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REVIEW

The aging of the immune system and its implications for transplantation

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Abstract By the last third of life, most mammals, including humans, exhibit a decline in immune cell numbers, immune organ structure, and immune defense of the organism, commonly known as immunosenescence. This decline leads to clinical manifestations of increased susceptibility to infections, particularly those caused by emerging and reemerging microorganisms, which can reach staggering levels—infection with SARS-CoV-2 has been 270-fold more lethal to older adults over 80 years of age, compared to their 18–39-year-old counterparts. However, while this would be expected to be beneficial to situations where hyporeactivity of the immune system may be desirable, this is not always the case. Here, we discuss the cellular and molecular underpinnings of immunosenescence as they pertain to outcomes of solid organ and hematopoietic transplantation.

Keywords Aging · Immunosenescence · Immune response · Transplantation

Abbreviations

AID	Activation-induced cytidine deaminase\
APC	Antigen presenting cell
BAFF	B cell activating factor
BECs	Blood endothelial cells
CCL	Chemokine (C–C motif) ligand
CCR	C-C motif chemokine receptor
CD	Cluster of differentiation
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CSR	Class switch recombination
CXCL	Chemokine (C-X-C motif) ligand
DAMP	Damage-associated molecular pattern
DCs	Dendritic cells
Dll	Delta-like ligand
E47	E2A-encoded transcription factor
ECM	Extracellular matrix
FRCs	Fibroblastic reticular cells
GC	Germinal center
GVHD	Graft versus host disease
HEVs	High endothelial venule cells
HVEM	Herpes virus entry mediator
IL	Interleukin
IRI	Ischemia-reperfusion injury

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LECs	Lymphatic endothelial cells
LNs	Lymph nodes
Ly6C	Lymphocyte-antigen 6
MHC	Major histocompatibility complex
NK	Natural killer
PAMP	Pathogen-associated molecular pattern
PGD	Primary graft dysfunction
pLNs	Peripheral lymph nodes
PTA	Peripheral tissue antigens
SLOs	Secondary lymphoid organs
Tem	T effector memory cells
Temra	T effector memory cells expressing CD45RA
Tfh	T follicular helper cells
Tfr	T follicular regulatory cells
TGF-β	Transforming growth factor β
Th	T helper type
TLR	Toll-like receptor
T_N	Naïve T cells
TNF	Tumor necrosis factor
Tregs	Regulatory T cells
Tvm	Virtual memory T cells

Introduction

It is well established that the structure of molecules, cells, and tissues of the immune system, as well as their function in immune defense and organismal homeostasis, undergo changes with aging [1]. Such changes are highly variable, affect individuals differently, and are commonly referred to as immune senescence. Their spectrum ranges from manifest qualitative immune response defects via temporal delays to imperfect coordination of molecular and cellular responses. Some of these changes are primary in nature and are due to the process of aging, whereas others may be precipitated by other external stressors, and yet others could be compensatory and reactive to the primary age-related changes. With regard to the outcome for the host, clinically, the most pronounced outcome involves increased vulnerability to acute microbial infections, particularly those caused by emerging and reemerging microbial pathogens [2]. It is believed that the age-related increase in cancer incidence also in part derives from immune senescence because similar immune defects have been observed in response to tumor antigens [3]; however, the efficacy of cancer immunotherapies has not been proven to uniformly decline with age in all studies so far [4, 5], and in some cases, older animals can exhibit increased cancer resistance [6]. The relationship between immune aging and transplantation has been similarly more complex than expected. Clinically, despite reduced immune responses, dosing of immunosuppressive regimens needed to maintain transplant tolerance is not reduced in older adults [7], suggesting robust alloreactivity with aging. Below, we discuss immune aging in light of known defects and put this in the context of existing data as well as likely speculations on their relationship to transplant tolerance and rejection.

Innate immune cells

While much of the research in transplantation immunology has historically focused on the role of adaptive immune responses in the success, or failure, of transplant procedures, the wide array of cell types which comprise the innate arm of the immune response plays a critical role in graft survival via their pro- and anti-inflammatory activities. The major functions of the innate arm of the immune response are to (1) orchestrate the resolution of sterile injury, (2) act as the vanguard of immunity against pathogens, and (3) prime and calibrate the ensuing adaptive immune response. The key players in these activities include monocytes, macrophages, neutrophils, natural killer (NK) cells, NKT cells, and γδ T cells, all of which are affected by the process of aging. It is therefore important to consider how these defects in innate immune function can influence outcomes in transplantation.

In the context of solid organ transplantation, monocytes and macrophages are the major cell types which infiltrate the allograft and surrounding tissues [8]. These populations of cells are critical in the resolution of sterile inflammation resulting from surgical trauma during the transplantation process and ischemia–reperfusion injury (IRI) in a manner largely dependent upon damage-associated molecular pattern (DAMP) signaling (reviewed in [9]). With age, there is a general decrease in the sensitivity of the pattern recognition receptors which recognize these DAMP ligands. For example, in both mice and man, the decreased activation potential of toll-like receptor (TLR) 4, which serves as a receptor for fibronectin, heat shock proteins, and DAMPs (as well as for microbial pathogen-associated molecular patterns, (PAMPs), such as

lipopolysaccharides), leads to decreases or delays in cytokine production and phagocytosis [10–12]. This age-linked dysregulation of cytokine production may in part underly diminished wound healing and delayed re-establishment of homeostasis in the surgical setting. This is an especially important consideration when older grafts are utilized, due to their increased susceptibility to IRI [13]. Indeed, IRI has been shown to induce oxidative damage [14], and decreased ability of older cells to deal with this type of insult [15] is well documented. This is further potentially relevant when considering that cytomegalovirus (CMV) reactivation readily occurs under IRI conditions due to oxidative damage [16], which would be expected to have additional deleterious effects on transplant outcomes.

Moreover, upon tissue infiltration, monocytes can differentiate into $Ly6C^{hi}$ and $Ly6C^{lo}$ populations of macrophages. Experiments in mice have demonstrated that $Ly6C^{hi}$ macrophages can contribute to graft injury and rejection through pro-inflammatory cytokine production and alloantigen presentation. Conversely, differentiated DC-$SIGN^{+}$ ($Ly6C^{lo}$) macrophages can join tissue-resident populations and promote allograft tolerance through interleukin (IL)-10 signaling [17]. While it is known that aging skews macrophage differentiation toward a pro-inflammatory and away from a reparative phenotype, how this impacts the outcome of transplantation with aging remains an understudied area [18].

Dendritic cells (DCs) are antigen-presenting cells (APCs) that capture and process antigens in tissues and present them to naïve T cells in secondary lymphoid organs, and thus, serve as a critical bridge between the innate and adaptive immune systems. In the setting of transplantation, DCs are responsible for stimulating (or, less commonly, tolerizing) alloreactive T cells via (1) presentation of intact donor major histocompatibility complex (MHC) molecules by donor DCs (direct allopresentation) or (2) recipient DC presentation of processed peptides from donor allogeneic proteins (including presentation of processed peptides from allo-MHC molecules themselves). The importance of DCs in both rejection and tolerance is thus self-evident. In older individuals, DCs exhibit impaired antigen uptake reduced maturation and consequently reduced migratory capacity and costimulatory function [19, 20]. Experiments in old mice have demonstrated decreased expression of MHC-II, CD40L, and CD86 upon infection—molecules critical in priming T cell responses [21]. These changes may in part explain the increased proportion and activation of inducible regulatory T cells (Tregs) in older individuals, which are crucial in immune tolerance [22]. However, studies in older recipients have shown in bone-marrow transplants a surprisingly enhanced allostimulartory capacity by old host DCs, leading to increased activation of donor T cells and exacerbated inflammation and disease [23]. The precise basis for this observation has not been elucidated, thus further study is warranted to help develop targeted anti-rejection therapies for older transplant recipients.

Lymphoid stromal cells and aging

Secondary lymphoid organs (SLOs) provide an optimal microenvironment for the induction of effector immune response during immunity, alloimmunity, and autoimmunity. Particularly, lymph nodes (LNs) serve a critical role in naïve T cell (T_N) maintenance, but also are active sites to maintain peripheral tolerance by targeting auto-reactive T cells which have escaped central tolerance in the thymus (Fig. 1) [24]. The LNs are equipped with a wide variety of tolerizing mechanisms including generation of induced regulatory T cells (iTregs), inducing anergy or deletion of auto-reactive T cells, and constraining T cell responses. The majority of such mechanisms are regulated by LN stromal cells. Stromal cells are non-hematopoietic cells that provide an intricate structural network for cellular compartmentalization, organization, and access to survival factors and tonic signals. They play a critical role in orchestrating the cellular interactions needed during various phases of the immune and tolerogenic responses [25]. Based on origin, phenotypic expression, and function, the LN stromal cells are subdivided into four major cell types, fibroblastic reticular cells (FRCs), lymphatic endothelial cells (LECs), blood-endothelial cells (BECs), and double-negative cells, a heterogenous subset believed to contain precursors of other populations. Under the steady-state conditions, the LN stromal cells provide trophic and survival factors, including IL-7, IL-15, chemokine (C–C motif) ligand (CCL) 19, CCL21, B cell activating factor (BAFF), and chemokine (C-X-C motif) ligand (CXCL)13 to T cells and B cells and maintain lymphocyte homeostasis throughout the lifespan [26].

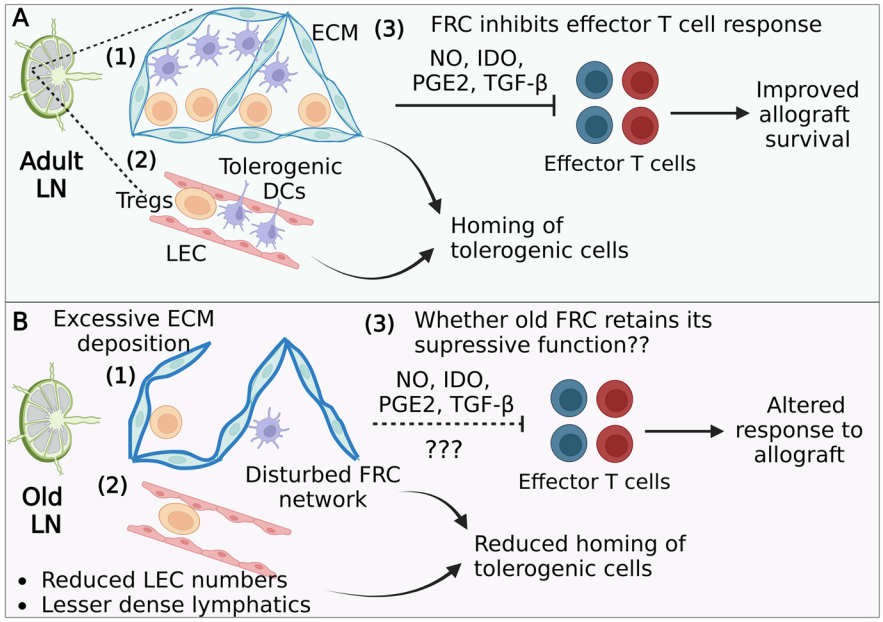

Fig. 1 Potential role of lymph node stromal cell aging in transplantation. **A** Structurally intact (1) FRC reticular network, (2) lymphatic vasculature, and HEV (not shown) in the adult LN support the homing and retention of tolerogenic DCs and Tregs [180, 181]. Such a lymph node near the allograft transplant in mice promotes the survival of grafted tissue by a variety of mechanisms that involve the induction of tolerance to the antigens expressed in the grafted tissue [54]. Further, (3) FRC-mediated diverse immunosuppressive pathways constrain effector T cell activation, proliferation, and differentiation leading to the generation of an environment favorable to support allograft survival [44]. **B** However, in old lymph nodes, numerical loss of LECs and structural deterioration of lymphatics and FRC networks [182] in focal areas in the paracortex (T-cell zones) and/or interfollicular areas (T cell/B cell interphase) might negatively affect the mechanisms that support tolerogenic DCs and Tregs. Further, age-related fibrotic changes (excessive extracellular matrix deposition along reticular network) in the old lymph nodes.[32] might obscure the DCs' and Tregs' access to signals required to maintain their immunosuppressive function. However, whether FRCs retain their capacity to inhibit polyclonal effector T cell responses is not known, but age-related inflammatory changes in the lymph nodes are capable of influencing FRC function and needs systematic investigation. (Created with BioRender.com)

FRCs are myofibroblastic cells that comprise the majority of stromal cells in the SLOs, including the LNs. FRCs produce a meshwork of extracellular matrix (ECM) components that help in the generation and maintenance of three-dimensional conduits for rapid transport of antigens and soluble molecules within the SLOs. FRC processes form the "superhighways" along which T, DC, and other cell types migrate to maximize contact and provide strength and flexibility for the expansion or contraction of SLOs during activation and resolution of immune responses. The deposition of ECM, survival (IL-7, IL-15, and BAFF), and migratory signals (CCL19, CCL21, and CXCL13) on the reticular network sheathing of the conduits facilitate APC-T cell interactions, FRC-T/B cell cross-talk, and leukocyte migration [27, 28].

The BECs and LECs form the blood and lymphatic endovasculature, respectively, and help in antigen and leukocyte trafficking during immunosurveillance, immunity, and alloimmunity. They further provide important factors to maintain FRCs, although the exact spectrum of these interactions is still under investigation. High endothelial venule cells (HEVs) are highly specialized BECs that regulate the entry of circulating leukocytes, soluble antigens, and immunological mediators to the LN. The LECs are specialized endothelial cells that form lymphatic vessels throughout the body and drain tissues into the SLOs via afferent lymphatics, allowing rapid transport of soluble mediators, antigens, pathogens, and immune cells [29]. Several studies have suggested that the dynamic response of these stromal cells to immune activation and regulatory signals regulates effector

immunity and tolerance [30, 31]. However, LNs and in particular stromal cells experience age-related dysregulation in their structure and function [32–35], which may affect the response in transplantation settings, ultimately affecting the survival of grafted tissue. Most notably, LECs decline numerically with aging, whereas FRC networks retract and disintegrate, sometimes unexpectedly early depending on the LN location and, likely, its exposure to environmental microorganisms [36].

Role of stromal cells in immune tolerance and transplantation

Many studies have indicated that FRCs and LECs possess the immunoregulatory properties and play an important role in maintaining immune tolerance in the periphery, leveraging some overlapping and distinct mechanisms [37, 38]. It has been shown that peripheral LN FRCs and LECs express transcriptional activators of tissue antigens, such as deformed epidermal autoregulatory factor 1 [39], that allows them to express a wide variety of endogenous peripheral tissue antigens (PTAs) to induce antigen-dependent tolerance [40, 41]. It remains to be determined if FRCs or LECs maintain their capacity to express PTAs and induce deletional tolerance or support tolerogenic DC and iTreg generation with aging. Although LECs lack the expression of functional MHC-II, it has been reported that LECs can capture antigen-loaded MHC-II from DCs [42]. Similarly, FRCs are also known to acquire self-peptide-MHC II complexes from DCs that induce $CD4^+$ T cell anergy or deletion [42]. Moreover, LECs archive antigens from the lymph flow and transfer them to DCs during steady-state conditions, as well as during infection and inflammation [43], thereby facilitating clonal deletion, anergy, or activation of T cells depending on the inflammatory context. It is currently unknown whether these functions of LEC are affected by aging, although the fact that LEC themselves are drastically reduced with aging [32] suggests that this function would be expected to be impaired.

FRCs induce antigen-independent suppression of T cell responses via different mechanisms, including nitric oxide, indoleamine-2,3-dioxygenase, adenosine 2A receptor, prostaglandin E2, and transforming growth factor (TGF)-β receptor pathways [44]. Other mechanisms include the generation of tolerogenic DCs, induction and migration of Tregs, expression of low levels of co-stimulatory molecules to induce T cell anergy, and expression of higher levels of co-inhibitory molecules, such as programmed death-ligand 1 (PD-L1) [44, 45]. LECs also support the maintenance of iTregs in the LN, and their ability to express PTAs allows the generation of antigen-specific iTregs, thus facilitating indirect antigen-specific tolerance in the LN [46]. Moreover, LECs in the afferent lymphatics support the migration of Tregs from tissue to the LN, which has been found to be a critically important step in the survival of allograft [47]. Further, it has been reported that HEVs induce the apoptosis of FasL-expressing lymphocytes thereby contributing to the maintenance of peripheral tolerance [48]. HEVs also support the entry of APCs such as DCs, which captured the antigen from the allograft. Through elevated expression of CCL19/21, DCs enter the host LN, facilitate the generation or maintenance of tolerance to alloantigens, and support the survival of the allograft. The CCL19/21 gradient-mediated entry of tolerogenic APCs to the donor LN seems a critical step, as a tolerance-inducing regimen with anti-CD40L did not induce tolerance in C–C motif chemokine receptor (CCR) $7^{-/-}$ mice [49]. The expression of different laminin isoforms on the reticular network has been shown to support immunity versus tolerance in a contextual manner by modulating $CD4^+$ T cell differentiation. Laminin 411 inhibits the differentiation of effector T helper type (Th) 1, Th2, and Th17 cells but supports the differentiation of iTregs, while laminin 511 acts in an opposite manner [50, 51]. Recently, it has been shown that expression of laminin ∝4 in FRCs is critical in maintaining a tolerogenic niche in murine lymph nodes and its deficiency leads to the generation of hyper-active effector alloreactive T cells and humoral responses and reduced Tregs, resulting in the failure of tolerance and ultimately the rejection of cardiac and lung transplant in the mice [52]. Collectively, the evidence suggests that LN stromal cells participate in the maintenance of immune tolerance in the periphery and may play a decisive role in graft survival or rejection.

Recently, the allogeneic donor-specific splenocyte transfusion plus anti-CD40L mAb has been successfully used as a regimen to improve allograft survival, and a part of its mechanism may be via modulation of FRC-T cell interaction. The FRC-T

cell interaction via CD40L-CD40 signaling has been shown to induce alloimmune responses and blockade of this pathway using anti-CD40L mAbs significantly improved cardiac transplant survival in mice [51, 53]. The reticular network of FRCs supports the migration of Tregs in the LN, and perturbations of this reticular structure have been shown to adversely affect Treg trafficking and facilitate the rejection of allogeneic cardiac transplant in mice [54]. Similar disruption in the reticular network and cellular organization has been described in the aged LN [33, 35, 55], which may be sufficient to disturb the trafficking of iTregs into and within the aged LN and has the potential to adversely influence allograft survival. In support of this, an experimental perturbation of FRCs and HEV networks has recently shown a negative affect the survival of allografts [47, 54, 56]. The exact spectrum of age-related changes in the above features of stromal cells remains to be established but may have profound implications for the outcome of transplantation.

Stromal cells in graft-versus-host disease

Evidence suggests that LN stromal cells, including FRCs and HEVs, are involved in graft-versus-host disease (GVHD) induced by allogeneic transplant. In murine allogeneic stem cell transplant models, transplanted stem cells have been shown to mount a response against recipient LN FRC structure, affecting the reticular network and HEV structure via Fas-FasL signaling, resulting in the immunological scarring of the recipient LN [57]. The FRCs also contribute to GVHD through activating delta-like ligands (Dll)-1 and Dll4-mediated Notch signaling in alloreactive T cells. Deleting these Notch ligands selectively in FRCs and follicular DCs has been shown to control GVHD [58]. Allogeneic donor graft-derived mast cells have been shown to target host FRCs in the nearest LN. The donor mast cells induce FRC expression of herpes virus entry mediator (HVEM), and stimulation of FRCs by the HVEM-LIGHT axis forced FRCs to acquire a senescence-like phenotype (as marked by expression of the $p16^{INK4a}$, p21, Trp53, and $p57^{KIP2}$ genes), secrete increased levels of collagen I, and made the LN fibrotic long after allograft rejection [59]. Countering these issues with transplantation of ex vivo expanded FRCs mitigated fibrosis in the LN and improved the ability of anti-CD40L to increase the survival of allogeneic cardiac transplant [59]. Therefore, therapeutically targeting the non-hematopoietic cells of the SLOs, especially in aged recipients is a viable avenue of investigation to increase transplantation success.

Possible effect of age-related changes on tolerogenic function of LN stromal cells

Recent studies from us and others have suggested that age-related changes affect the LN reticular structure, alter the T and B cell localization, and perturb the overall architecture and organization of SLOs, leading to poor antibody and T cell responses to infection and vaccination [32, 55, 60, 61]. Reduced priming of T cells is a characteristic of old DCs, limiting the ability of old T cells to mount an appropriate response to foreign antigens and alloantigens [12]. Aged peripheral lymph nodes (pLNs) show signs of fibrosis [32], and T cells in the proximity of accumulated collagen slow their migration within the LN [35]. Aged LNs also fail to support the homeostatic proliferation of T_N [33]. A recent report has shown that homeostatic aging of the mouse spleen is characterized by the erosion of the podoplanin + networks, corresponding to a reduction in T cell zone FRC numbers [55]. Interestingly, it has been recently shown that aged pLNs lose their ability to undergo remodeling and expansion in response to viral infections such as West Nile virus and Chikungunya virus [34, 61]. In response to infection, aged FRCs respond poorly, exhibit delayed and slower proliferation, and fail to optimally stretch and elongate, resulting in poor expansion of the LN and a weak immune response [62]. Such age-related defects at the level of LN stromal cells may have the ability to influence the tolerance to alloantigens and grafts. Nonetheless, quantitative and direct studies are needed to address the exact role of aged stromal cells and the mechanisms involved in the transplantation setting where either donor, recipient, or both are experiencing age-related changes. This is particularly necessary to incisively dissect the relative contributions of decreased induction of T cell priming as opposed to reduced induction of transplant tolerance.

T cell aging and transplantation

The function of T cells as the cellular immunity mediators of the adaptive arm of the immune system depends on the structural and functional integrity of the lymphoid organs. Following positive and negative selection in the thymus, T_N cells migrate to the SLOs where they are activated by their first encounter with antigen. T cells then proliferate and differentiate into several types of effector T cells: cytotoxic T cells (which kill cells infected with intracellular pathogens), helper T cells (which provide signals to support the functions of other cells like macrophages and B cells), and Tregs (which help dampen immune responses). In addition to affecting the extrinsic factors that T cells depend on for optimal function and survival, aging affects intrinsic T cell functions in several ways. Age-related thymic involution is the earliest dramatic change in our immune system, resulting in a 90% drop in T_N output by the time of late puberty [63] and another drop of 90% between the ages of 40 and 50 in humans [64].

Lymph node atrophy (as described above) contributes to T cell defects over time. Overall, aging in the T cell compartment is characterized by reduced numbers and increased turnover of T_N [64], an increasing proportion of T_N cells converting to virtual memory T cells (Tvm) [65], reduced proliferation of Tvm [66], and reduced TCR repertoire [64, 67]. While there is an unquestionable and reproducible impaired response to new pathogens with aging, that includes reduced numbers and frequencies of responding T cells, as well as the reduced magnitude and polyfunctionality of effector T cell responses [68, 69], it is less clear which of the features of T cell aging directly contribute to impaired immunity. It is now likely that initial innate sensing of microbial infection [70–73] as well as defective SLO environments [34, 36, 61] may be exceptionally important. This is further highlighted by our data showing that on a cell-by-cell basis, old Tn cells are at least equivalent to adult Tn cells in responding to *L. monocytogenes* when adoptively transferred into young recipients, whereas adult Tn cells cannot respond well in the old environment [74]. It is therefore most likely that the main problem with Tn cells in old age lies in their numerical loss (so that only ~ 25–33% remain), a defect that can be corrected by transfers of antigen-specific T cell precursors [75]. By contrast, memory responses produced in youth and young adulthood appear to be well preserved during aging [69, 76].

All of this, then, needs to be reconciled with the clinical observations and protocols suggesting that in aging, transplant rejection occurs as vigorously (if not more vigorously) as it does in younger organisms. There are several changes in the older immune system that would heighten the likelihood of stronger alloreactivity. First, several lines of the investigation show that with aging, the T cell repertoire undergoes peripheral selection so that $CD8^+$ Tvm, which arise from T_N due to competition for trophic factors in the lymph nodes, exhibit both stronger affinity towards self-MHC [65] and a propensity to make cytokines rapidly after stimulation (i.e., appeared partially primed) [66], whereas $CD4^+$ T cells exhibit broader crossreactivity [77]. Second, 70–95% of older individuals are infected with cytomegalovirus (CMV), which leads to a life-long absolute expansion of fully differentiated and highly cytotoxic T effector memory (Tem) and T effector memory re-expressing CD45RA (Temra) cells [78]. Tem and Temra cells likely keep their alloreactive potential and are poised for rapid allograft destruction. Third, deterioration of lymph node structure, and with it the erosion of the LN stromal cell tolerogenic function (see above), also likely potentiates the propensity for strong alloreactivity.

A major complication of bone marrow transplantation is T cell-mediated graft GVHD. An especially devastating consequence of GVHD is the damage done to the GI tract, which naturally harbors and abundance of T cells that can be both protective and pathogenic. Although immune-mediated damage as a result of GVHD has long been observed [79], recent mouse studies have revealed the crypt base stem cell compartment to be the primary target of infiltrating donor T cells [80]. It has been found that the extent of antigenic disparity directly correlates with the number of T cells that infiltrate the intestinal tissue, and T cell infiltration increases over time, but the stem cell compartment always remains the primary target [80]. This finding points to the necessity for targeted therapeutics for the treatment of GVHD, perhaps in addition to general immunosuppressive treatments to ensure the success of the graft. The known age-related dysregulations in T cell biology, discussed at the end of the previous paragraph, should stimulate specific studies to address the roles of each of the changes in GVHD, with the goal to modulate

immunosuppressive therapies based on the immunobiology of the older recipient.

A major goal in the field of transplantation is to effectively target Tregs to modulate T-cell-mediated and antibody-mediated graft rejection [81]. Tregs dampen immune responses by producing IL-10 [82, 83], modulating the amount of available IL-2 [84], and even by inducing apoptosis in effector T cells [85, 86]. Trials of Treg therapies in solid organ transplants have only recently begun; thus, no long-term data exists on its efficacy or safety [87, 88]. However, there are aspects of Treg biology that will need to be considered in future trials. The first is bystander suppression, where Tregs suppress responses in a non-antigen-specific manner following Treg activation. This phenomenon has already been demonstrated in mice [89]. The second is Treg plasticity and their ability to take on Th-17 effector functions, which may contribute to graft rejection. Conflicting murine data exist on whether conversion to a Th-17-like phenotype and function can be prevented in humans [90, 91]. In short, Treg therapy has the potential to transform post-transplant patient care so long as specificity for regulating the immune responses within the graft can be achieved without further suppressing immune responses against malignancies or infections.

Aging of B cells

The quality and quantity of newly generated B cells in the bone marrow are impacted by age. While the mechanisms responsible remain to be fully characterized, cell intrinsic and microenvironment changes have been described with aging in mice. Myeloid-biased hemopoietic stem cells accumulate with age in the bone marrow of both mice and humans, promoting the age-related decline in B lymphopoiesis [92]. In the bone marrow of old mice, there is a lower frequency of common lymphoid progenitors and reduced numbers of pro-B, pre-B, and immature B cell subsets when compared to young mice [93, 94]. Bone marrow stromal cells regulate B lymphopoiesis by controlling access to essential growth factors such as IL-7 to progenitor cells. In the aging microenvironment, studies have shown that stromal cells are impaired in IL-7 secretion, with a consequent decrease in pre-B cell numbers [95]. Additionally, alterations in the aged microenvironment are responsible for less efficient V(D)J recombination in pro-B cells due to reduced *rag2* gene expression [96]. Evidence also exists that key B cell maintenance factors, including BAFF/APRIL/BLyS, are also altered with aging [97]. Therefore, reduced B cell generation and maintenance lead to reduced naïve B (and sometimes total B) cell numbers with aging. Cell-intrinsic factors also contribute to the age-related deficit in B cell generation. Studies show that old common lymphoid progenitor cells express less of the transcription factor, EBF, necessary for B cell commitment and differentiation [98]. Moreover, mature B cells from old mice express less of the transcription factor, PAX5, required for the maintenance of B cell fate [99].

Humoral immune responses are also impaired in old mice and humans. It is well established that antibodies produced by aged individuals provide less protection against bacterial and viral infections when compared to their young adult counterparts. The ability of B cells to undergo class switch recombination (CSR) and switch immunoglobulin classes is vital for an effective and appropriate antibody response. Splenic B cells isolated from old mice undergo limited CSR, produce fewer class-switched antibodies, and express less of the E2A-encoded transcription factor E47 [100]. E47 induces activation-induced cytidine deaminase (AID) which is essential for CSR and somatic hypermutation. Therefore, under-induction of AID leads to antibodies of inferior quality in aged mice. There is evidence that the age-related decline of E47 expression in activated B cells is due to the downregulation of the p38 MAPK signal transduction cascade resulting in elevated degradation of E47 mRNA [101, 102].

The germinal center (GC) reaction is critical for the secretion of high-affinity antibodies. Within the GC, antigen-specific B cells receive crucial signals from $CD4^+$ Th cells. $CD4^+$ T cells undergo differentiation into various functional subsets, including Th1, Th2, Th9, Th17, T follicular helper (Tfh), T follicular regulatory (Tfr), and Tregs which allow the immune response to be tailored to the specific threat encountered. Of these, Tfh cells are essential to the GC reaction; these cells localize to B cell follicles and GCs to provide help to B cells for the efficient production of antibodies [103]. In old mice, there is a defect in the differentiation of $CD4^+$ T cells into Tfh cells which results in fewer GCs [104]. Additionally, reduced levels of CXCL13, a chemokine important for Tfh

cell trafficking to the B cell follicle, leads to reduced recruitment of T cells to GCs and impaired B cell help provided by T cells during aged immune responses [105]. Tfr cells have an opposing effect on humoral responses by limiting available T cell help and GC formation [106]. The ratio of Tfr and Tfh cells determines the robustness of the antibody response [104]. Increases in Tfh and Tfr cells are observed in aged mice but there is a greater proportion of Tfr cells, which may contribute to the suppression of the B cell response with aging [107]. Importantly, the suppressive capacity of Tfr cells is not different between young and adult animals, suggesting that the ratio of Tfh and Tfr, and not the quality of suppression, plays a key role in determining the magnitude of the antibody response [107]. Evidence suggests that elevated TGF-β in the aged environment induces expression of FOXP3 in Tfh cells, driving their differentiation and contributing to impaired humoral responses in aged mice [108].

With all the above changes leading to dysregulation and general reduction of antigen-specific humoral immune responses, there are also changes in B cells that may favor hyper-reactivity and increased inflammation, with the potential to maintain or enhance allograft rejection. Specifically, age-associated B cells (ABCs), that accumulate with aging in both mice and humans [109], react to innate receptor ligands and secrete large amounts of cytokines to promote inflammatory responses. Thus, it comes as no surprise that B cells are gaining increasing recognition for their complex effects on the outcomes of transplantation in aged individuals [110].

Aging B cells and transplantation

In the context of transplantation, acute and chronic rejection can be mediated by alloreactive antibodies produced by B cells. HLA incompatibility between donors and recipients is a major cause of solid organ rejection mostly due to antibody-mediated rejection (ABMR) in which antibodies against donor HLA molecules and other non-HLA donor antigens attack allografts and impair their survival. Donor-specific HLA antibodies can be present before transplantation or de novo donor-specific HLA antibodies (dnDSA) can appear late posttransplantation often due to insufficient immunosuppression [111, 112]. A study by Moos et al. found that the risk of developing dnDSA is lower in older adult recipients when compared to pediatric recipients [113]. This finding may be explained by the impaired ability of aged adults to generate effective humoral responses against novel antigens; however, the mechanism responsible for this observation has yet to be established.

In humans, anti-CD20 monoclonal antibody treatments such as Rituximab are used to deplete B cells to improve graft survival in HLA antibody incompatible transplantation [114]. However, there are few studies that describe how B cell depletion affects transplantation in the context of aging. A study by Mori et al. demonstrated that B cell depletion in mice undergoing skin transplantation has disparate effects on allograft survival depending on the age of the recipient mouse [115]. Using a skin allograft model, B cell depletion resulted in the rapid rejection of the transplant in young mice. In contrast, aged mice treated with anti-CD20 had a 7-day delay in allograft rejection. This difference was attributed to ABCs and the adoptive transfer of ABCs into young mice reduced the skin allograft survival rate [115]. While the specific role of ABCs in human allograft reaction has yet to be directly addressed, it is tempting to speculate that they could have adverse effects on allograft survival.

Age-related changes in systemic cytokine/chemokine environment

Many studies reported that with aging, there is a subtle but significant increase in blood levels of inflammatory markers, including IL-6, TNF-α, C-reactive protein, IL-8, IL-18, IL1ra, macrophage inflammatory protein (MIP)-1b, and soluble TNF receptor (sTNFR) I and II [116–119]. The increase of those factors in blood can be interpreted as the existence of chronic, systemic, low-grade inflammation, which has been associated with many age-related diseases, including frailty and sarcopenia [119–124]. The effect of the age-related increase in inflammation is a problem from the standpoint of solid organ transplantation. Because of this increased proinflammatory status, older organs can exhibit more pronounced immunogenicity, may respond suboptimally to stress, and may repair less well than younger organs following transplantation [110, 125–127]. The inflammatory

response in transplantation plays an important role in the allograft loss or dysfunction [128, 129]. It is reported that TNF-α, IL-6, IL-8, and IL-10 are expressed and released in circulation in the case of primary graft dysfunction (PGD) [130], and TNF-α and CCL2 have both been strongly associated with PGD development in lung transplant recipients [131]. Furthermore, pro-inflammatory cytokines IL-1, IL-6, and TNF-α are all upregulated in chronic lung allograft dysfunction (CLAD) [132, 133]. Many of those inflammatory factors are regulated by the TLR4-MyD88 pathway, and the upregulation of the MyD88 gene or TLR4 mRNA was reported to be associated with cell-mediated rejection [134] or kidney graft rejection [135].

Proinflammatory cytokines and chemokines, however, are not the only ones dysregulated and oversecreted with aging, and there is, unfortunately, an oversimplified tendency by many authors to describe the dysregulation of soluble mediators only in proinflammatory terms (often using the popular but misleading term "inflammaging"). Indeed, age-related dysregulation in soluble immune and inflammatory mediators affects equally strongly the mediators involved in the wound healing response, that are usually considered anti-inflammatory, most notably TGFβ and its family members, as well as other profibrotic mediators such as type 2 cytokines IL-4, 13 and others [1]. TGFβ is overproduced by older organisms in many infections, including those with intracellular parasites [136, 137], alphaviruses [61] and flaviviruses (J.L. Uhrlaub, personal communication), although the basis of this overproduction has not been established. It will be of interest to evaluate to what extent this response can lead to scarring and fibrosis of transplanted organs.

The presence of cells carrying signs of cellular senescence has recently been documented in an increasing number of tissues, and their removal has been shown to improve the function of some tissues under certain disease conditions as well as in chronological aging [138]. With regard to transplantation, it has been shown that cells accumulated in the organs from older donors increase immunogenicity and elevate the risk of the rejection [139]. Many, but not all, of those senescent cells are characterized by a senescent-associated secretory phenotype (SASP), which is characterized by high expression of pro-inflammatory cytokines and chemokines such as IL-6, IL-8, TNF-α, and CCL2 [140]. The SASP can contribute to tissue dysfunction, development of chronic diseases, accelerated aging-like state, and impairing tissue homeostasis [138]. The removal of senescence cells has been shown to be effective to ameliorate age-related tissue dysfunctions in old mice [141–145]. Iske et al. found that senescent cell accumulation is a key source of cell-free mitochondrial DNA, which drives alloimmune responses to organs from older donors [146]. Therefore, the use of senolytics may represent a promising avenue to improve the outcome of older organ transplantation and prevent the spread of senescence.

Solid organ transplantation in older adults

Solid organ transplant is the most effective therapy for end-stage organ failure, even in older individuals. The number of people over 65 years of age receiving transplants is rising and so is the number of older adults on a waitlist to receive the organ transplant. However, our limited understanding of age-related changes, and their direct and indirect effects on donor organs and recipients, hinders the development of consensus protocols for solid organ transplantation in older adults (Table 1). Increased age of the donor organ negatively influences the longevity and outcome of transplantation, as it affects the organ's homeostasis, inflammatory status, antigenicity, metabolic and bioenergetic activities, reparative capacity, and ability to handle a wide variety of stress and malignancies [147]. The kidney (> 55 yrs.) [148], heart (> 50 yrs.) [149], and lungs (> 60 yrs.) [150] from old donors have lower longevity compared to those from young adult donors, and this might be due to diminished functionality such as decreased glomerular number and function, chronotropic incompetence, and diminished airway epithelial function, as well as to the above inflammatory, wound healing/reparative, and immunogenic differences. The CMV seropositive status of the donor also affects the quality of the donor organ, as persistent CMV infection may be associated with some features of immunosenescence [151]. Further, IRI-related innate immune activation in the donor organ can contribute to faster allograft rejection [152]. It has been shown that aging compromises innate immunity and also induces chronic low-grade dysregulation of soluble

Table 1 Age-related changes in immune responses that may change transplant outcome

Cellular compartment	Transplant type	
	Solid organ	Bone marrow
T cells	- Bystander suppression by accumulated Tregs -Reduced frequency of T cell-mediated rejection	-Increased bias away from lymphocytes in older donors -Delayed reconstitution of the T cell compartment
B cells	-Accumulation of age-associated B cells (ABCs) -Lower risk of acute organ rejection as compared to pediatric recipients -Lower risk of developing de novo donor-specific HLA antibodies	-Reduced B cell progenitors in aged mice and humans
Innate immune cells	-Bias towards differentiation of infiltrating macrophages and monocytes towards proinflammatory phenotypes -Decreased DAMP recognition by PRRs, leading to faulty wound healing and IRI repair	-Defective direct allopresentation by donor DCs, possibly leading to decreased alloreactive T cell tolerization

mediators (elevated serum IL-6 and TNF-α) [153], elevated TGFβ following infection [61, 137]. In such a situation, aberrant innate immune activation in the donor organ itself can alter intrinsic repair mechanisms and induce the recipient's immune effectors, fueling the alloimmune responses. Older organs transplanted into older recipients show lower rejection than those in younger recipients [154], suggesting that age-matching in addition to immunological matching can help achieve realistic goals in transplant settings. Supporting this notion, transplantation of older (18 months) or younger (2.5–3 months) murine cardiac allograft into younger recipient mice showed that older hearts are rejected more rapidly than younger hearts, and aged DCs played a decisive role in mediating recipient's alloimmune response, as depletion of DCs prior to transplantation resulted in comparable survival of old and young donor hearts [125]. Such findings highlight that age-related alterations in the innate immune compartments of the donor organ may determine transplant outcome. In that context, targeting innate mechanisms in older organs may represent a logical avenue to help alleviate some of the negative effects of donor organ age on the outcome of a transplant, as well as to broaden the pool of donor organs available for transplantation. Along these lines, transplantation studies in transgenic mice that lack the components of innate signaling such as TLR2, TLR4, and MyD88, have shown beneficial effects by delaying both acute and chronic allograft rejection [155, 156].

Adjustment of immunosuppressive treatment in older adults

Since the pharmacokinetics and pharmacodynamics change with age, the administration of immunosuppressive drugs needs to be adjusted for age [157, 158]. Jacobson et al. analyzed calcineurin inhibitor (CNI) troughs in different age groups for 6 months following kidney transplant and showed that despite lower drug doses, the aged group (65–84 years old) showed higher troughs than younger groups [159].

The topmost adverse transplant outcome in older adults is death with a functioning graft [160, 161], and the most frequent cause of death more than 5 years after transplantation is an infection due to immunosuppression [162–166]. Since it has become widely accepted that older transplant recipients may encounter less acute rejection episodes after transplantation as compared to younger recipients due to immunosenescence [167–169], the application of a moderate immune suppression treatment strategy for the elderly seems to be reasonable. A rationale for age-adjusted immunosuppression in organ transplant is also reviewed by Krenzien et al. in 2015 [7]. However, many attempts to use lower immunosuppressive drug doses or withdrawal of drugs with high toxicity in kidney transplant patients result in a higher rejection rate [170–175]. These studies did not specifically target older adults, but included patients older than 65, and no age-associated benefit was found in those trials. A literature review of lowering or withdrawing immunosuppressive drugs in older kidney

transplant patients by Swinski et al. concluded that the current data do not support definitive conclusions, but that there may be a possible benefit from lowering doses or withdrawing of CNI in low-risk populations [176]. Withdrawal or minimization of immunosuppressive drugs at late time points after liver transplant have been more promising, but they also require selection of low-risk patients and close monitoring to be successful [177, 178]. Those studies showed that fine adjustments will be required to find a balance between sufficient immunosuppression for successful allograft survival and maintenance of sufficient immune function to fend off infections or malignancies in older populations. We suggest that high-resolution immune profiling may be of use in these situations to dissect likely correlations and to appropriately monitor the immune system's reactivity in the face of titrated immunosuppression.

Conclusion

Overall, aging abounds in changes to both the innate and adaptive immunity, to systemic cytokine and chemokine milieu, and encompasses alterations in immune cells, stromal cells, and the ECM. With regard to immunity to new infection, the net outcome is often manifested as lower immune reactivity and impaired immune defense, although these changes, like most of aging, exhibit great individual variability.

The situation is not quite as simple when it comes to the transplant setting, and the simple expectation that lowered immune reactivity would translate to better transplant acceptance is often incorrect. Despite the reduced efficacy of primary immune responses to new antigens, alloreactivity remains an exceedingly strong force that is built into the very nature of T and B cell receptor recognition. Therefore, while, for example, precursor frequencies of T cells specific for viral antigens drop by 60–80% in a mouse with aging [65, 179], and in absolute numbers down to 30–200 cells, alloreactive cell numbers remain in tens if not hundreds of thousands despite some numerical reduction. Moreover, increased inflammation, and reduced tolerogenicity of certain microenvironments (e.g., lymph node stroma), further play into allograft rejection.

Finally, older organs themselves tend to invite higher rejection rates, due to innate and inflammatory activation, with senescent cells being a potential culprit. Modulation of these processes by senolytics and by innate cell manipulations/depletions may expand the age of donor organs available to those in dire need of transplantation.

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Declarations

Conflict of interest The authors declare no competing interests.

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