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# Renal Aging and Kidney Transplantation

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<http://dx.doi.org/10.5772/55469>

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## 1. Introduction

Kidney transplantation is the preferred therapy for most patients with end-stage renal disease. The demand for kidney grafts however far exceeds the supply of available organs. As a result, transplant teams increasingly use organs from extended criteria donors, of older age or with significant comorbidity. This use of extended criteria organs is not without consequences.

Older donor age is strongly related to impaired kidney graft function and graft failure because older kidneys are limited in their capacity to tolerate injury [1]. Aging is associated with renal structural changes and functional decline. Older kidneys lose renal parenchyma and through this have a decreased renal plasma flow and tubular dysfunction. The mechanisms required for tissue repair after damage become less reliable, resulting in a decrease in repair capacity. This functional decline in the potential to repair and regenerate is often considered a hallmark of the aging phenotype [2] [3].

Another major component of the aging phenotype is replicative or cellular senescence, which is defined as permanent, irreversible growth arrest. In this chapter we draw the parallel between the aging kidney in the transplantation setting and cellular senescence.

## 2. Impact of older donor age on transplantation outcome

The success of organ transplantation in patients with end-stage renal damage gave rise to waiting lists and organ shortage. This in itself led to the increasing use of kidneys from older or expanded criteria donors for transplantation. In 2002 the term Expanded criteria donor (ECD) was codified to be deceased donors aged 60 years of older and those aged 50-59 years with at least 2 of the following characteristics: history of hypertension, serum creatinine level

greater than 1.5 mg/dL and cerebrovascular cause of death. The risk of graft failure after an ECD kidney transplant is 70% higher than after a non- ECDtransplant [4].

Also Ojo *et al.* have reported on the survival of recipients of marginal kidneys, defined as kidneys with one or more of the following pretransplant factors: donor age >55 years, non-heartbeating donor, cold ischemia time >36 h, and donor hypertension or diabetes mellitus of >10 years duration. Also in this study, marginal kidney transplants had a lower allograft outcomes compared with organs from ideal donors [5].

In another study, Woo *et al.* compared two groups only divided by age. There was a larger increase in graft failure rates of kidneys from donors >55 years of age. Also the mean estimated glomerular filtration rate 6 months post-transplant and the stability of the glomerular filtration rate in the first transplant year were significantly higher in the recipients of donors <55 years [6].

Recent data on 1063 kidney grafts from living donors confirm the association between older donor age and graft outcome even after living donation, where living donors are screened prior to transplantation and comorbidities are avoided. Increasing living donor age was associated with lower kidney function after transplantation, loss of glomerular filtration rate beyond 1 year and reduced graft survival [7].

With the increasing use of older and extended criteria donor kidneys, the intrinsic quality of the kidneys at transplantation is nowadays much more important for the post-transplant histological evolution and long-term graft survival than acute T-cell mediated rejection [1, 8, 9]. The causes by which older kidneys lose function after transplantation remain however incompletely understood. This may involve both early and late-onset processes and is likely to be found mainly in a significant effect of donor age on the subclinical progression of chronic histological damage [10]. In a large study using protocol biopsies, it was not only demonstrated that higher donor age is the major determinant of this non-specific chronic allograft damage, but also that the association between donor age and post-transplant histological damage is independent of the histological quality of the graft at implantation [11]. This suggests that donor age and the aging process in itself are playing an independent role on renal allograft histological progression and long-term outcome. From these studies, it can even be hypothesized that the aging process in itself is accelerated after transplantation, and contributes to transplant outcome [10].

### 3. Mechanisms of renal aging

It is essential to distinguish aging from age-related disease. Aging itself is not a disease but seems to be the greatest risk factor for age-related pathology [12]. The altered molecules with aging involve many different pathways, including cell integrity, cellular proliferation, cell transport and energy metabolism. Many of these molecules and processes are not unique to aging and are likely general pathways involved in tissue damage and repair. Aging is a programmed biological process that is associated with small transcriptional differences in many genes, rather than large expression changes in a small number of genes [13-16].

The aging phenotype is the consequence of cellular senescence, of increased susceptibility to apoptosis with older age, of impaired regeneration and repair, of decreased functional capacity of stem cells and progenitor cells, of changes in the expression of growth factors with increasing age, of mitochondrial changes, of dysregulation of autoregulatory pathways and of immune system alterations and different immunogenicity of older tissue.

Of the previously mentioned mechanisms of aging, cellular senescence is classically seen as one of the most important drivers of the aging process. Cellular senescence leads to permanent and irreversible growth arrest and was detected in seminal *in vitro* studies by Hayflick and Moorhead [17, 18]. Senescent cells remain viable but show a changed morphology, greater heterogeneity, expression of SA- $\beta$ -gal, accumulation of lipofuscin granules and lack of response to mitogenic stimuli.

Cellular senescence is a specific response of mitotically active cells to various stressors. It is determined by multiple factors, including the genetic regulation of metabolism, time, the number cell cycles of replication, and most importantly the answer to injury and stress [11, 19]. Examples of these different factors are telomere shortening and telomere dysfunction, non-telomere DNA damage (e.g. due to X-rays, oxidative stress and UV irradiation), mitogenic signals including those produced by oncogens (which also cause DNA damage) and non-genotoxic stress like chromatin perturbation (epigenetic changes) and other stress factors [20, 21]. Cellular senescence thus not only comprises exhaustion of a predetermined proliferative capacity (intrinsic senescence or replicative senescence), but can also be induced by extrinsic factors (stress-induced premature senescence).

In this light, the impact of cellular senescence goes beyond the importance for aging. Cellular senescence pathways play essential roles in tumor suppression, tumor promotion and tissue repair.

There is increasing evidence that cellular senescence is a tumor suppressive system (by inducing growth arrest) and a tumor-promoting phenomenon (by secretion of inflammatory cytokines) [22]. To reconcile the apparently conflicting impact of cellular senescence on cancer, Campisi *et al.* suggest that cellular senescence is a biological process that was selected to promote fitness in young organisms (beneficial: tumor suppression, tissue regeneration), but is deleterious in old organisms (harming: aging, tumor promotion) [23]. In the evolution, senescence pathways evolved in an environment where organism lifespan was short. Therefore tumor-suppressor mechanisms needed to be effective for only a relatively short (reproductive) period [21]. Even if this mechanism was harmful later on, this would not affect selective pressure. This concept is the essence of the “antagonistic pleiotropy hypothesis” and makes us understand the senescence concept much better [23].

#### **4. The replicative senescence pathways in renal disease and transplantation**

Replicative senescence depends mainly on two pathways: the ARF-p53-p21 signaling pathway that is partially telomere dependent and the p16-pRb pathway, which is independent of telomere dysfunction. These pathways interact but can act independently [21, 24].

### 1. Replicative senescence pathways ARF-p53-p21 (associated with telomere shortening).

Telomeres comprise tandem TTAGGG repeats of 5000 to 15000 base pairs that normally reside at the ends of chromosome ends as protection and prevent end-to-end fusion of chromosomes. Telomeric DNA is synthesized and its length is regulated by telomerase. Most somatic cells don't express telomerase and mature telomeres tend to progressively shorten with every cell division. The crucial role of telomerase absence in the telomere shortening is proven *in vitro* as telomere shortening can be bypassed by transfection with telomerase [25].

Telomere length reflects several important factors such as heredity, telomerase activity, the efficiency of telomere-binding proteins, the rate of cellular proliferation and oxidative stress in the milieu. Although telomere length is partly heritable, there are major differences in telomere length even among monozygotic twins, which suggests that environmental factors (e.g. hyperglycemia, oxidative stress [26, 27]) play a major role in telomere attrition and aging.

When the telomeres become critically short (reach the "Hayflick limit") a classical DNA-damage response is triggered with participation of several protein kinases (e.g. ATM and CHK2), adaptor proteins (e.g. 53BP1 and MDC1) and chromatin modifiers (e.g. gammaH2AX). Telomere shortening also leads to activation of the p53 pathway (through p53 phosphorylation) and herewith associated p21 (also termed CDKN1a, p21Cip1, Waf1 or SD11) expression. Also other DNA damage responses (DDRs) and ARF (alternate reading frame, p14) can lead to activation of the p53 pathway. SIRT1 (sirtuin 1) can negatively regulate p53 localization to the nucleus and its function as a transcription factor.

The clinical importance of telomere shortening has been suggested in a very interesting study, where leukocyte telomere length was used as a biomarker of aging. In this study, the association between telomere length and various disease processes was independent of chronological age, which suggests the value of telomere length measurement as a biomarker of biological or cellular age [28].

In contrast to, e.g. blood cells, the association between age and telomere shortening in renal tissue was only studied scarcely. The supposed association with reduced regenerative capacity during aging and chronic diseases, and after acute injury, seems valid but has never been proven in humans. Only Westhoff's study in telomerase deficient mice suggests that critical telomere shortening in kidneys leads to increased senescence and apoptosis, thereby limiting regenerative capacity [29].

In adult kidneys, telomerase activity is very low, which results in telomere shortening by every cell division, as was demonstrated by Melk *et al* [25]. Also ischemia can induce telomere shortening as has been shown in different animal models [30-32]. Finally, glomerular diseases like IgA nephropathy, lupus nephritis and focal glomerulosclerosis are associated with increased p53 expression compared to kidneys without lesions, both in animals [33] and in humans [34, 35]. Whether this relates to telomere length has not been studied to date.

After bone marrow transplantation telomere shortening occurs significantly more rapidly than would be expected in graft-derived leukocytes. Probably due to the replicative stress on the blood cell caused the kinetics of haemopoietic engraftment [36]. After solid organ transplantation there are arguments to state that transplantation is associated with accelerated shortening of telomere length in the transplanted cells [12]. In transplanted renal cells, there is



evidence for an increased cell turnover at the time of transplantation and a phase of increased cell regeneration directly after transplantation that correlates with cold ischemia time [37, 38]. Also a small study showed that shorter telomere length in biopsies obtained at implantation was associated with lower graft function at 12 months after transplantation, but no correlation with p21 or p53 was found [39]. These studies need further validation to confirm the role of telomere shortening on transplant outcome.

## 2. p16-pRB pathways (independent of telomere dysfunction).

DNA damage by environmental stress is the main stressor for activation of the p16-pRB pathway although dysfunctional telomeres can also induce p16 [21]. This telomere-independent senescence pathway is currently often referred to as 'STATIS' (Stress and Aberrant Signaling-Induced Senescence). P16 (encoded by *CDKN2A*) is an important tumor suppressor in the p53 pathway. P16 keeps pRB in an active hypophosphorylated form, which inhibits cell proliferation and induces growth arrest [12]. The p53 and p16-pRB pathways interact with each other and there is a reciprocal regulation.

In native kidneys increased p16 expression is found in human kidneys with glomerular disease [16], interstitial fibrosis, diabetic nephropathy [40] and animal kidneys with hypertension [41]. Furthermore p16 is induced by cyclosporine, catch up growth in low birth weight and is attenuated by calorie restriction [12]. Finally, p16 expression correlates significantly with kidney age [42].

Like the p53 pathway p16 expression relates to ischemia-reperfusion, at least in mice [43]. Furthermore, a rapid increase in p16 expression after transplantation has been described in murine kidney grafts, which was most pronounced in older animals. Whether these findings are also valid in humans, remains unknown.

## 5. Summary

In summary, there is extensive data that the outcome of kidney transplantation is heavily influenced by the age of the transplanted kidneys. There is some scant evidence that transplantation in itself increases cell turnover and leads to accelerate replicative senescence. Whether the association between older kidneys and impaired graft outcome relates to this accelerate replicative senescence after transplantation is however not clear, and the few suggestions in the literature need to be validated in large-enough patient cohorts.

## Author details

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## References

- [1] Meier-Kriesche, H.U., et al., Lack of Improvement in Renal Allograft Survival Despite a Marked Decrease in Acute Rejection Rates Over the Most Recent Era. *Am J Transplant*, 2004. 4(3): p. 378-383.
- [2] Epstein, M., Aging and the kidney. *J.Am.Soc.Nephrol.*, 1996. 7(8): p. 1106-1122.
- [3] Zhou, W., et al., Predominant role for C5b-9 in renal ischemia/reperfusion injury. *Journal of Clinical Investigation*, 2000. 105(10): p. 1363-1371.
- [4] Port, F.K., et al., Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation*, 2002. 74(9): p. 1281-6.
- [5] Ojo, A.O., et al., Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J.Am.Soc.Nephrol.*, 2001. 12(3): p. 589-597.
- [6] Woo, Y.M., et al., The advanced age deceased kidney donor: current outcomes and future opportunities. *Kidney Int*, 2005. 67(6): p. 2407-2414.
- [7] Noppakun, K., et al., Living donor age and kidney transplant outcomes. *Am J Transplant*, 2011. 11(6): p. 1279-1286.
- [8] Summers, D.M., et al., Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet*, 2010. 376(9749): p. 1303-1311.
- [9] Opelz, G. and B. Dohler, Influence of immunosuppressive regimens on graft survival and secondary outcomes after kidney transplantation. *Transplantation*, 2009. 87(6): p. 795-802.
- [10] Naesens, M., et al., Donor age and renal P-glycoprotein expression associate with chronic histological damage in renal allografts. *J Am Soc Nephrol*, 2009. 20(11): p. 2468-80.
- [11] Halloran, P.F., A. Melk, and C. Barth, Rethinking chronic allograft nephropathy: the concept of accelerated senescence. *J.Am.Soc.Nephrol.*, 1999. 10(1): p. 167-181.
- [12] Naesens, M., Replicative senescence in kidney aging, renal disease, and renal transplantation. *Discov Med*, 2011. 11(56): p. 65-75.
- [13] Weindruch, R., et al., Microarray profiling of gene expression in aging and its alteration by caloric restriction in mice. *J Nutr.*, 2001. 131(3): p. 918S-923S.
- [14] Rodwell, G.E., et al., A transcriptional profile of aging in the human kidney. *PLoS.Biol.*, 2004. 2(12): p. e427.

- [15] McCarroll, S.A., et al., Comparing genomic expression patterns across species identifies shared transcriptional profile in aging. *Nat.Genet.*, 2004. 36(2): p. 197-204.
- [16] Melk, A., et al., Increased expression of senescence-associated cell cycle inhibitor p16INK4a in deteriorating renal transplants and diseased native kidney. *Am J Transplant.*, 2005. 5(6): p. 1375-1382.
- [17] Kawai, T., et al., HLA-mismatched renal transplantation without maintenance immunosuppression. *N.Engl.J.Med.*, 2008. 358(4): p. 353-361.
- [18] Hayflick, L. and P.S. Moorhead, The serial cultivation of human diploid cell strains. *Exp.Cell Res.*, 1961. 25: p. 585-621.
- [19] Hayflick, L., Biological aging is no longer an unsolved problem. *Ann.N.Y.Acad.Sci.*, 2007. 1100: p. 1-13.
- [20] Finkel, T., M. Serrano, and M.A. Blasco, The common biology of cancer and ageing. *Nature*, 2007. 448(7155): p. 767-774.
- [21] Campisi, J. and F.F. dda di, Cellular senescence: when bad things happen to good cells. *Nat.Rev.Mol.Cell Biol.*, 2007. 8(9): p. 729-740.
- [22] Coppe, J.P., et al., Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS.Biol.*, 2008. 6(12): p. 2853-2868.
- [23] Campisi, J., Cellular senescence: putting the paradoxes in perspective. *Curr.Opin.Genet.Dev.*, 2010.
- [24] Collado, M. and M. Serrano, Senescence in tumours: evidence from mice and humans. *Nat.Rev.Cancer*, 2010. 10(1): p. 51-57.
- [25] Melk, A., et al., Telomere shortening in kidneys with age. *J Am Soc Nephrol*, 2000. 11(3): p. 444-453.
- [26] Yoshida, T., et al., ATF3 protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol*, 2008. 19(2): p. 217-224.
- [27] Avogaro, A., S.V. de Kreutzenberg, and G.P. Fadini, Insulin signaling and life span. *Pflugers Arch.*, 2010. 459(2): p. 301-314.
- [28] Wong, J.M. and K. Collins, Telomere maintenance and disease. *Lancet*, 2003. 362(9388): p. 983-8.
- [29] Westhoff, J.H., et al., Telomere shortening reduces regenerative capacity after acute kidney injury. *J Am Soc Nephrol*, 2010. 21(2): p. 327-336.
- [30] Joosten, S.A., et al., Telomere shortening and cellular senescence in a model of chronic renal allograft rejection. *Am J Pathol.*, 2003. 162(4): p. 1305-1312.



- [31] Kelly, K.J., et al., P53 mediates the apoptotic response to GTP depletion after renal ischemia-reperfusion: protective role of a p53 inhibitor. *J Am Soc Nephrol*, 2003. 14(1): p. 128-138.
- [32] Megyesi, J., et al., The p53-independent activation of transcription of p21 WAF1/CIP1/SDI1 after acute renal failure. *Am J Physiol*, 1996. 271(6 Pt 2): p. F1211-F1216.
- [33] Turner, C.M., et al., Increased expression of the pro-apoptotic ATP-sensitive P2X7 receptor in experimental and human glomerulonephritis. *Nephrol Dial. Transplant*, 2007. 22(2): p. 386-395.
- [34] Takemura, T., et al., Proto-oncogene expression in human glomerular diseases. *J Pathol.*, 1996. 178(3): p. 343-351.
- [35] Qiu, L.Q., R. Sinniah, and S.I. Hsu, Coupled induction of iNOS and p53 upregulation in renal resident cells may be linked with apoptotic activity in the pathogenesis of progressive IgA nephropathy. *J Am Soc Nephrol*, 2004. 15(8): p. 2066-2078.
- [36] Wynn, R.F., et al., Accelerated telomere shortening in young recipients of allogeneic bone-marrow transplants. *Lancet*, 1998. 351(9097): p. 178-181.
- [37] Oberbauer, R., et al., Apoptosis of tubular epithelial cells in donor kidney biopsies predicts early renal allograft function. *J.Am.Soc.Nephrol.*, 1999. 10(9): p. 2006-2013.
- [38] Vinuesa, E., et al., Macrophage involvement in the kidney repair phase after ischaemia/reperfusion injury. *J Pathol.*, 2008. 214(1): p. 104-113.
- [39] Koppelstaetter, C., et al., Markers of cellular senescence in zero hour biopsies predict outcome in renal transplantation. *Aging Cell*, 2008. 7(4): p. 491-497.
- [40] Verzola, D., et al., Accelerated senescence in the kidneys of patients with type 2 diabetic nephropathy. *AJP - Renal Physiology*, 2008. 295(5): p. F1563-F1573.
- [41] Westhoff, J.H., et al., Hypertension induces somatic cellular senescence in rats and humans by induction of cell cycle inhibitor p16INK4a. *Hypertension*, 2008. 52(1): p. 123-129.
- [42] Chkhotua, A.B., et al., Increased expression of P21((WAF1/CIP1)) CDKI gene in chronic allograft nephropathy correlating with the number of acute rejection episodes. *Transplant Proc.*, 2003. 35(2): p. 655-658.
- [43] Hochegger, K., et al., p21 and mTERT are novel markers for determining different ischemic time periods in renal ischemia-reperfusion injury. *AJP - Renal Physiology*, 2007. 292(2): p. F762-F768.