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Immunosenescence in renal transplantation: A changing balance of innate and adaptive immunity

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Abstract

Purpose of review—With global demographic changes and an overall improved healthcare, more older end-stage-renal-disease (ESRD) patients receive kidney transplants. At the same time, organs from older donors are utilized more frequently. Those developments have and will continue to impact allocation, immunosuppression and efforts improving organ quality.

Recent findings—Findings mainly outside the field of transplantation have provided insights into mechanisms that drive immunosenescence and immunogenicity, thus providing a rationale for an age-adapted immunosuppression and relevant clinical trials in the elderly. With fewer rejections in the elderly, alloimmune responses appear to be characterized by a decline in effectiveness and an augmented unspecific immune response.

Summary—Immunosenescence displays broad and ambivalent effects in elderly transplant recipients. Those changes appear to compensate a decline in allospecific effectiveness by a shift towards an augmented unspecific immune response. Immunosuppression needs to target those age-specific changes to optimize outcomes in elderly transplant recipients,

Keywords

Immunosenescence; aging; kidney transplantation; rejection; tolerance

Introduction

Aging is of broad relevance and affects a wide range of physiological conditions. Consequences include a deteriorating and less effective immune response towards

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Conflict of interest

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exogenous antigens. This phenomenon has been coined immunosenescence by the geriatrician Roy Walford [1]. To date, the concept of immunosenescence remains loosely defined, but is receiving increasing attention with the demographic shift and an overall improved healthcare.

In organ transplantation, data provided from the Organ Procurement and Transplantation Network (OPTN) emphasize on the relevance of the current demographics. Strikingly, patients on waiting lists for renal transplants > than 65 years have tripled during the last decade [2]. Similar tendencies have been observed for organ donors. [2,3].

Of clinical relevance, donor organ age has been identified as an independent risk factor for graft survival [4]. Demographic changes, in addition to the growing shortage of donor organs in general, have impacted organ allocation in the US and in Europe. In the US, the introduction of the Expanded Criteria Donors (ECD) classification attempted to increase the recruitment of marginal donor organs. Notably, age determined the principal criteria for the ECD classification [5]. The recently introduced Kidney Donor Profile Index (KDPI) determines the relative organ quality by calculating a numerical score from ten characteristics which include the donor age [6]. Along the same lines, Eurotransplant launched the European Senior Program (ESP) in 1999 that matched kidney recipients and deceased donor organs ≥65 years without emphasizing on HLA-matching while keeping cold ischemic times brief [7]. The introduction of the ESP led to a doubling of transplanted kidneys from donors older than 60 years from 1998 to 2002 [8].

The concept of immunosenescence in kidney transplantation

Immunosenescence affects both recipients' immune response and organ aging with consequences on injury, repair and immunogenicity. For any detailed analysis, effects of increased prevalences of co-morbidities in the elderly need to be distinguished from changes related to immunosenescence. Although, mortality rates after kidney transplantation are elevated in older recipients, well-selected older patients clearly benefit from renal transplantation. Indeed, death-censored graft survival is best in older transplant recipients [9,10]. Moreover, rates of acute rejections are lowest in older recipients [11], effects clearly attributed to immunosenescence.

Alloimmunity in the elderly

Telomere length is playing a critical role in the aging of cellular compartments [12]. Telomere length is determined by telomerase activity, which is compromised by aging [13,14]. In experimental kidney models, for example, compromised regenerative capacities subsequent to Ischemia/Reperfusion Injury (IRI) have been linked to telomere attrition [15].

Lymphocyte subsets and proliferation capacity

The effect of aging on absolute lymphocyte counts remains controversial [16–18]. In general, it is presumed that changes of absolute numbers of T cells and NK cells play only a minor role in immunosenescence. Of relevance, numerous studies have characterized a modified distribution of subsets within these populations, in addition to a diminished

proliferative response of T and NK cells to mitotic stimuli [18–22]. These compromised proliferative T cell responses limit the effectiveness of alloimmunity, thus characterizing functional consequences rather than numerical T cell responses in immunosenescence. Distributional changes within T cell populations are characterized by a shift from the naïve CCR7+ CD45RA+ subset to an effector memory CCR7− CD45RA− population [18]. This phenomenon can be explained, at least in part, by thymic involution and a subsequent decline in naïve T cell production [17]. The shift from naïve to effector memory T cell subsets emphasizes on the predominant role of 'experienced' T cells in aging while reflecting a compromised '*de novo*' T cell response to new antigens in addition to an impaired chemotactic migration capacity towards secondary lymphoid organs. Thus, the elderly T cell response is mainly built on less effective memory responses that lack the migratory- and naïve *de novo*-production capacity of younger T cells [23].

Phenotypic changes in aging

The decline of CD28 expression on CD4+ and CD8+ T cells has been characterized as a hallmark of T cell senescence [24]. CD28 is a key co-stimulatory surface receptor and the blockade of this pathway has been shown to prolong graft survival in mice [25,26]. In elderly kidney recipients, an increased proportion of peripheral $CD28^{-}$ $CD4^{+}$ has been associated with an absence of acute rejections [27]. More recently, the blockade of co-stimulation gained further clinical relevance with the approval of belatacept, a T lymphocyte antigen-4 immunoglobulin fusion protein (CTLA-4-Ig) that blocks the CD28 co-stimulatory pathway. Additional *in vitro* studies have shown that a loss of CD28 is accompanied by an increased gene expression of its antagonist, the CTLA-4 receptor, which potentially augments the already inhibitory effect [28,29].

The loss of CD28 may be compensated by a *de novo* expression of cytotoxic NK cell receptors on senescent T cells. Recently, *de novo* expression and transcriptional upregulation of the stimulatory NKG2D receptor on elderly $CD4^{+}$ $CD28^{-}$ T cells have been reported clinically [30]. Of note, old $CD8^{+}$ T cells displayed a transcriptional upregulation of activating killer cell lectin-like receptors (KLR) and killer-cell immunoglobulin-like receptors (KIRs). Together, it seems that CD8+ T cell resemble an innate NK cell receptor repertoire with aging [31]. These findings correlate with a general increase of $CD3^{+}$ T cells that co-express NK cell receptors in elderly individuals [32]. Noteworthy, pre-existing or *de novo* synthesized antibodies against the MHC class I polypeptide-related sequence A (MICA) that bind to the NKG2D receptor have been linked to either an early graft loss or late graft dysfunction in kidney transplantation [33,34].

These alterations indicate that the increased expression of NK cell receptors will impact alloimmune responses in the elderly, potentially reflecting relevance of an augmented innate immune response. While the overall significance of NK cell receptors in kidney transplantation remains sparsely investigated, recent work has shown phenotypic changes of NK cell repertoires driven by immunosuppressive treatment [35].

NK cell senescence, in turn, is attributed to a distributional shift from the $CD56^{bright}$ subset to the cytotoxic $CD56^{dim}$ subset [19,36]. Moreover, $CD56^{dim}$ NK cells of elderly individuals

have been shown to increasingly express the senescence-associated surface molecule CD57 [37,38]. The expression of CD57 was additionally identified on $CD8^+$ $CD28^-$ T cells [39]. The CD57 subset is associated with an advanced cytotoxic and proinflammatory cytokine capacity and several studies have reported on a potential link between circulating $CD57^+$ $CD28^-$ $CD8^+$ T cells, HLA mismatch and late kidney graft dysfunction, although the impact of *de novo* expressed NK cell receptors has not been investigated [40*,41**–44].

Furthermore, the tendency for a high $CD28^-$ $CD57^+$ $CD4^+$ T cell frequency in kidney recipients treated with polyclonal anti-thymocyte globulin (ATG) has recently been associated with acute rejection, whereas ATG was thought to accelerate cellular senescence [45*]. Another recent study indicated that the expression of CD57 on $CD8^+$ T cells might have utility as a predictive marker for the development of cutaneous squamous cell carcinoma in renal transplant recipients [46*]. Thus, despite an impaired *per cell* NK cell activity, the overall *de novo* synthesis of NK cell receptors on T cells, CD57 expression and the general $CD56^{dim}$ shift may enhance an overall, however less specific cytotoxic capacity during immunosenescence, [47–49]. Moreover, the ability of $CD56^{dim}$ NK cells to bind anti-HLA antibodies (donor-specific antibodies, DSA) has been linked to complement-independent pathways of antibody-mediated rejections (AMR) in kidney transplantation, leading to the assumption that NK cells contribute to a chronic active antibody-mediated rejection [50,51].

Cytokine capacity

Maintenance immunosuppression critically relies on calcineurin inhibitors that specifically target the production of IL-2 in T cells. Strikingly, it has been shown that both IL-2 cytokine capacity and sensitivity of $CD4^+$ T cells decreases with aging, at least in murine models [52–54]. This effect may be most likely accounted for by the distributional shift to memory T cells. Indeed, naïve CD4+ T cells responded with an unimpaired IL-2 production to neoantigenic stimulation in the elderly [55]. Moreover, age-dependent downregulation of CD28 on CD4+ and CD8+ T cells correlated with an impaired IL-2 production as the co-stimulatory cell surface receptor CD28 is critical for the activation of T cells and their subsequent production of IL-2.

Taken together, loss of CD28 and diminished IL-2 release may represent critical drivers of a compromised alloimmune response in the elderly affecting both, immunosuppression and tolerance protocols.

B cells and humoral responses

It is noteworthy to recognize that B cell development and humoral responses depend on interactions between provided by T- and dendritic cells (DC). The downmodulation of CD154 (CD40L) and CD28 on CD4+ T cells, in addition to a diminished IL-2 production may lead to an impaired B cell proliferation and antibody production [56–58]. Moreover, compromised T cell help will impair B cell diversity linked to a hampered humoral response and affinity of antibodies [59]. Similarly, as with age-mediated shifts in T cell compartments, distributional shifts of B cell subsets are observed. Moreover, the production of naïve B cells appears affected by shifts towards myelopoiesis at the expense of the

lymphopoiesis [60–62]. Furthermore, aging-associated $CD11b^+$ $CD11c^+$ B cells (ABC) with innate immune responsive characteristics have been identified as unique B cell subset in the periphery of elderly mice and were linked to autoimmunity [63,64].

In summary, immunosenescence appears to alter B cell development contributing to a compromised *de novo* donor specific HLA antibody (DSA) production that has been linked to allograft function [65]. Although DSAs have not been shown to be impacted by age, the *de novo* DSA genesis has not been studied in an age-dependent approach [66].

Innate immunity in the elderly

Initial studies on immunosenescence focused on alterations within the adaptive immune system and have only marginally investigated effects on the innate immunity. It has now become evident that aging will not only affect innate immunity, but also equips adaptive immune components with tools of innate immune responses, potentially enabling players of adaptive immunity to act in an antigen-independent manner. DCs with their cardinal feature as antigen presenting cells are potent instigators of T cell stimulation and it is presumed that the change of the absolute numbers of DCs plays an inferior role in aging [67]. Depending on their maturity, DCs in rodents have been shown to critically impact rejection or tolerance in kidney transplantation [67,68]. Several studies have addressed TLR expression on old DCs and neutrophilic granulocytes, and at least for TLR-4, a downmodulation over age has not been identified [69,70]. However, migration, cytokine and phagocytotic responses of DCs encountering new antigens had been compromised, linked to an impaired functional status [69]. Similarly, function of neutrophilic granulocytes appears to diminish with age in parallel with a compromised capacity for phagocytosis, Fcγ receptor type III (CD16) expression and subsequent superoxide production [71,72]. Of interest, an elevated basal cytokine production of DCs and macrophages has been reported in elderly individuals [73]. This phenomenon touches upon the “paradox” of aging and immune functions with a general decline of immune functions and effectiveness appears balanced with an overall augmented reactivity towards self antigens, a process called inflamm-aging [69].

Organ age and immunogenicity

While old macrophages and DCs appear to have a compromised capacity for phagocytosis, this aspect may contribute to a diminished clearance of apoptotic cells [74]. Indeed, a prolonged presence of apoptotic cells may lead to proteolytic degradation and a subsequent release of intracellular damage associated molecular pattern molecules (DAMPs), potentially enhancing immunogenicity [75]. Mounting evidence acknowledges the link between renal IRI in the elderly linked to an augmented release of DAMPs [76,77]. DAMPs in aging are more likely of mitochondrial origin related to a direct exposure to the reactive oxygen species (ROS) [78]. The severity of IRI thereby depends on the level of ROS, again shown to be elevated in elderly individuals [79]. The subsequent recruitment and inflammatory degranulation of neutrophilic granulocytes is facilitated through the binding of DAMPs to Pattern Recognition Receptors, most notably TLRs. More recently, we have been able to show that old donor DCs accelerated rejection, demonstrating the relevance of an augmented immunogenicity when utilizing older organs for transplantation (unpublished data). Of

additional relevance, young donor organs may induce significantly more tolerogenic ILT4+ DCs compared to older donor organs [80]. Others have suggested that cellular senesescence might contribute to an impaired physiological potential of old nephrons to cope with stress stimuli [81].

Conclusion

The immunology of elderly recipients presents an ambivalent picture of changes. On the one hand, an impaired naïve T and B cell alloresponse through the diminished production of high affinity antibodies as well as less effective $CD28^-$ memory T cell subsets may be the driving force behind less potent immune responses in elderly recipients. On the other hand, the aging immune response appears to promote a compensation of lost allospecific functions through the expression of innate immune receptors in memory subsets, providing a more unspecific immune response (Fig. 1).

Understanding this ambivalent concept of immunosenescence bears the potential of developing age-adjusted immunosuppressive therapies for older transplant recipients, as their less effective adaptive response may not be the primary target for treatment.

With regards to donor organ age, recent studies indicate that advanced age may augment injuries subsequent to ischemia and reperfusion, potentially eliciting the release of DAMPs, which in turn can lead to an increased inflammatory response and eventually enhance a potential rejection.

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* of special interest

** of outstanding interest

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Key points

- Immunosenescence may shift the balance between innate and adaptive immunity towards more dominant unspecific immune responses.
- Key players of adaptive immunity acquire receptors characteristic of innate immunity
- Enhanced expression of CD57 on $CD8^+$ T cells has been linked to rejection, yet current studies remain rather descriptive and mechanisms require a more detailed investigation.
- Changes of co-stimulatory pathways in addition to compromised IL-2 responses provide additional opportunities for age-specific treatments.

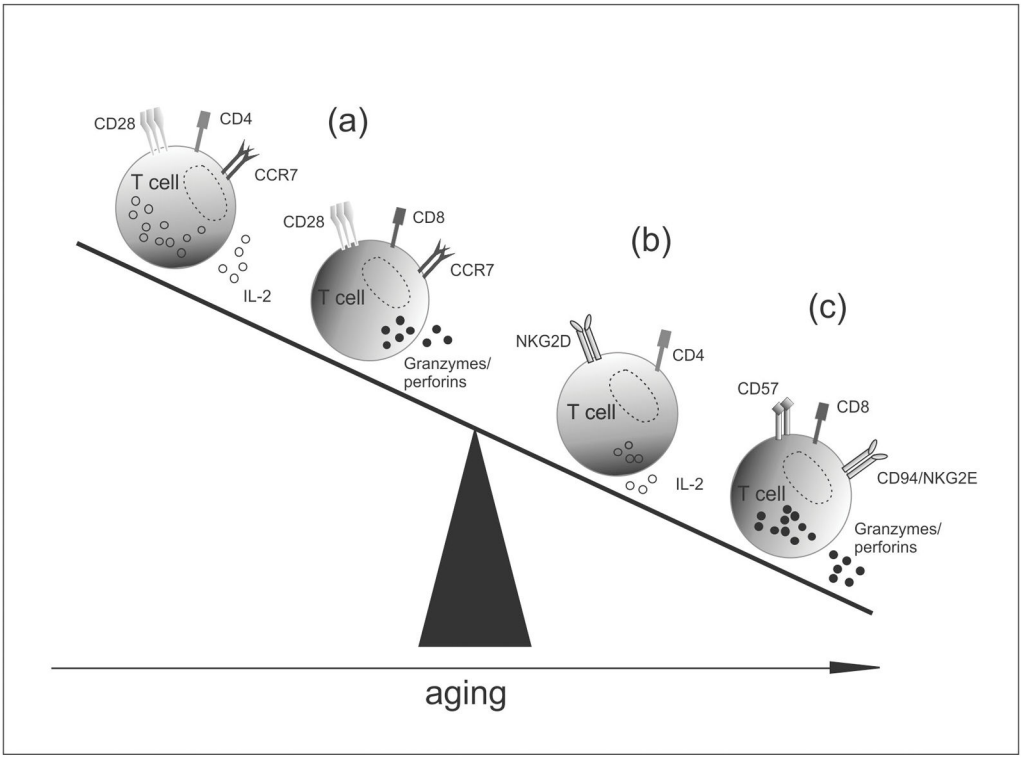

Figure 1.

Concept of a less effective allospecific but augmented unspecific immune response in the elderly. (a) T cell subsets in the healthy individuals. (b) Old $CD4^+$ T cell with diminished alloresponse potential, including an impaired IL-2 capacity and CD28 downregulation coincide with an increasing NK cell receptor equipment [30,52–54]. (c) Enhanced cytotoxic capacity of old $CD28^-$ $CD8^+$ T cells that upregulate CD57 while co-expressing NK cell receptors [43,44].