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Senescent Cells in Kidney Transplantation: Hidden Drivers of Graft Aging, Inflammation, and Long-Term Dysfunction

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ABSTRACT
Although kidney transplantation is the best option for ESRD, many issues have been identified that can affect long-term success, such as progressive graft aging and chronic allograft dysfunction. Persistent inflammation, decreased tissue repair and fibrotic remodeling have become clear mechanisms linking transplantation-associated injury to cellular senescence. Renal tissue senescent cells are generated via donor aging, ischemia–reperfusion injury, oxidative and mitochondrial stress, alloimmune response, and treatment-related insult. These cells, although permanently arrested in the cell cycle, continue to be metabolically active, and exhibit a senescence-associated secretory phenotype that can lead to propagation of inflammation, modification of immune-cell function, induce secondary senescence and promote extracellular matrix remodeling. In this review, the molecular mechanisms and transplant-specific mechanisms of renal senescence, its relationship to immune dysregulation, fibrosis, progressive graft dysfunction, and what methods are available to detect the presence of senescence in kidney allografts are discussed. It also reviews the predictive capacity of senescence markers and novel senolytic and senomorphic therapies. The ability to comprehend and therapeutically modulate graft senescence may offer novel means to maintain graft function and enhance long-term transplant survival.

Keywords: cellular senescence, kidney transplantation, graft aging, senescence-associated secretory phenotype, chronic allograft dysfunction

1. Introduction

For patients with end stage kidney disease who are a candidate for kidney transplantation, the advantages of transplantation are significant regarding survival, quality of life and physiological function when compared to long term dialysis. The early outcomes of transplant are significantly better as a result of advances in donor selection, surgery, immunosuppressive therapy, infection prevention, and follow-up. However, the long-term graft survival is limited by the progressive loss of graft functions due to the interplay of a number of immunological and non-immunological insults. The donated kidney is subjected to donor-related biological ageing, ischemic/reperfusion injury, allosensitization, metabolic stress, infections, nephrotoxic immunosuppression, and recurrent inflammatory stimuli. These stresses may lead to accelerated biological ageing at the graft and provide conditions for on-going cell damage. Renal dysfunction is associated with altered immune homeostasis and immunosenescence, and there is evidence that this is a bidirectional relationship [1].

Increasedly, it has become a biological possibility that cumulative stress involving transplantation could contribute to premature senescence of grafts, a process which has been linked to a variety of underlying conditions.Cellular senescence has become a biologically plausible pathway that connects above mentioned cumulative stress during transplantation with premature aging of the grafts. A key feature of senescence is the long-lasting arrest of cell cycle and massive changes in cellular metabolism, chromatin organization, stress signaling and secretory activity. Persistent senescence of cells can become problematic if clearance of these cells is impaired, while transient senescence can be beneficial for tissue remodeling and damage containment. Experimental transplantation data show that pre-existing inflammatory changes and biological age are important in graft responses after transplantation, as renal inflammaging sets the stage for the pro-inflammatory environment in the graft [2]. This is especially important as more elderly donors provide kidneys, especially if these kidneys have a higher baseline senescence or senescent cell burden.

One of the hallmark pathological effects of senescence is the senescence-associated secretory phenotype (SASP) which involves the release of cytokines, chemokines, growth factors, proteases, and extracellular matrix-modifying molecules by metabolically active senescent

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cells. Chronic, sustained SASP activity may injure cells beyond the initial population, causing chronic sterile inflammation, disruption of tissue homeostasis, and inducing "secondary senescence" of neighbouring cells. Systemic inflammaging is now known to be associated with ageing-related disorders such as progressive kidney dysfunction [3]. In transplantation, these mechanisms can trigger the development of chronic molecular stress and create a vicious cycle characterized by inflammation, cell dysfunction and impaired regeneration.

The impact of senescence is not confined to intrinsic renal cells, however, as the aging of immune populations affects tissue surveillance, inflammatory regulation and elimination of damaged cells. The role of cellular senescence in altering the resistance of transplanted tissues and organs and in influencing the course of disease has been described in several solid-organ transplantations [4]. Macrophages might play a special role in this interaction as they display senescence associated macrophage phenotypes which show context-dependent protective and pathological effects, and they are involved in age-related renal inflammation [5]. Aging may also lead to defective mechanisms of tissue injury resolution and resolution of inflammation through progressive immune aging. There are reports of immune aging that results in changes in immune competence and organ responses during severe systemic inflammatory stress, highlighting the potential for dysfunctional immune aging to worsen organ injury [6].

Immune activation after transplantation could be a further factor in increasing this aging phenotype. Chronic viral exposure may be especially important in immunologically vulnerable populations given the possibility that latent viral infections can maintain inflammatory signaling and drive biological aging. Chronically immune activated populations, for instance, have been associated with a range of inflammation, frailty and ageing issues [7] as a consequence of cytomegalovirus associated immune activation. At a higher level, biological aging has come to be viewed as a complex process of chronic inflammation, metabolic dysfunction, cellular ageing, mitochondrial dysfunction and loss of regenerative ability [8]. These dynamic processes offer a useful conceptual framework to explain how kidney allografts can progressively lose function despite effective management of overt episodes of acute rejection.

In addition, cellular senescence may interact with well-known molecular signal transduction pathways involved in kidney graft damage. Complement activation is involved in renal inflammation, ischemia/reperfusion injury, alloimmune responses and tissue damage associated with transplantation, making it a potential link between innate inflammatory signaling and cellular stress leading to senescence [9]. Maladaptive tubular repair, endothelial dysfunction, fibroblast activation, extracellular matrix accumulation, tubular atrophy and/or interstitial fibrosis can then be encouraged by persistent inflammatory signaling. This evidence from other organ systems also supports the notion that senescent stromal cells can actively promote inflammation and promote disease progression [10]. The observations further support the idea that senescent cells are not just bystanders of tissue ageing but can serve as active pathogenic signalling hubs. Their progressive accumulation may thus play a role in the evolution of repeated cellular damage to irreversible structural remodelling within kidney transplantation, and/or in accelerated graft ageing and chronic allograft dysfunction.

While there is increasing mechanistic data, there is much that is still not understood about which populations of renal cells are most clinically relevant, when transplantation induced senescence becomes persistent or permanent, and whether the assays of senescence can be used to predict long-term graft outcome. Another challenge in translation is the lack of a single definitive biomarker of cellular senescence, and the context dependent physiological role of transient senescence. Therefore, it is crucial to understand the timing and location of graft senescence, in order to be able to implement senolytic, senomorphic, and SASP-modulating therapies in kidney transplantation. Accordingly, this review aims to:

1.Explain the molecular mechanisms and transplantation-specific stressors responsible for senescent-cell accumulation within kidney allografts.

2.Evaluate how senescence and SASP signaling promote graft inflammation, immune dysregulation, fibrosis, and progressive dysfunction.

3.Assess senescence biomarkers and emerging therapeutic strategies for improving long-term kidney allograft function and survival.

2. Cellular Senescence: Biological Foundations and Relevance to the Kidney

2.1 Hallmarks and Molecular Regulation of Cellular Senescence

Cellular senescence is a stress-induced state of stable cell-cycle arrest with a high level of cellular metabolic activity. The establishment is mainly controlled by the p16^INK4a^–retinoblastoma and p53–p21 pathways, which inhibit the growth of damaged cells. This arrested phenotype is reinforced by ongoing responses to DNA damage, loss of telomeres, and epigenetic changes and gradually impairs cellular function. These molecular changes are common across age and can influence the action of immune cells as well as the ability of cells to regenerate [11]. Excessive production of ROS, oxidative damage, metabolic changes and prolonged activation of stress-signaling pathways are other mechanisms by which mitochondrial dysfunction contributes to senescence [12].

2.2 Senescence-Associated Secretory Phenotype (SASP)

Senescent cells actively remodel their microenvironment through the secretion of pro-inflammatory cytokines, chemokines, growth factors, proteases, and remodeling of the extracellular matrix, known as the senescence-associated secretory phenotype (SASP). Persistent SASP signalling supports sterile inflammation, and promotes the disruption of tissue homeostasis, leading to progressive renal injury. However, due to metabolic changes that occur with kidney aging, this could further drive inflammatory and senescence-associated pathways, which can now be

linked to changes in cellular metabolism driving disease progression [13]. Additionally, the SASP factors also regulate themselves (autocrine effect) to maintain the senescent phenotype and exert other effects (paracrine effect) that induce secondary senescence and increase tissue dysfunction beyond the initial damaged cells.

2.3 Senescent Cell Populations in Renal Tissue

Renal senescence is not a single population of cells but rather a complex interaction between several cellular compartments. Tubular epithelial cells are especially vulnerable since continued metabolic, oxidative and ischemic stressors can lead to chronic growth arrest and repair. The endothelial-cell senescence may damage the microvascular integrity while senescent fibroblasts and pericytes may affect the remodeling of the extracellular matrix and the fibrogenesis. Additionally, the immune-cell phenotypes of transplanted organs are influenced by immunomodulatory conditions [14]. Dysfunctional cells, such as the glomerular cells and infiltrating leukocytes, could also contribute to the senescent microenvironment, suggesting that targeting these cells specifically and preserving protective immune functions could be relevant [15] (Table 1).

Table 1. Key Biological Features and Renal Consequences of Cellular Senescence

Senescence feature	Principal mechanism	Relevance to kidney	References
Cell-cycle arrest	p16^INK4a^–RB; p53–p21	Restricts epithelial regeneration	[11]
DNA damage	Persistent DDR; telomere dysfunction	Maintains senescent phenotype	[12]
Mitochondrial dysfunction	ROS and metabolic disruption	Promotes renal cellular stress	[13]
SASP	Cytokines, chemokines, proteases	Sustains inflammation and secondary senescence	[14]
Immune dysregulation	Altered immune surveillance	Reduces senescent-cell clearance	[14]
Cellular heterogeneity	Epithelial, endothelial, stromal, immune cells	Creates multicellular renal senescence	[15]

3. Why Kidney Transplantation Creates a Senescence-Promoting Environment

3.1 Donor Age and Pre-existing Renal Senescence

The responses of a kidney allograft to the stress of transplantation are based on a biological baseline that consists of donor characteristics. Older and expanded-criteria donor kidneys often have decreased nephron reserve, accumulation of molecular damage, decreased regenerative capacity, and structural changes associated with aging that may result in increased vulnerability after implantation. The importance of biological heterogeneity in the assessment of kidney status and disease trajectories is increasingly recognized in today's nephrology [16]. Thus chronological age is not a sufficient proxy for graft resilience. The pre-existing load of senescent cells and molecular markers of biological aging may be more indicative of tissue fitness especially when cellular senescence has already impacted regenerative responses before transplantation [17].

3.2 Ischemia–Reperfusion Injury and Oxidative Stress

Procurement of kidney inevitably results in warm and cold ischemia of the graft tissue, followed by abrupt reperfusion in the recipient. This cascade produces reactive oxygen species, DNA damage, inflammatory signaling, and metabolic derangements that can lead to acute cellular senescence. Age-related immune dysfunction may also interfere with proper resolution of injury and clearance of damaged cells [18]. In addition, oxidative stress impairs mitochondrial respiration and energy production, further damaging the cell. Chronic inflammatory states may potentiate oxidative and metabolic abnormalities relevant to renal deterioration [19]. This permits transient ischemic injury to progress to persistent stress signaling and a tissue environment conducive to senescent-cell accumulation.

3.3 Immunological and Treatment-Related Stress

After transplantation renal cells are still exposed to alloimmune recognition, inflammatory mediators, rejection episodes and continuous immunosuppressive therapy. Recurrent immune-mediated injury may result in long-term cellular stress. Calcineurin inhibitors and other therapeutic exposures can lead to metabolic, vascular, and renal toxicity. Growth differentiation factor 15 is an example of stress-responsive biomarkers that illustrate the close connection of cellular stress, tissue injury and adverse responses following major physiological insults [20]. Metabolic stress can be additionally connected to inflammatory and senescence-associated signaling via mitochondrial dysfunction [21]. In aggregate, recurrent immune activation, therapy-induced toxicity, and imperfect tissue repair may progressively reinforce a pro-senescence allograft microenvironment (Table 2) (Figure 1).

Table 2. Major Senescence-Promoting Factors in Kidney Transplantation

Transplant factor	Major cellular stress	Senescence-related consequence	References

Advanced donor age	Accumulated molecular damage	Higher baseline vulnerability	[16]
Pre-existing senescence	Reduced regenerative reserve	Lower graft resilience	[17]
Ischemia–reperfusion	ROS and DNA damage	Acute senescence induction	[18]
Chronic inflammation	Oxidative/metabolic stress	Persistent senescence signaling	[19]
Surgical/cellular stress	Stress-response activation	Impaired tissue recovery	[20]
Mitochondrial dysfunction	Bioenergetic failure	Reinforces inflammatory senescence	[21]

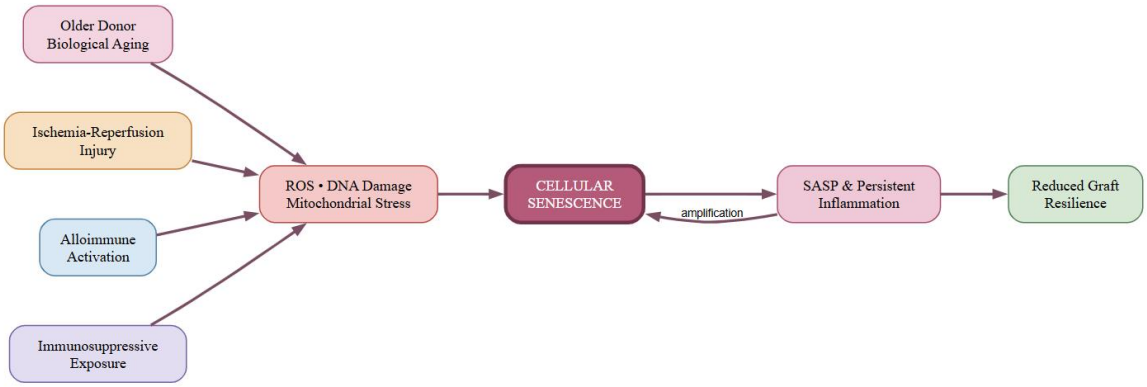

Figure 1. Transplantation-Associated Drivers of Cellular Senescence in the Kidney Allograft

4. Senescent Cells as Drivers of Graft Inflammation and Immune Dysregulation

Persistent inflammatory signaling can be observed in the kidney allograft microenvironment despite irreversible cell-cycle arrest, as a result of changes induced by senescent cells through the senescence associated secretory phenotype (SASP). Typical components of SASP are pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, plus chemokines, growth factors, and matrix-modifying mediators. All of these work to recruit inflammatory cells, affect tissue homeostasis and propagate stress to neighbouring cells. Age-related vascular abnormalities and progressive tissue damage is caused by similar senescence-associated inflammatory mechanisms [22]. It is therefore possible within the transplanted kidney that the continued activity of SASP can drive chronic sterile inflammation that can lead to a vicious cycle of inflammation-induced tissue damage and inflammation-induced senescence.

Graft inflammation is further complicated by the interaction between senescent cells and immune populations. SASP chemokines may facilitate macrophage recruitment and shape macrophage polarization to either perform tissue repair or maintain inflammatory and fibrogenic responses. Persistent tissue inflammation has been more and more associated with cellular senescence, where impaired communication between senescent and immune cells leads to chronic inflammation [23]. The immune surveillance and clearance of damaged or senescent cells is typically performed by T cells and natural killer (NK) cells, but this ability is diminished during immune aging and chronic antigenic stimulation. Therefore, inefficient clearance allows senescent cells to exist and further drive SASP signaling. The duality is clinically relevant, as senescence can have beneficial transient effects, while the accumulation of senescent cells becomes pathological, hindering therapeutic approaches aimed to remove these cells [24]. Chronic renal inflammatory and vascular stress can also sustain oxidative damage, endothelial dysfunction, and recruitment of immune cells, thus continuing renal damage [25].

This process is exacerbated by recipient aging by way of immunosenescence and systemic inflammaging. The aging process is correlated with changes in T-cell composition, a reduced proliferative capacity, the presence of exhaustion-like phenotypes, decreased NK-cell activity, and dysregulated innate immune responses. In cells where immune surveillance is sub-optimal, therefore, cellular senescence may become a source of persistent inflammatory and tissue-destructive signaling [26]. However, in kidney transplantation, systemic immune aging may interact with transplant-associated senescence induced by donor age, ischemia–reperfusion injury, rejection and chronic exposure of the transplanted kidneys to drugs. This interaction may create a self-reinforcing senescence–SASP–immune deregulation axis, which relates intragraft inflammatory amplification with systemic inflammaging. Aging is associated with potentially modifiable changes in the cellular programs, instead of mere chronological deterioration, as shown by age-related shifts in cellular identity and tissue states [27]. These processes, taken together, select senescent cells as active players in chronic inflammation and immune dysfunction, which could drive accelerated biological aging of grafts and thus influence long-term deterioration of allografts (Figure 2).

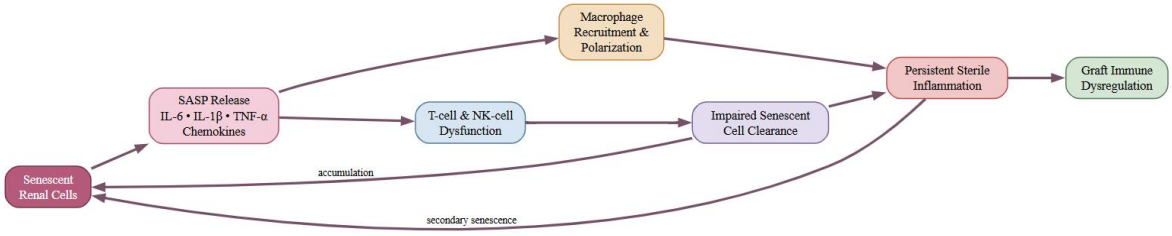

Figure 2. Senescence–SASP–Immune Dysregulation Axis in the Transplanted Kidney

5. From Cellular Senescence to Fibrosis and Chronic Allograft Dysfunction

The ability of the kidneys to repair post repeated cellular stress plays a significant role in the development of chronic allograft dysfunction. Ischemia–reperfusion injury produces metabolic, inflammatory and oxidative disturbances that may lead to impairment of cell recovery and contribute to the initiation of persistent injury responses [28]. In tubular epithelial cells, chronic activation of the senescence pathways leads to stable cell-cycle arrest, allowing only for limited replacement of damaged cells. Affected tubules may be in a maladaptive repair state in which there is incomplete recovery of the epithelial layer, phenotypic changes in the epithelial cells, and progressive decline in number of functioning renal epithelial cells. Preservation of tubular polarity and intracellular organization are crucial for normal epithelial function, demonstrating the negative effect of tubular-cell homeostasis disruption on renal integrity [29].

Then, a persistent senescence allows fibrogenic remodeling to take place. With aging, epithelial and stromal cells may produce inflammatory and profibrotic signals that lead to activation of stromal cells and deposition of extracellular matrix. TGF-β signaling is especially important due to its ability to trigger the transition of fibroblasts to myofibroblasts and synthesis of collagen and other matrix molecules. There are also evidences that shifting the environment of the cells could improve fibrosis as a function of aging, suggesting a mechanistic connection between aging-related cell environment and pathological tissue remodeling [30]. Progressive matrix accumulation compromises normal renal architecture and facilitates tubular atrophy and interstitial fibrosis thus reducing the functional capacity of the remaining nephrons. A chronic inflammatory state may also contribute to systemic immunosenescence, which can then maintain this process, as age-related changes in the immune system, such as those caused by chronic exposure to cytomegalovirus, can be responsible for these inflammatory changes [31]. On the other hand, preserved surveillance by NK cells may be relevant to the clearance of senescent cells and to the prevention of the deterioration of tissues with age [32].

The net effect is reduced graft resistance. With a decline in the number of functioning nephrons, the remaining ones are subjected to a higher physiological load and are more vulnerable to the subsequent immunological, metabolic and hemodynamic insults. Transplant evaluation and outcomes stratified by solid-organ transplantation are modified by aging-related changes; these changes are known to be important [33]. Other systemic changes such as changes in the microbiome associated metabolic and inflammatory pathways could also play a role in tissue homeostasis and regenerative processes [34]. Recurrent graft injury may be restricted by age of the hematopoietic stem-cell and immune compartments which can further impact immune competence and inflammatory regulation [35]. These mechanisms interact and form a continuum: transplant injury, ongoing senescence, maladaptive repair, fibrogenic signaling, tubular atrophy and interstitial fibrosis, and impaired renal function. The progressive structural damage can be clinically expressed as reduced eGFR and chronic allograft dysfunction, which can lead to susceptibility for graft failure. This mechanistic trajectory should then be reflected and should highlight the possibility of senescence serving as a step towards irreversible fibrotic graft damage with recurrent transplantation-related injury (Table 3) (Figure 3).

Table 3. Senescence-Associated Mechanisms Linking Renal Injury to Chronic Allograft Dysfunction

Pathological stage	Senescence-associated mechanism	Graft consequence	References
Tubular injury	Persistent cell-cycle arrest	Impaired epithelial regeneration	[29]
Maladaptive repair	Incomplete cellular recovery	Loss of functional epithelium	[30]
Fibroblast activation	Profibrotic signaling	Matrix deposition	[31]
Immune aging	Persistent inflammatory milieu	Sustained tissue injury	[32]
Reduced surveillance	Impaired removal of damaged cells	Senescent-cell persistence	[33]
Progressive remodeling	Fibrosis and nephron loss	Chronic graft dysfunction	[34,35]

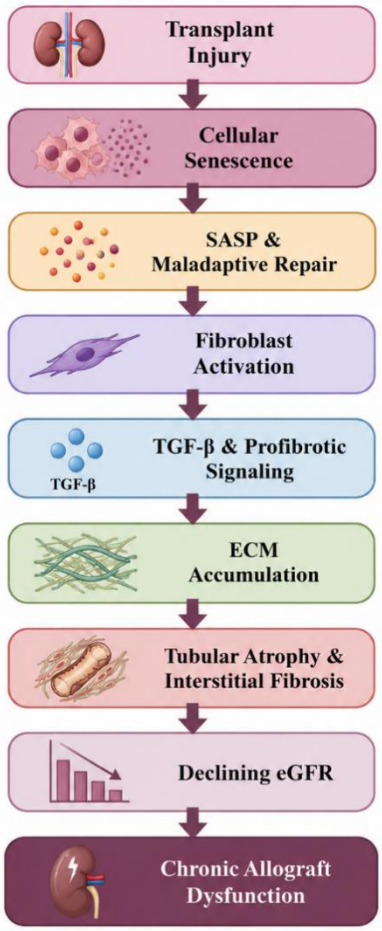

Figure 3. Mechanistic Progression from Transplant Injury to Fibrosis and Chronic Graft Dysfunction

6. Detecting and Measuring Senescence in Kidney Transplantation

6.1 Tissue-Based Biomarkers

Assessment of tissue remains at the core of the identification of senescent cells in kidney allografts as it allows to define the local distribution of molecular changes to specific renal compartments. They can be identified by elevated levels of p16^INK4a^ expression, p21 expression, DNA-damage foci, senescence-associated β-galactosidase activity, and accumulation of lipofuscin. When interpreting, be careful as each marker is not specific for senescence. It is also important to consider immune-cell composition because the state of CD8+ T cells can significantly affect the inflammatory tissue context and cell regulation [36]. The use of several senescence markers in combination with histopathological evaluation might thus enhance specificity in detection of graft localized senescence.

6.2 Circulating and Urinary Biomarkers

Non-invasive biomarkers would allow for longitudinal monitoring of senescence without the need for serial allograft biopsies. Candidate circulating indicators include SASP-associated cytokines, chemokines, growth factors and other inflammatory mediators. Renal aging markers such as Klotho may provide complementary information about systemic and kidney-specific biological aging [37]. Urine has special advantages in that it is a direct mirror of renal cellular activity. The molecular content of urinary extracellular vesicles can be cell-specific, and recently podocyte senescence has been identified in this way in human renal disease [38]. Cell-free nucleic acids and molecular signatures may augment dynamic graft surveillance.

6.3 Omics and Emerging Technologies

Opportunities for characterizing senescence beyond individual biomarkers using omics technologies. Transcriptomics and proteomics can reveal coordinated molecular signatures associated with cellular aging, inflammation, metabolic dysfunction and tissue injury that complement emerging biomarker frameworks across interrelated renal and systemic disorders [39]. Single cell RNA sequencing can detect senescence associated transcriptional states in tubular, endothelial, stromal and immune populations, and spatial transcriptomics can detect their anatomical distribution and cellular interactions. These approaches may be particularly informative following ischemia-reperfusion injury, a major transplantation stressor with complex molecular consequences [40]. Ultimately, integrated multi-omic signatures may improve classification of senescence and graft-risk stratification (Table 4).

Table 4. Current and Emerging Approaches for Detecting Senescence in Kidney Transplantation

Detection approach	Representative markers/technology	Potential application	References
Tissue biomarkers	p16^INK4a^, p21, SA-β-gal	Localize graft senescence	[36]

Aging biomarkers	Klotho-related signals	Biological aging assessment	[37]
Urinary biomarkers	Extracellular vesicles	Non-invasive renal monitoring	[38]
Circulating biomarkers	SASP/inflammatory mediators	Longitudinal surveillance	[39]
Transcriptomics	Senescence gene signatures	Cell-state classification	[39]
Single-cell/spatial omics	Cell-specific expression maps	Identify senescent niches	[40]

7. Clinical and Prognostic Significance of Senescence

Cellular senescence is relevant to kidney transplantation, both for the assessment of the donor and for long-term graft surveillance. Currently, assessment of the conventional donor is largely based on chronological age, kidney function, comorbidities, histological features, and procurement related factors, but chronological age does not always correlate with the biological status of an organ. Assessing senescence burden may be a useful complementary measure of biological graft age, as it would identify a cumulative burden of cell damage, diminished regeneration potential and vulnerability to future stress. Oxidative stress and endothelial dysfunction are strongly related phenomena that can potentially cause vascular damage and impair tissue resilience [41]. Therefore, it is possible that this assessment of senescence-associated molecular changes might distinguish between biologically resilient kidneys and grafts with accelerated senescence despite identical chronological characteristics.

Senescence burden may be also be prognostic after transplant. Pre-existing or rapidly induced senescence in the kidneys may lead to reduced ability to overcome ischemia–reperfusion injury, and thus to higher risk of delayed graft function. Senescent cells may constantly signal inflammation, affect epithelial regeneration, cause endothelial dysfunction, and stimulate fibrogenic remodeling; these are all plausible mechanisms for the relationship between persistent senescent cells and acute and chronic rejection, progressive interstitial fibrosis and declining renal function. Experimental data that metabolic and immunomodulatory pathways can modify renal senescence further supports the idea that senescence is an active biological process, not just a marker of chronological age [42]. Longitudinal assessment of changes that occur during senescence in grafted organs may therefore offer a means of gaining insight into the trajectory of graft deterioration, and may be able to identify recipients at high risk of significant functional decline prior to it occurring.

These features make cellular senescence a promising framework to serve as a biomarker in precision transplantation. Multidimensional profiles for individualized risk stratification could be created by combining tissue markers (e.g., p16^INK4a^, p21, DNA-damage indicators, and lipofuscin) with circulating SASP factors and urinary EVs, as well as transcriptomic and proteomic signatures. Serial assessment may allow biological graft aging to be monitored and treatment responses to be assessed, as well as earlier detection of maladaptive repair, or fibrosis. However, translation is not straightforward due to senescence being heterogeneous, dynamic, and context-dependent and the absence of a single biomarker identifying all populations of senescent cells. More general senescence studies also highlight the need to address biomarker specificity, therapeutic targeting and clinical translation problems [43]. A validation of composite senescence signatures with delayed graft function, rejection, progression of fibrosis, estimated glomerular filtration rate decline, and graft survival in future kidney transplant studies are, therefore, warranted. This evidence can then enable senescence profiling to be leveraged clinically as a tool for the selection of donors, the frequency of their surveillance, and individual therapeutic decisions (Figure 4).

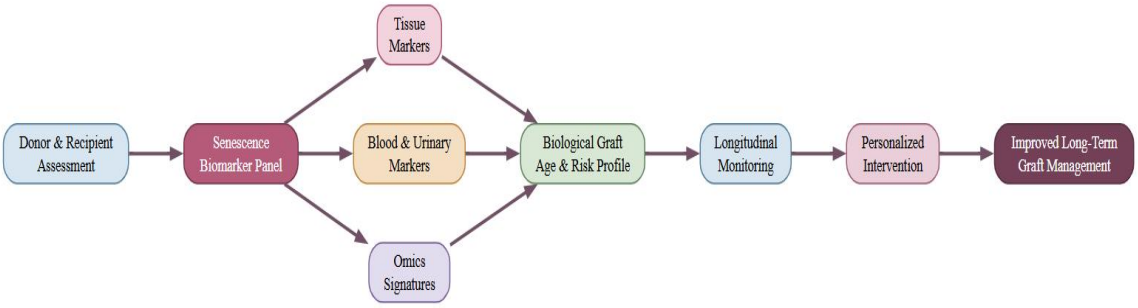

Figure 4. Proposed Clinical Framework for Senescence-Based Precision Kidney Transplantation

8. Targeting Senescent Cells: Therapeutic Opportunities

8.1 Senolytic Therapies

Senolytic therapy is intended to selectively clear senescent cells by exploiting their dependence on particular pro-survival pathways. In kidney transplantation, reduction of persistent senescent-cell burden could theoretically abrogate SASP-driven inflammation, restore a more favorable regenerative environment, and slow fibrotic remodeling. We are testing dasatinib plus quercetin, fisetin and other novel agents that are designed to be more specific to the cells. Strategies targeting dysfunctional aged immune populations have shown the wider therapeutic potential

of manipulating immunosenescence [44]. However, transplantation-specific evidence is limited and selective removal of pathological senescent cells without disturbing beneficial transient senescence needs to be carefully evaluated.

8.2 Senomorphic and SASP-Modulating Strategies

Senomorphic approaches, compared to senolytics, do not kill senescent cells but rather suppress their deleterious functions. Modulation of mTOR, NF-κB, JAK/STAT and associated inflammatory pathways could reduce SASP production and thus limit cytokine release, paracrine senescence and chronic graft inflammation. Research on regeneration and longevity increasingly combines strategies for improving tissue repair and functional restoration with control of cellular aging [45]. Such approaches may be especially attractive in kidney transplantation where indiscriminate cell elimination could compromise tissue integrity. Selective SASP modulation may allow for the maintenance of beneficial senescence-associated responses while blunting chronic inflammatory and fibrogenic signaling.

8.3 Timing of Senescence-Targeted Intervention

Whether senescence-targeted treatments protect or harm kidney allografts may depend on the timing of therapeutic intervention. Potential opportunities include donor pretreatment, intervention during ex vivo organ preservation, peri-transplant administration, and treatment after chronic dysfunction appears. Aging is due to complex molecular processes, not one pathway, indicating that interventions need to target multi aging mechanisms at the biological level of graft injury [46]. The ex vivo approach is particularly attractive because it would reduce senescent-cell burden before implantation with minimal systemic exposure of the recipient. Biomarker-guided therapy may help to further define optimal therapeutic windows.

8.4 Translational Barriers and Safety

The clinical translation of senotherapy is faced with substantial challenges, including heterogeneity of senescent cells, lack of universal specific biomarkers, off-target toxicity, and unknown long-term effects of senescent population elimination. These issues are further compounded in transplant recipients receiving multidrug immunosuppression, where drug interactions and altered immune surveillance require careful consideration. Mitochondrial dysfunction [47] is another interconnected driver of renal injury and CKD progression that may influence therapeutic responsiveness. Future trials should thus include cell-specific biomarkers, pharmacokinetic assessment, graft-function monitoring, and immune safety endpoints to ascertain whether senolytics or senomorphics can safely improve long-term kidney allograft outcomes (Table 5) (Figure 5).

Table 5. Senescence-Targeted Therapeutic Strategies Relevant to Kidney Transplantation

Strategy	Primary target/action	Potential transplant benefit	References
Senolytics	Eliminate senescent cells	Reduce pathological cell burden	[44]
Senomorphics	Suppress SASP activity	Limit chronic inflammation	[45]
Pathway modulation	mTOR/NF-κB/JAK-STAT	Reduce inflammatory signaling	[46]
Mitochondrial targeting	Improve cellular bioenergetics	Reduce senescence-promoting stress	[45]
Ex vivo intervention	Treat graft before implantation	Minimize systemic exposure	[46]
Biomarker-guided therapy	Select high-risk grafts/recipients	Improve treatment precision	[47]

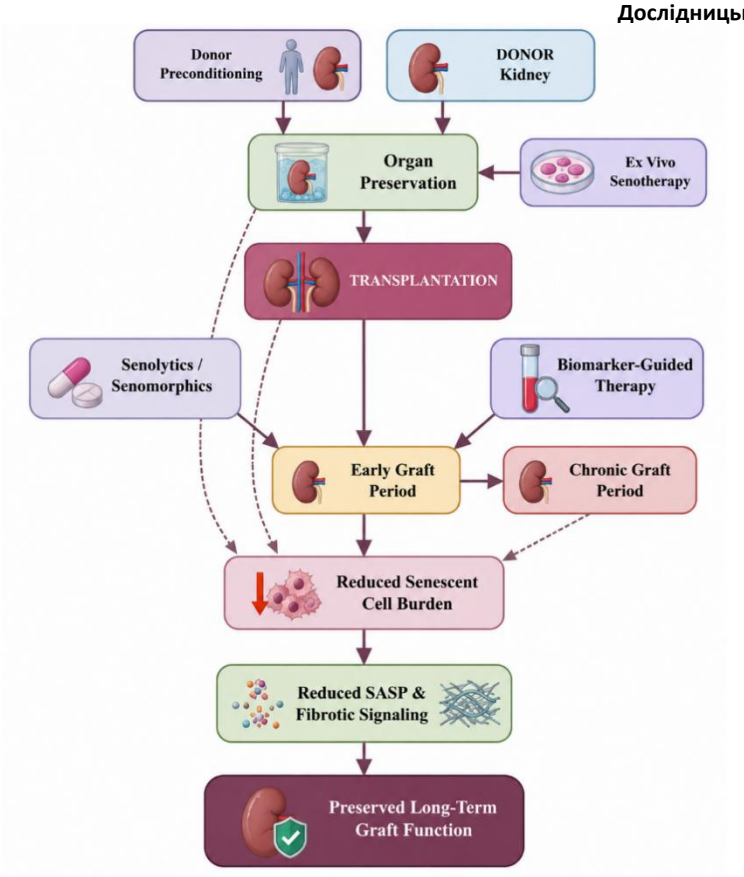

Figure 5. Therapeutic Intervention Points for Targeting Senescence Across the Kidney Transplantation Pathway

9. Current Knowledge Gaps and Future Research Directions

Although there is increasing evidence that cellular senescence plays a role in the aging of kidney allografts, there are significant conceptual and translational challenges. There is a need for standardized definitions and validated panels of biomarkers since none of them alone can reliably distinguish senescence from transient cell-cycle arrest, inflammation or tissue injury. Senescence-associated signals should also be considered causal, since they could be responsible for graft deterioration or markers of graft injury. To elucidate the timing of senescence and its correlation with rejection, fibrosis, functional deterioration, and graft failure in human studies with serial biospecimens and clinical outcome is therefore warranted. Future studies should combine donor biological age with recipient immunosenescence and systemic inflammaging to describe the impact of these two on graft trajectories. Single-cell RNA sequencing and spatial transcriptomics may enable the identification of populations of senescent tubular, endothelial, stromal and immune cells and their anatomical localization and inter-cell contacts. The data might be used to develop composite senescence signatures for donor-organ evaluation, post-transplant surveillance and high risk graft identification. From a therapeutic point of view, there is a need for kidney and cell-specific senolytics to ensure that the beneficial transient senescence is maintained, while minimizing the off-target effect. Special focus should be placed on interactions with maintenance immunosuppression and other issues, such as impact on immune surveillance and risk for infections. The optimal timing of treatment, patient populations, and clinically meaningful endpoints should be determined by biomarker-driven clinical trials. Ultimately, the integration of multi-omics data with machine-learning technologies may be able to predict senescence, differentiate biologically meaningful molecular signatures and inform individualized decisions throughout the kidney transplantation landscape.

10. Conclusion

The relationship between transplantation associated stress and accelerated kidney allograft ageing may be biologically connected through cellular senescence. Accumulation of senescent cells in renal compartments and immune compartments can be induced by aging in donors, ischemia–reperfusion injury, oxidative stress, alloimmune responses, and treatment-related insults. If the senescent cells remain, they can then affect the functioning of the graft by influencing inflammatory signalling, changing the behaviour of immune cells and transferring senescence to neighbouring cells via the SASP. These processes offer a mechanistic link between repeated cellular damage, impaired tubular regeneration, maladaptive repair, activation of the fibroblasts, extracellular matrix accumulation and progressive interstitial fibrosis. Senescence might thus not only be a sign of chronological tissue ageing, but it can also be linked to the loss of graft resilience and chronic allograft dysfunction. The potential to use tissue, circulating, urinary and omics-derived senescence biomarkers to estimate biological graft age, identify patients at higher risk for graft and to monitor graft deterioration, and support the use of personalized post-

transplant clinical management. Moreover, therapies that specifically kill the senescent cells (senolytics) or reduce the harmful SASP activity (senomorphic therapies) offer additional strategies to break this pathological continuum. Nevertheless, senescence is context and heterogeneity dependent and transient senescence can still have beneficial physiological functions. Robust longitudinal human studies, well-established biomarker frameworks, and well-conceived clinical trials are thus necessary to safely integrate senescence-targeted interventions into standard kidney transplant care.

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