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Aging Kidney Transplantation

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ABSTRACT

There are several immunological and non-immunological factors related to renal graft deterioration, and histological lesions such as interstitial fibrosis and tubular atrophy overlap with those observed in aging kidneys. Consequently, it has been proposed that kidney transplant senescence could contribute to graft loss. The process of cell senescence displays characteristics such as an increased expression of specific aging suppressor genes, shortened telomeres, mitochondrial changes, increased expression of negative regulators of the cell cycle, and immunological senescence. Additionally, tubular frailty characterizes the aged kidney, making it more susceptible to ischemia, reperfusion, toxic injury, and consequently, to inflammation. Moreover, renal tissue injury predisposes the older graft not only to progressive deterioration due to glomerular hyperfiltration, but also triggers acute rejection due to increased immunogenicity. In conclusion, renal graft senescence is a complex process, and its better understanding will help the nephrologist in its management in order to achieve a longer graft survival. (REV INVES CLIN. 2016;68:68-74)

Key words: Aging. Senescence. Kidney. Transplant.

INTRODUCTION

Kidney transplant is the therapy of choice for patients with end-stage chronic renal disease, increasing their quality of life, survival, and longevity[1].

Organ shortage continues to be a major issue in kidney transplantation, and counteracting this problem is the current acceptance of older donors[2]. However, long-term graft survival is influenced by donor age, being one mechanism how aging increases acute kidney injury, and reduces tissue regenerative capability[3-5]. Moreover, there are several immunological and non-immunological factors related to renal graft deterioration, and histological lesions such as interstitial fibrosis and tubular atrophy overlap with those observed in aging kidneys. Consequently, it has been proposed that kidney transplant senescence could contribute to graft loss[3].

The complex process of cell senescence displays characteristics such as shortened telomeres, increased expression of negative regulators of the cell cycle, increased expression of specific aging suppressor genes, and immunological senescence[6,7].

Additionally, tubular frailty is one of the major changes that characterize the aged kidney ('nephro-geriatric giants'), because old kidneys are more susceptible to

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ischemia, reperfusion, and toxic injury, and this damage contributes to a cascade of inflammation[3,5,6]. Renal tissue injury, irrespective of the cause (aging, ischemia, or toxic agents) predisposes older grafts not only to progressive mass deterioration due to glomerular hyperfiltration, but also to trigger acute rejection due to an increase in their immunogenicity. This increased immunogenicity can be explained by a rise in proinflammatory cytokines and increased expression of major histocompatibility complex antigens on epithelial and endothelial cells[8,9].

To better understand how senescence influences the survival of kidney transplants, the main graft aging mechanisms previously mentioned are explained in detail as follows[10].

KLOTHO GENE

Klotho (kl) is one of the main "aging suppressor" genes since it facilitates the removal of reactive oxygen species (ROS) [11,12]. It has been documented that Klotho protein activates the forkhead box O (FoxO) transcription factors, which facilitate ROS removal and confer oxidative stress resistance by inducing manganese superoxide dismutase expression and regulating the apoptotic process[11-13]. Conversely, a defect in its expression (Klotho anti-aging protein) leads to symptoms that resemble human senescence, including reduced lifespan, arteriosclerosis, infertility, osteoporosis, cardiac valve calcification, skin atrophy, emphysema, and osteoporosis[11].

Klotho overexpression leads to aging suppression and consequently to longer lifespan in animal models[14], while angiotensin II, which is involved in age-related organ damage in mice, plays a central role in reducing renal *Klotho* gene expression. Besides, *Klotho* gene induction could protect the kidney against angiotensin II-induced damage, and angiotensin II receptor antagonists (e.g., losartan) increase *Klotho* expression[11,15]. On the contrary, angiotensin II-induced oxidative stress can downregulate *Klotho* expression[11].

It is worth mentioning that Klotho protein mediates nitric oxide vascular production, promoting vessel relaxation and endothelial dysfunction improvement in experimental atherogenesis models[12]. Even though Klotho trans-membrane protein is mainly expressed in the choroid plexus and kidney (distal tubules), where it functions as a coreceptor for fibroblast growth factor 23, it acts on various organs suppressing the expression of multiple aging-like phenotypes[14,15]. This evidence suggests that Klotho protein, or its metabolites, can function as a humoral factor[15]. Additionally, it has also been observed that *Klotho* gene influences calcium, phosphorus, and vitamin D metabolism[13].

Klotho gene has been reported to be markedly suppressed in acute renal failure, chronic kidney disease, diabetes mellitus, as well as in acute stress states. Finally, there is also a relationship between *Klotho* gene expression and immunosuppressant drugs, which is discussed in another section of this article[12,16].

TELOMERE SHORTENING

Somatic cells have a limit in their replicative capacity (around 50 divisions), a phenomenon known as "Hayflick limit" or "replicative senescence"[3,7]. Beyond this limit, cells stop proliferating and become senescent because they are resistant to growth factor signaling, and then they arrest irreversibly in the G1 phase of the cell cycle, although they remain metabolically active, a situation that contributes to their damage, loss of mass, decrease in their physiological capacity, reduction in their resistance to stress, and finally death[3]. Telomere shortening is a heterogeneous process since it is faster in the cortex compared to the medulla in aging human kidneys, and it has been interpreted as a homeostatic mechanism to prevent neoplastic cell transformation[3].

Telomeres are located at the end of eukaryotic chromosomes, and their role is to protect them from degradation in order to maintain genome integrity and stability[17]. This protective activity of the telomeres depends on many factors such as proteins linked to their role (tumor necrosis factor receptor associated factors 1 and 2), degree of telomerase activity, and telomere length itself[17]. Telomere shortening of about 50-200 bp occurs with each cell division in a state of telomerase inactivity, and when telomere length reaches a critical value the cell starts a process of apoptosis. In this sense, individuals who inherit longer than average telomeres usually have an increased lifespan; thus, cell replicative limit has been attributed to the loss of telomeres[17,18].

In addition to from normal aging, telomere shortening has also been documented in lymphocytes from HIV patients, delayed renal graft function, acute and chronic rejection, and chronic allograft dysfunction. Telomere length was positively significantly correlated with recipient age, but negatively significantly correlated with donor age, time of dialysis before transplantation, panel reactive antibodies, and long-term creatinine concentration in graft biopsies[19]. It has been postulated that telomere erosion occurs due to graft ischemia and reperfusion. In these cases, there is a transient increase of ROS, which are DNA damage inducers, and injured tissue cannot be replaced by healthy cells, thus causing persistent inflammation and thereby scarring[3,17,18].

MITOCHONDRIAL CHANGES

Sahin et al., demonstrated that telomere attrition activates p53, which in turn binds and represses mitochondrial activity regulators (PGC-1α and PGC-1β promoters)[19]. These transcriptional changes reduce the cellular energy supply, decrease respiratory function, and increase ROS production, a potential cell senescence mechanism induced by DNA damage[19,20]. Thus, these authors found a direct link between telomere dysfunction and mitochondrial aging[19,20,23-25].

It has also been reported that PGC-1α can be stabilized in the kidneys by increasing sirtuin 1, a NAD-dependent histone deacetylase, during an anti-aging intervention such as caloric restriction[19,21,22].

Additionally, it is known that angiotensin II is implicated in the generation of both cytosolic and mitochondrial ROS[25-27]. Mitochondrial aging induces an increase in angiotensin II type 1 receptor (AT1R), as well as a decrease in type 2 receptor density, which are reversed by chronic treatment with an angiotensin II type 1 receptor blocker such as losartan[26]. Besides, AT1R genetic disruption has been shown to promote longevity and reduce age-related mitochondrial dysfunction in renal tubular epithelial cells[27].

P16, P21, AND P27 CYCLIN-DEPENDENT KINASE INHIBITOR GENES

It has been documented that renal ischemia and reperfusion is associated with overexpression of cyclin-dependent kinase inhibitor genes (CDKIG), indicating DNA damage and/or accelerated histological senescence[28].

P16^{INK4a} is a cell cycle inhibitor associated with somatic cell senescence, which is considered an indicator of premature aging secondary to stress and disease[7].

Chronically diseased native kidneys show histological changes, which are qualitatively similar but quantitatively greater than changes secondary to normal senescence. Also, they display increased P16^{INK4a} expression in glomerular and tubular-interstitial cells beyond the area affected by these structural changes, thus this extensive expression of P16^{INK4a} seems to cause these changes more than to be their consequence[10]. Regarding kidney transplantation, an increase of P16^{INK4a} has been documented in grafts with tubular atrophy, interstitial fibrosis, and impaired function (findings that affect 60% of cadaver transplants), suggesting that a part of the changes suffered by senescent grafts is induced by multiple insults associated with transplantation. Among these insults are the injuries from brain death, organ preservation, cold ischemia, transplantation process, drug toxicity, infections, hypertension, and dyslipidemia, which contribute to premature kidney aging accelerating its atrophy[7,10]. Additionally, P16^{INK4a} is induced in allografts from old donor kidneys soon after transplantation (about a week), while young non-transplanted kidneys showed very little basal expression of P16^{INK4a}, but an increased expression not until later after transplantation (about a month). Conversely, isografts have no effect on P16^{INK4a} expression[6,28,29]. Besides, it has been documented that renal cold ischemia and reperfusion are associated with up-regulated p16, p21, and p27 CDKIGs in kidney tissue, indicating DNA damage and/or accelerated histological senescence[28].

IMMUNOSENESCENCE AND INFLAMMAGING

There is a gradual deterioration of the immune system with aging, a phenomenon known as "immunosenescence", which affects both innate and adaptive (T- and B-cell) immune components[1]. However, age-related immune deficiency is more prominent in adaptive immunity, and it consists of an accumulation of anergic terminally differentiated lymphocytes, mainly due to telomeres erosion, and a deficit of fully active

naïve cells[1,30]. Regarding the innate immune system (macrophages, neutrophils, and natural killer cells), it triggers adaptive immune responses, while dendritic cells are antigen-presenting cells that function as a bridge between the innate and the adaptive immune systems[31]. Intragraft interstitial dendritic cells can increase old donor immunogenicity, but older monocyte-derived dendritic cells show an impaired phagocytosis and pinocytosis capability. Besides, aged macrophages show a significant reduction in their number as well as in their chemotaxis, phagocytosis, cytokine, and chemokine production capabilities[31]. Regarding neutrophils, they play an important role in the defense against microorganisms and in the inflammatory response. Even though there is no decrease in their number with aging, they decrease their chemotaxis and phagocytic capability[31]. Finally, natural killer activity, which plays a key role in immunity to tumoral cells and pathogens, is impaired in the elderly[4].

With regards to T-cells, thymic involution starts at the age of one year and advances fast with puberty, and it has a residual capacity of producing naïve T-cells in the elderly, but they are less functional in response than in young people[31]. Although senescence loss in thymic output does not result in significant changes in the total amount of peripheral T-cells because this is regulated via a thymus-independent expansion of mature T-cells, they have a reduced allorecognition capability[4]. This exhaustion of the immune system was documented in $CD8^+$ T-cells rather than in $CD4^+$ T-cells. This phenomenon could be attributed to the time necessary for the $CD4^+$ T-cells to become senescent, since even in extreme conditions, when $CD8^+$ T-cells shorten their telomeres relatively quickly, telomere erosion in $CD4^+$ T-cells may take years[30]. Aging characteristically increases the expression of $CD8^+$ T-cells that lack the expression of CD28. This loss of expression has been attributed to repeated antigenic stimulation and telomere erosion. Inflammation (e.g., chronic viral stimulation) or acute renal rejection increase the proportion of $CD28^-$ T-cells[3,32]. Additionally, $CD28^-$ expression has been associated to telomere shortening, replicative senescence, and proinflammatory cytokine production (interleukin 10 and interferon-γ)[3,32]. An increased proportion of $CD8^+$ $CD28^-$ T-cells has also been documented in other inflammatory states, such as HIV infection, systemic lupus erythematosus, rheumatoid arthritis, and Wegener granulomatosis[32].

Senescence decreases the production rate of immature bone marrow B-cells; however, peripheral B-cell numbers seem to be maintained due to a reduced turnover of mature B-cells[3]. Besides, quantitative and qualitative antibody response is reduced in the elderly[31].

Uremic toxins induce oxidative stress and inflammation, which alters innate and adaptive immune systems, changes that weaken immunity in chronic kidney disease (CKD) patients[33]. Studies on T-cells in end-stage chronic renal disease patients documented that their telomere shortening showed an immunological age that was advanced by 20 years compared to their chronological age[33]. Neither hemodialysis nor peritoneal dialysis has shown to reverse telomere shortening in CKD patients[33]. A uremic environment also causes epigenetic changes that may contribute to aging; for instance, methylation of the *Klotho* gene is initiated by oxidative stress in CKD patients, and leads to a syndrome that resembles human aging. Even so, despite that kidney transplantation solves a uremic proinflammatory environment, it is not able to reverse epigenetic changes[33].

This senescence process could be pharmacologically modified since it has been documented that bardoxolone can attenuate T-cell aging in advanced CKD patients, but it has the inconvenience of increasing cardiovascular diseases. Another alternative that has been reported is to stimulate T-cell function using interleukin 7 in this group[33].

Immunosenescence in allograft recipients seems to be useful since it can downturn immune reactivity against the allograft or even induce tolerance to the donor antigens. On the other hand, it promotes a particular phenomenon in grafts known as inflammaging, which is the term coined for explaining the impact of donor advanced age on graft immunogenicity[4]. In this sense, chronic subclinical cytomegalovirus infection could be the main accelerator of senescence, particularly in transplant patients on immunosuppressant drugs, since it represent a persisting challenge to the immune system[4,30].

IMMUNOSUPPRESSANT DRUGS

It is important to note that a kidney graft always suffers a fast senescence rate compared to a native kidney, since the development of severe functional reduction

(glomerular filtration rate around 10 ml/min/1.73 m²) would take a longer time in the native organ: about 120 years. Thus, the aging process suffered by a kidney graft seems to be a sort of progeria or premature senescence[34,35].

Even though immunosuppressant drugs play a central role in organ transplantation, their role in graft senescence is also known. The described aging mechanisms induced by immunosuppressant are the following :

– Cyclosporin A (calcineurin inhibitor) nephropathy and renal aging share some histopathological findings such as renal fibrosis and tubular atrophy[36]. This drug significantly increases the rate of cell apoptosis, $p16^{INK4a}$ and p21 expression, telomere shortening, decreased *Klotho* expression, and intra-renal renin-angiotensin system (RAS) activation, all changes related with senescence[11,29]. Moreover, it has been proposed that cyclosporine downregulates *Klotho* via direct toxicity or via RAS activation, and that cyclosporine-induced graft aging is induced by increasing oxidative stress[13]. Besides, losartan treatment restores *Klotho* expression in cyclosporine-induced renal injury[11].

– The BENEFIT study has shown that senescent, $CD4^+$/$IL\text{-}17A^+$, p16 positive cells, and interstitial fibrosis were significantly increased in graft biopsies among patients on cyclosporin A compared to those on belatacept[29].

– Telomerase, the enzyme which repairs telomere shortening, is inhibited in most human differentiated cells because of the repression of the *hTERT* gene, and consequently these cells present telomere erosion, senescence, and finally apoptosis. It has been documented that cyclosporine and FK-506 dose-dependently block hTERT and promote telomerase inhibition, and consequently premature aging of T-cells[1,17,18].

– Prednisone and mycophenolate mofetil can also induce T-cell senescence[1].

– Food restriction without malnutrition prolongs the lifespan of animal species. Since the mammalian target of rapamycin (mTOR) enzyme acts as a sensor of energy supply, it could have a role in the life-prolonging effect of caloric restriction. This could also explain why rapamycin (mTOR) inhibitor delays aging and prolongs lifespan in experimental models[14].

– Some evidence suggests that rapamycin (sirolimus) could cause an increase of *Klotho* gene expression, inhibiting FGF23 coreceptor by tubular cells[14]. However, in the presence of cyclosporine-induced renal damage, rapamycin can accelerate it by enhancing oxidative stress[13].

– Immunosuppressive treatment predisposes to viral infection, which can induce aging[1,4,30].

KIDNEY FROM OLDER DONORS

Kidneys from older donors usually show worse graft survival: transplanted kidneys from elderly donors generally have a projected half-life significantly lower (5 years) compared to kidneys from young donors (10 years), and this phenomenon has been attributed to the presence of a reduced number of glomeruli in the aged kidneys[3,4]. However, there are studies that found no significant difference between older and younger donors in allograft survival[8].

Since the transplant procedure can induce telomere shortening, and telomeres are already shortened in aged grafts, it is conceivable that older kidney transplantation usually has a worse course compared to younger kidney transplantation[3].

Besides, independent of telomere shortening, older grafts have an impaired capacity to handle stress, control inflammation, and repair structural damage[37].

Additionally, older donors are more likely to have hypertension, microvascular renal damage, and glomerulomegaly with associated hyperfiltration, and these preexisting structural abnormalities could amplify external insults such as glomerular ischemia from superimposed arteriolar hyalinosis from calcineurin inhibitors, hypertension, or dyslipidemia[37]. Moreover, senile tissue injury facilitates immune recognition and a subsequent increased immunogenicity of the old donor kidney[4,9,37]. This is one of the main reasons for proposing to transplant an older kidney into an older recipients since it may optimize the outcome, since the less vigorous alloresponses of old recipients may counterbalance the increased immunogenicity of old

grafts. Conversely, it has been documented that old kidneys that are transplanted into young recipients show the highest rejection rates, while this phenomenon is blunted when aged organs are transplanted into old recipients[9,38]. Another reason for an "old-for-old program" strategy is that older grafts may be sufficient for handling metabolic demands of older recipients[4].

It is worth taking into account that defining as elderly an individual older than 64 years of age is not a biological concept but a social one. It is known that the aging process in the native kidney starts around 35 years of age, so it should be realized that a young adult donor (55 years old) may in fact be providing an old organ since it has already started its aging process 20 years ago, with the clinical consequences that this will have on graft evolution when other variables start playing a role, such as a CKD setting and the use of immunosuppressant drugs.

The following are strategies described as potentially useful for ameliorating the senescence process in kidney transplantation:

– Belatacept, an indolamine 2,3-dioxygenase immune modulator, induces tryptophan deficiency, and since tryptophan deficit contributes to suppress lymphocyte apoptosis, this drug leads to a less deleterious effect on senescent inflammatory cells[29].

– Kidney transplant patients usually show increased oxidative stress and reduced anti-oxidative markers, suggesting that oxidative stress plays a crucial role in the progression of graft damage. This oxidative stress generates free radicals, which induce DNA breaks and telomere erosion. Thus, the use of antioxidants in kidney preservation solutions could be helpful in preventing this sort of graft damage and influence long-term function[3].

CONCLUSIONS

Renal graft senescence is a complex process, and its better understanding will help nephrologists to improve its management in order to achieve a longer graft survival. This therapeutic approach would be very useful particularly in grafts obtained from older donors whose functional durability would be significantly increased.

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