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Mechanisms and consequences of injury and repair in older organ transplants[1]

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Abstract

Donor organ scarcity remains a significant clinical challenge in transplantation. Older organs, increasingly utilized to meet the growing demand for donor organs, have been linked to inferior transplant outcomes. Susceptibility to organ injury, reduced repair capacity, and increased immunogenicity are interrelated and impacted by physiological and pathological aging processes. Insights into the underlying mechanisms are needed to develop age-specific interventional strategies with regards to organ preservation, immunosuppression, and allocation. In this overview, we summarize current knowledge of injury and repair mechanisms and the effects of aging relevant to transplantation.

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Introduction

In an effort to meet the increasing demand for supply in transplantation, the utilization of organs from older donors has become commonplace. Indeed, donor age has steadily increased over the last decades. Some countries have initiated efforts to optimize allocation of older donor organs. The Eurotransplant Senior Program (ESP), for example, was established in 1999 with the aim of increasing the utilization of organs from donors >65 years and allocating them to older recipients. This program has focused on limiting ischemic times, thereby recognizing age-specific injury and repair processes. Consequently, the utilization of older organs for transplantation has risen in this program. Although transplantation of older organs has proven to be effective in expanding the donor pool, advanced donor age has been linked to inferior transplant outcomes. A thorough understanding of age-related injury and repair mechanisms is needed to develop effective interventional strategies with the goals of improving transplant outcomes while increasing the utilization of older organs.

Effects of donor age on clinical transplant outcomes

In kidney transplantation, donor age is a limiting factor of long-term graft survival for organs from both deceased and living donors (1, 2). Likewise, donor age has been linked to delayed graft function (DGF) (1, 2) and higher rates of acute rejection (3, 4). At the same time, DGF has been associated with higher rates of acute rejection episodes (5). Both DGF (5) and acute rejection episodes (6), in turn, are independent predictors of graft survival. Of note, frequencies of acute rejection (4) and graft survival (7) improve when older organs are transplanted into older recipients. Age does not only impact outcomes in renal transplantation, and organ-specific aspects are of relevance. In liver transplantation, donor age is a strong risk factor of graft failure (8). In addition, donor age increases the risk of HCV recurrence (9) and fibrosis progression (10), and antiviral therapies are less efficient (11). Donor age has also been shown to predict patient survival in heart transplantation (12). Moreover, donor age was associated with the highest increase in graft failure for pancreas transplantation (13). In lung transplantation, donor age >65 year correlated with compromised patient survival in a large retrospective series (14). Of note, however, other studies demonstrated comparable outcomes of donors >55 years with those of younger donors (15, 16).

Physiological aging

Aging is characterized by processes of cellular senescence and low-grade inflammation. Cellular senescence refers to a cellular state of growth arrest that can be induced by endogenous or exogenous stressors. These stressors comprise critical telomere shortening, DNA damage, oncogene mutations and oxidative stress, all activating the p53 and $p16^{INK4a}$ tumor suppressor pathways and resulting in cell cycle arrest (17). During the aging process,

senescent cells accumulate (18). Although senescent cells remain viable, they exhibit an altered phenotype. While remaining metabolically active, senescent cells are characterized by compromised replication and resistance to apoptosis. The accumulation of senescent cells induced by telomere shortening impairs an organ's ability to repair and to regenerate subsequent to injury (19, 20). Interestingly, elimination of senescent cells has experimentally been shown to delay onset and progression of age-related diseases (21).

Chronic inflammation is a hallmark of aging and has been termed inflamm-aging (22). Chronic antigenic stress originating from a compromised clearance of self-antigens and exogenous antigens, such as microbes is thought to contribute to inflammation (23). Moreover, age is related to increased levels of reactive oxygen species (ROS) (24). ROS, in turn, activate MAPK and NF-kB pathways, leading to the expression of inflammatory cytokines and chemokines (25). Additionally, ROS induce formation of the NLRP3 inflammasome, leading to the expression of IL-1β (26). More recently, a role for senescent cells in chronic inflammation has been established. Senescent cells maintain a state of low-grade inflammation by secreting proinflammatory cytokines, chemokines and proteases in response to DNA damage, which has been labeled as the senescence-associated secretory phenotype (SASP) (27). DNA injury induces the activation of DNA damage response (DDR) genes that ultimately activate NF-kB pathways, leading to cell activation and death (28).

Injury and repair in the aging organ

During transplantation, temporary deprivation of oxygen and nutrients is inevitable, which in combination with subsequent reperfusion events, results in organ damage. As a consequence to aging processes, older organs are more prone to deleterious insults (Fig 1.).

Organ-specific age-related injuries

The aging process and related diseases affect organs in distinct ways and have organ-specific effects relevant to transplantation. All organs experience a decline in functional mass with age (29–31). For the kidney, these processes have been linked to a reduced ability to recovery from graft injury and compromised transplant outcomes. A reduced nephron mass is known to be a predictive factor for renal disease progression and graft outcome (32). Moreover, reduced numbers of nephrons have been linked to hyperfiltration and subsequent damage (33). Additionally, donor age correlates with interstitial fibrosis, tubular atrophy and glomerulosclerosis (34), possibly mediated by mechanisms of cellular senescence (35). In the liver, aging is associated with nonalcoholic steatohepatitis (NASH) and fibrosis (36). Consequences of steatosis on microcirculatory flow, energy homeostasis and inflammation have been implicated as injury mechanisms (37). In heart transplantation, development of cardiac allograft vasculopathy (CAV) is a significant factor of long-term graft survival (38) and donor age has been shown to be the strongest predictor for the onset of CAV (39). CAV is characterized by diffuse intimal thickening and luminal narrowing, caused by both alloimmune-dependent and -independent factors (40). The prevalence of coronary lesions varies from 17% in individuals <20 years old to 85% in individuals >50 years old (41), with pre-existing lesions predicting the development of CAV (42). Taken together, there is strong

evidence that age imprints an organ-specific propensity of graft injury and a compromise in the ability to recover, leading to reduced allograft function and survival.

Ischemia reperfusion injury

Ischemia reperfusion injury (IRI) encompasses the combined injury to an organ subsequent to ischemia and deprivation of nutrients and oxygen, with subsequent reperfusion injury caused by mitochondrial failure, sterile inflammation, and endothelial cell dysfunction. During the ischemic phase, cellular maintenance of pH, ion homeostasis, and cell integrity are compromised by ATP depletion, leading to a process called oncosis that comprises cell swelling, rupture and cell death (43), Moreover, apoptotic pathways are activated and result in further cell loss. The capacity to maintain adequate levels of ATP is reduced with aging, possibly linked to the down-regulation of electron transport enzymes (44) or ROS-induced damage of mitochondrial DNA, impairing mitochondrial function (45).

The reperfusion phase is characterized by a burst of reactive oxygen species (ROS), induction of a sterile inflammatory response, congestion of the microcirculation known as the no-reflow phenomenon, and endothelial dysfunction. Under physiologic conditions, mitochondria generate ROS by leakage of electrons from the oxidative chain. It is well-established that aging is associated with an increase in basal levels of ROS linked to mitochondrial DNA mutations and consequent respiratory chain dysfunction (46). Following ischemia and reperfusion, older organs generate higher levels of ROS (47), which are directly cytotoxic and increase the production of inflammatory cytokines (25). Induction of the mitochondrial permeability transition pore (mPTP) is a critical pathological process leading to cell death (48). The mPTP constitutes a non-specific pore that opens the inner mitochondrial membrane and allows entry of molecules <1.5 kDa into the mitochondrion. Influx of ions disrupts the electrochemical gradient and uncouples oxidative phosphorylation, resulting in ATP depletion. These mechanisms lead to mitochondrial swelling, membrane rupture and release of apoptotic proteins, resulting in apoptotic cell death or necrosis (49). Induction of mPTP has been linked to an accumulation of matrix calcium (50), and to oxidative stress during ischemia reperfusion injury (51). Of note, aging increases mPTP activity subsequent to increased ROS production and impaired calcium homeostasis (52, 53).

Following reperfusion, a sterile inflammatory response is initiated by endogenous molecules that are released by necrotic and injured cells. These molecules have been characterized as danger associated molecular patterns (DAMPs) that activate pattern recognition receptors such as the Toll-like receptors (TLR), C-type lectin receptors (CLR) and NOD-like receptors (NLR). These events, in turn, stimulate an augmented expression of inflammatory cytokines (54) and upregulate MHC and costimulatory molecules (55), thus promoting the induction of alloimmune responses. In kidneys that expressed TLR4 mutations, graft function immediately post-transplantation was improved (56) and acute rejection rates were reduced (57). Aging may enhance the inflammatory response through multiple mechanisms. Phagocytic capacities of dendritic cells (DC)(58) and other phagocytic cells (59, 60) decline with aging, resulting in diminished clearance of apoptotic cells (61). While the clearance of apoptotic cells is associated with the induction of tolerance (62), apoptotic cells undergoing

secondary necrosis induce the release of DAMPS that activate DCs through C-type lectin receptors (63), leading to dendritic cell maturation and proinflammatory cytokine secretion. Furthermore, it is conceivable that increased ischemia-induced injury and necrotic cell death in aged organs lead to an augmentation of DAMP signaling, which further enhances the inflammatory response.

Organ age augments immunogenicity

Clinically, organ age has been linked to higher acute rejection rates (4), providing another means by which older organs may suffer injury following transplantation. Age-associated epigenetic changes that result in hypermethylation of the CpG regions or hypomethylation of the non-CpG regions (64, 65) may increase the immunogenicity of the DNA. In particular, hypomethylation of aged DNA has been reported to elicit a stronger activation of dendritic cells (DCs) compared to DNA from young donors (66). Furthermore, old DCs have been shown to secrete larger amounts of inflammatory cytokines upon stimulation, possibly as a result of a decreased activation of PI3K-signaling pathways and a reduced suppression of p38-MAPK activation (58). Although immunosenescence leads to an overall decline of immune function, enhanced antigen-presenting capacities have been reported (67, 68). Experimental data from our laboratory confirm that older intragraft DCs stimulate the alloimmune response more potently compared to DCs from younger grafts (unpublished data). Graft endothelial cells may be another contributor to an enhanced immunogenicity as older endothelial cells express higher levels of VCAM-1 and MCP-1, thereby facilitating leukocyte adhesion and infiltration (69). Taken together, these observations support the hypothesis that the magnitude of the alloreactive T cell responses directed against older grafts will be enhanced relative to younger, better-preserved allografts. Furthermore, the magnitude of the alloantibody response, as well as the breadth of the specificity of this response may be enlarged to include cryptic self-antigens exposed during necrotic cell death following the transplantation of older compared to younger allografts.

Cellular stress responses

Heat shock response—Heat, oxidative stress, osmotic stress, and infection all induce heat shock responses (HSR), through the expression of heat shock proteins (HSP) that are regulated by heat shock factors (HSF). HSPs are involved in protein homeostasis and serve as molecular chaperones that aid the folding and repair of damaged proteins, thereby preventing protein aggregation and cell apoptosis (70). HSF1 also promotes ubiquitination and proteolysis (71). Following an acute injury, such as IRI, HSPs assist in restoring normal organ function (72). Aging is associated with elevated basal levels of HSPs, possibly due to continuous stress signals (73). However, induction of HSPs during stress diminishes with aging (74) and is associated with increased injury (75). The protective capacity of HSP-32, or hemeoxygenase 1 (HO-1), has been comprehensively reviewed elsewhere (76). Briefly, while not having a chaperoning function, HO-1 exhibits anti-inflammatory, anti-oxidant, and anti-apoptotic properties (77). During acute injury and transplantation of older kidneys, HO-1 induction is diminished while the pharmacological induction of HO-1 ameliorates injury (78, 79). Although HSPs have been regarded as immunostimulatory due to their property to activate TLRs, this paradigm has recently been disputed (80), and their immunosuppresive functions have been described and confirmed (81). In experimental

transplantation models, HSP treatment resulted in improved graft outcomes (82). Thus, impaired induction of HSP may contribute to inferior outcomes when transplanting older organs.

Unfolded protein response—The endoplasmic reticulum (ER) is the cell organelle responsible for protein synthesis and folding. As a quality control mechanism, only correctly folded proteins are released from the ER, whereas incorrectly folded proteins are retained for refolding or targeted for degradation. When ER function is disturbed by stressors such as IRI, unfolded proteins accumulate, inducing an adaptive response termed the unfolded protein response (UPR) (83). This response comprises the upregulation of the ER folding machinery, shutdown of protein synthesis, and upregulation of ER associated degradation (ERAD) via the proteasome (84). Mitochondria also synthesize a limited amount of proteins and induce a similar mitochondrion-specific UPR upon stress (85). Apoptosis is the ultimate response if repair is inadequate (86). Stressors from ischemia and reperfusion, such as hypoxia, glucose depletion, and ROS cause ER stress and activate the UPR (83). ER stress is involved in renal (87), hepatic (88), and cardiac (89) IRI. With age, the molecular chaperones and enzymes involved in the UPR exhibit reduced expression, leading to increased cell loss through apoptosis (90). One might speculate that a dysfunctional UPR caused by aging impairs organ repair in transplantation; however, evidence for this phenomenon remains lacking.

Ubiquitin-proteasome function—The ubiquitin-proteasome system (UPS) is a proteolytic mechanism for proteins marked for degradation. This system is involved in normal protein turnover and in the removal of damaged proteins during repair processes. The target protein is ubiquitinated and subsequently degraded by the proteasome. Proteasome activity declines with aging, while the ubiquitination system appears not to be affected (73, 91). Compromised protein clearance, in turn, leads to accumulation of damaged proteins during cardiac ischemia (92), conceivably augmenting organ injury. Indeed, proteasome inhibition has been shown to aggravate injury in cardiac (93) and renal (94) IRI. However, reduction of proteasomal activity also suppresses NF-kB activity. Other studies have reported on the protection by pharmacological proteasomal inhibition against IRI, possibly through NF-kB inhibition (95). Cell specificity of UPS function appears to be an important factor in mediating protection from or aggravation of IRI (96). The only age-specific study on UPS function and acute injury concluded that an age-dependent reduction of UPS activity resulted into both NF-kB reduction and augmented tissue injury, possibly through increased apoptosis. In transplantation, proteasome inhibition has successfully been used to counter antibody-mediated rejection, possibly by inducing apoptosis of plasma cells (97). These contradicting data make it difficult at this time to assess the net effect of an age-mediated reduction in proteasomal activity.

Autophagy—Autophagy is a process by which dysfunctional organelles and cytoplasmic proteins are degraded. During this process, part of the cytoplasm is isolated in a double membrane vesicle, denoted by the term autophagosome. The autophagosome fuses with a lysosome, which is followed by enzymatic degradation of the enclosed material. Autophagy is essential for normal cell homeostasis and also plays an important role during periods of

cellular stress, e.g., ischemia, oxidative stress and nutrient deprivation (98). By degrading non-essential cell constituents, metabolic demand is reduced, and substrates for ATP generation are provided. At the same time oxidative damage may be reduced by maintaining TCA cycle function. The relevance of autophagy in transplantation is demonstrated by IRI experiments providing evidence of the protective role of autophagy (99–101). Of note, autophagy function declines with age (102) and may contribute to an increased IRI sensitivity of older organs (100, 103).

Organ age-dependent regulation of repair and regeneration

Epithelial proliferation is regulated by the interaction of epithelial and supporting cells, such as monocytes/macrophages, endothelial cells, stellate cells, and mesenchymal stem cells (104–106). These cells exert autocrine and paracrine functions by producing growth factors subsequent to injury. Genes that encode insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF), epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), and fibroblast growth factor (FGF), are upregulated and stimulate epithelial proliferation in response to kidney injury (107). Similarly, HGF, EGF, HB-EGF, TGF-α and amphiregulin stimulate hepatocyte growth (108). The injured endothelium is also in need of repair after ischemic injury (109) and damaged tissue requires neovascularization for recovery. Angiogenesis is mediated by hypoxia-inducible factor-1 (HIF-1) and the subsequent transcription of angiogenic growth factors. Endothelial cells and pericytes are stimulated by their cognate receptors to form new capillaries (110). Proliferation of endothelial cells to restore the sinusoid network in liver regeneration is stimulated by vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), stem cell factor (SCF), angiopoietins and TGF-α (108). VEGF (111) and angiopoietin (112) are known to be involved in restoring vasculature in renal IRI. Aging is associated with a downregulation of growth factors, receptors and receptor signal transduction (113–115). Moreover, a compromised induction of mitogenic signals may impair the initiation of repair and regeneration.

Bone marrow-derived circulating cells also assist in repair. Endothelial progenitor cells (EPCs) are now recognized to encompass two distinct populations: early and late outgrowth EPCs (116). Circulating EPCs assist in vascular recovery either directly by incorporation (late outgrowth EPCs), or indirectly through the secretion of paracrine factors (early outgrowth EPCs) (117). These cells are recruited to the site of injury through chemotaxis, mediated by stromal derived factor (SDF), a ligand for chemokine receptor CXCR4 (118) and CXCR7 (119) or by angiopoietin (120), a ligand for Tie-2. Mobilization of these cells occurs after ischemic injury (116, 118). With aging, there is a reduced expression of chemokines and angiogenic growth factors, caused by an impaired induction of hypoxia inducible factor 1 (HIF-1) that regulates SDF, angiopoietin, and VEGF (121), which may result in inhibited recruitment of EPCs by older organs. In an experimental model, homing of mesenchymal stem cells (MSCs) was impaired in older animals through SDF-1/CXCR4-dependent mechanisms (122).

Immune cells do not only cause tissue injury, but play also a critical role in the resolution of inflammation and promotion of repair. Depending on micro-environmental cues,

macrophages can be activated to a proinflammatory or an anti-inflammatory state, a phenomenon called macrophage polarization. Based on in vitro studies, macrophages are classified in subsets where M1 macrophages represent a proinflammatory type and M2 macrophages an anti-inflammatory, tissue repair type. M1 macrophages can be induced by IFN-γ, LPS, and TLR ligation, whereas IL-4 and IL-13 promote M2 skewing (123). Clearance of apoptotic neutrophils and epithelial cells also induces M2 polarization with relevance in resolving inflammation (124). M2 macrophages produce IL-10, IL-1Ra, and TGF-β that suppress inflammation. M2 macrophages have also been shown to promote tubular proliferation subsequent to IRI (125). Macrophages may act through the production of growth factors (126) and secretion of Wnt protein (127), which is involved in promoting epithelial cell-cycle progression. Aging impairs macrophage polarization, subsequent to age-related changes of the microenvironment, including increased expression of inflammatory cytokines (128). Macrophages from the recipient are therefore likely to have an impaired ability to polarize to a M2 phenotype, which may inhibit resolution of inflammation and initiation of repair subsequent to the transplantation of old organs.

Reparative and regenerative capacity

Organs have distinct reparative and regenerative capabilities. The liver, for instance, regenerates excellently (129), demonstrated by a remarkable compensatory growth after surgical resection, although hepatic regenerative capacity diminishes with aging (130). Cardiac injury tends to result in fibrotic scarring (131). New heart cells can be generated, predominantly by cardiomyocytes during normal cell homeostasis as well as post injury (132), but may also be generated by resident progenitor cells (133) or bone marrow cells (134). Both cardiomyocyte renewal in normal cell homeostasis (135) and the number of stem/progenitor cells decline with aging (136), suggesting an impaired regenerative capacity after injury. During the recovering phase of acute kidney injury, resident epithelial cells repopulate the zones of injury. This process involves epithelial de-differentiation of the renal tubular cells, spreading of the cells over the uncovered basement membrane, and proliferation and differentiation to complete repair (137). Of note, epithelial proliferation is impaired by aging (138) thus impacting the kidney's ability to recover from injury. Cellular senescence has been implicated with regards to this impairment in IRI (35, 139). Although most of the newly generated cells appear to derive from surviving epithelial cells (140), resident progenitor/stem cells also have been identified as participants in the regenerative process (141). These are thought to contribute to renal repair by epithelial differentiation and proliferation. Moreover, there is an age-associated decline of progenitor cells (142), with cellular senescence assumed to be the main driver (143). Cellular senescence also affects endothelial cells and impairs their ability to proliferate, reducing angiogenic potential (144).

Organ preservation

As older organs are more prone to injury, optimal preservation appears of critical clinical significance. Cold static preservation has long been the standard method of preservation, but hypothermic machine perfusion is gaining ground. Machine perfusion has been implemented for kidney transplantation, and experimental and clinical pilot studies in machine perfusion for extra-renal organs appear promising (145–147). For cardiac transplantation, warm

machine perfusion with oxygenated blood is currently being studied in a randomized trial (NCT00855712). A large trial has demonstrated that machine perfusion results in better outcomes of all deceased-donor kidneys (148, 149) with reduced rates and intensities for delayed graft function (DGF) and improved graft survival. Much attention has been given in the past years to machine perfusion of marginal organs, namely, for organs from expanded criteria kidney donors (ECD) or organs from donation after circulatory death (DCD). Three-year graft survival improved in renal transplantation, particularly when transplanting ECD kidneys (149–151). Donor age is a key component for the assessment of organ quality and a constituent of the ECD criteria. One-year graft survival rates for older grafts (>65 years) that incurred DGF demonstrated improvements with pulsatile perfusion, although an overall survival benefit of older grafts could not be established in this small cohort study (152). A phase 2 trial exploring the potential of machine perfusion of livers from extended criteria donors, defined by age >65 years, macrosteatosis, impaired liver function, and Hepatitis C with macrosteatosis, is currently in progress (NCT01274520). Preliminary data showed a low incidence of allograft dysfunction (153). A lung machine perfusion study was designed to include only high-risk donor lungs, defined by the following criteria: PaO_2-FIO_2 ratio <300, pulmonary edema, poor lung deflation/inflation, blood transfusions exceeding 10 units, and DCD (145). In this small, non-randomized study, outcomes of those marginal lungs were comparable to standard criteria lungs. These data suggest that marginal organs, frequently those from older donors, may benefit most from machine perfusion.

Our understanding of the mechanistic aspects of pulsatile perfusion is currently limited. The rationale behind machine perfusion has typically been linked to the supply with nutrients and substrates, thereby preserving ATP levels and ameliorating subsequent injury (154). More recently, the importance of flow for maintaining endothelial cell function has been described (155). Shear stress-dependent expression of Kruppel-like factor 2 (KLF2) decays rapidly after flow cessation. KLF2 is necessary for the inhibition of proinflammatory cytokines, adhesion molecules, and prothrombotic genes expressed by endothelial cells. Sustaining endothelial homeostasis and the suppression of inflammation may therefore be another mechanism by which machine perfusion mediates superior graft outcomes (156). Statins have been shown to induce KLF2 expression and reversed the detrimental effects of flow cessation when added to the preservation solution (155).

Organ allocation

Optimal allocation of organs appears imperative during times of limited supply, thus the current discard of approximately 50% of ECD kidneys in the US is alarming (157). The recently approved revised kidney allocation system attempts to address the high discard rate by improving allocation efficiency. Under this newly implemented allocation system, 20% of the highest quality kidneys, determined by the Kidney Donor Profile Index (KDPI), will be allocated to candidates with the highest estimated post-transplant survival (EPTS). The remaining 80% will be allocated to candidates within 15 years of the donor range. The introduction of the ESP in Europe has already resulted in increased utilization of older organs. In 2012, 25% of deceased donors in the Eurotransplant area were >65 years old (Eurotransplant Annual Report 2012). Moreover, outcomes when utilizing older kidneys in the ESP were comparable to those of younger kidneys transplanted into older recipients

outside the program (158). Of note, older recipients have been shown to mount a less potent immune response (4), which may offset the increased immunogenicity of older donor organs. Levels of cellular senescence in pretransplant renal biopsies have been shown to more accurately predict postoperative function than donor age alone (159), and have thus been proposed as an additional component assessing transplant outcome (160).

Future perspective

Developing strategies minimizing organ damage and improving outcomes of older organs should receive high priority. Adaptations of practical nature, such as an optimization of allocation protocols to limit cold ischemic times have already shown good outcomes in the ESP and could be implemented on a broader scale. Moreover, widespread implementation of machine perfusion could also aid in better preserving damage-prone older organs. Particularly appealing, however, is the prospect of directly targeting age-dependent deficiencies and pharmacological interventions could be deployed to address impaired cellular stress responses. *Ex vivo* conditioning may provide an additional avenue of interest. Presently, most interventions remain on an experimental level, but as age-specific research progresses, we expect a clinical demand to implement age- and injury-specific preservation methods.

Concluding remarks

Aging affects a majority of organs currently utilized for transplantation. Organ damage caused by physiological aging or pathological processes accumulate and impact transplant outcomes. An increased sensitivity to ischemia reperfusion injury and enhanced immunogenicity aggravate graft injury. Additionally, defective cellular stress and maintenance systems, as well as a diminished cell proliferation debilitate the capacity for repair and regeneration. It is to be expected that the rate of older donors will furthermore increase in the future. At the same time, discard rates of organs, particularly from older donors are alarming. Age-specific research will therefore become even more clinically relevant to guide policies for organ recovery, distribution, and to optimize treatments.

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Abbreviations

ATM	Ataxia telangiectasia mutated
CAV	Cardiac Allograft Vasculopathy
CLR	C-type lectin receptor
CXCR	Chemokine Receptor
DAMP	Danger-associated Molecular Pattern

DCD	Donation after Circulatory Death
DDR	DNA damage response
ECD	Expanded Criteria Donors
EGF	Epidermal Growth Factor
EPC	Endothelial Progenitor Cell
ERAD	ER-associated Degradation
ESP	European Senior Program
FGF	Fibroblast Growth Factor
HB-EGF	Heparin-binding EGF-like Growth Factor
HGF	Hepatocyte Growth Factor
HIF-1	Hypoxia Inducible Factor 1
HO-1	HemeOxygenase 1
HSP	Heat Shock Protein
HSR	Heat Shock Response
IRI	Ischemia Reperfusion Injury
KLF2	Kruppel-like factor 2
MAPK	Mitogen-activated Protein Kinase
MCP-1	Monocyte Chemotactic Protein 1
mPTP	Mitochondrial Permeability Transition Pore
MSC	Mesenchymal Stem Cell
NF-kB	Nuclear Factor Kappa B
NLR	NOD-like receptor
NLRP3	NOD-like receptor family, pyrin domain containing 3
ROS	Reactive Oxygen Species
SCF	Stem Cell Factor
SDF	Stromal-derived Factor
TGF-α	Tissue Growth Factor-α
TLR	Toll-like receptors
UPR	Unfolded Protein Response
UPS	Ubiquitin-Protease System
VCAM-1	Vascular Cell Adhesion Molecule 1
VEGF	Vascular Endothelial Growth Factor

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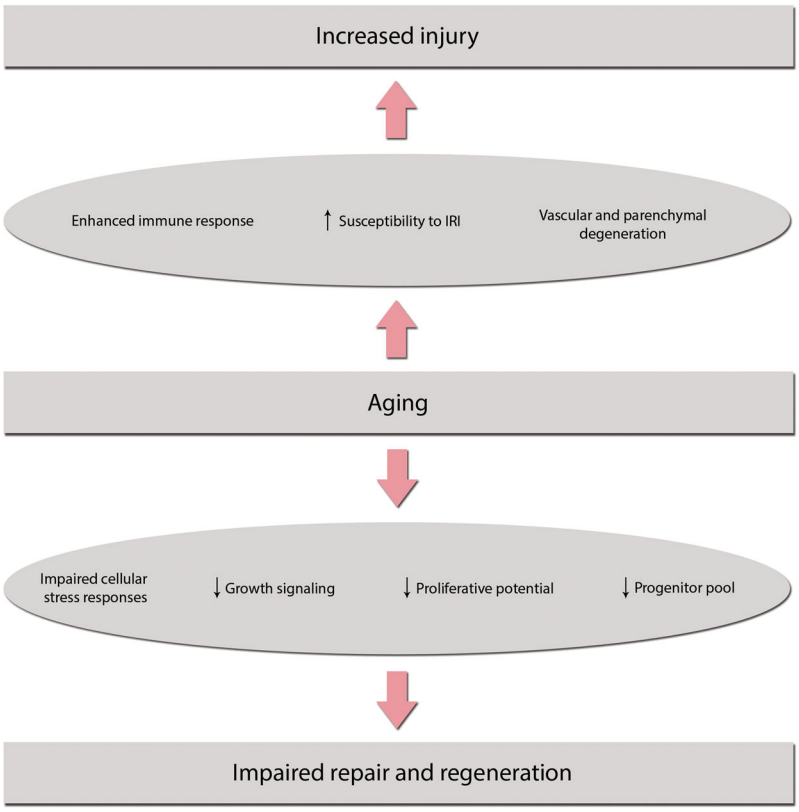

Figure 1.

Organ age contributes to an augmented susceptibility to injury and to an impaired repair and regenerative capacity. Recipient immune responses are augmented subsequent to an inflammatory environment of the donor organ, increased antigenic burden, epigenetic DNA alterations and an enhanced antigen presentation by resident dendritic cells. Additionally, the old organ is more prone to acute injuries such as ischemia reperfusion injury. Degenerative processes of the organ such as reduced functional mass, vasculopathies, steatosis and fibrosis advance the injury furthermore, while impaired cellular stress responses and diminished growth signaling and receptor responsiveness debilitate repair function.