drugs in the elderly may be altered by reduced gastric emptying and decreased splanchnic blood flow, in addition to changes in cytochrome isoenzymes, P-glycoprotein, and protein

binding [156]. Decreased hepatic blood flow and renal clearance are age-related factors that may augment organ-specific toxicities [157] and numerous comorbid conditions and drug–drug interactions in the elderly increase side effects furthermore.

Protocols designed for the minimization of maintenance immunosuppression in the elderly have mainly focused on CNI avoidance or withdrawal. In two studies with mycophenolate mofetil (MMF) and steroid maintenance following induction with basiliximab, patient and allograft survival as well as graft function were comparable to standard protocols [158,159]. 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 an increased risk of AR [160].

Thus, a less potent maintenance immunosuppression in the elderly with reduced levels of CNIs and anti-proliferative agents seem feasible, but require confirmation in prospective clinical trials.

Although the augmented immunogenicity of older organs may require a more potent early immunosuppression, its clinical benefit and the preferred induction immunosuppressive agent in the elderly remain unclear. Interleukin 2 receptor antagonists, however, seem preferable over anti-lymphocytic agents in older recipients because of a reduced risk of infections and malignancies [161,162].

The role of mammalian target of rapamycin (mTOR) inhibitors in immunosuppressive protocols for the elderly is still controversial. Although an improvement in renal function [159] and reduced incidences of post-transplant malignancies [163] have been reported with mTOR-based CNI-free immunosuppressive protocols, abnormal lipid metabolism, pulmonary infections, and impaired wound healing may be side effects that limit the benefit of mTOR inhibitors for old transplant recipients [164].

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 [88] and altered expression of CTLA4 was reported for T cells of aged individuals [165,166], thus leaving the role of co-stimulatory blockade approaches in age-adapted immunosuppressive protocols unclear.

Conclusions

Understanding the misbalanced and overzealous immune responses linked to the complex modifications of the immune system during aging is rapidly gaining clinical significance. Older organs show impaired repair mechanisms and compromised functional reserves while at the same time, an augmented immunogenicity of older organs has been reported. Older recipients mount compromised alloimmune responses in experimental and clinical studies. Both, advanced donor and advanced recipient age are thus risk factors for inferior transplant outcome and require adapted organ allocation concepts and modified, clinically validated immunosuppressive protocols.

The relevance of organ-specific aging processes reaches far beyond the field of transplantation. As our current knowledge of transplant-relevant immunosenescence remains in its infancy, organ-specific aging effects remain unclear.

Clinically, immunosenescence may not only require a reduced but also an age-specific immunosuppressive therapy as some approaches such as co-stimulatory blockade may be less effective in the elderly. Thus, with an increasing clinical significance, it will be important to integrate older recipients and older organs into clinical trials to confirm the relevance of experimental data for clinically age-adapted immunosuppression. From a general biological perspective, advancing our understanding of immunosenescence may help to explore novel treatment approaches in and beyond organ transplantation.

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