Review

Genetics and Epigenetics of Chronic Allograft Dysfunction in Kidney Transplants

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Chronic allograft dysfunction is the most common cause of allograft lost. Chronic allograft dysfunction happens as a result of complex interactions at the molecular and cellular levels. Genetic and environmental factors both influence the evolution and progression of the chronic allograft dysfunction. Epigenetic modification could be considered as a therapeutically modifiable element to pause the fibrosis process through novel strategies. In this review, the PubMed database was searched for English-language articles on these new areas.

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INTRODUCTION

Chronic allograft dysfunction (CAD), also called chronic allograft nephropathy, is the most common cause of allograft loss, and the picture has not changed despite of recent advances in immunosuppression therapy.[1,2] Chronic allograft dysfunction is a multifactorial process and happens as a result of complex interactions at various molecular and cellular levels. Both genetic and environmental factors influence the progression of the condition.

Chronic allograft dysfunction is characterized by progressive kidney dysfunction, hypertension and proteinuria, and pathologically it is a state of interstitial fibrosis/tubular atrophy with glomerulosclerosis,[3-5] and a cumulative damage to the allograft happens because of immunologic and nonimmunologic factors (Table).[6-39]

Donor-related factors include age, sex, ethnicity, and donor source. Acute tubular necrosis at the time of donation, nephron mass, and human leukocyte antigen antibody mismatch with the recipient are all involved in the graft outcome. On the recipient side, these factors are preexisting disease (eg, hypertension, diabetes mellitus, and hyperlipidemia), cold ischemia-reperfusion injury, mechanical injuries during transplantation, positive panel reactive antibodies, acute rejection, timing of the first acute rejection, subclinical rejection, delayed graft function (DGF), body mass index, diet, smoking, intestinal microorganisms, and drug nephrotoxicity (Figure 1).[1,2,38-46] In addition to the donor-recipient genetic interactions, epigenetics factors also play an important role; for instance, epigenetic modifications within the allograft induced by environmental stimuli or drugs may affect the allograft survival.[47,48]

REVIEW STRATEGY

For this review, we searched the MEDLINE via

Immunologic and Nonimmunologic Factors Involved in Chronic Allograft Dysfunction*

Factors	Description	Reference
Age	Old donor and young recipient age affect graft outcome. Higher donor age is associated with increased risk of CAD, atherosclerosis, glomerulosclerosis, interstitial fibrosis/tubular atrophy, decreased long-term graft function and increased cardiovascular events; thereby, decreases patient survival.	7-10
Sex	Male sex is an independent prognostic factor for poor kidney transplant survival in addition to acute rejection and delayed function. Better long-term prognosis in women may be mediated by protection afforded by hormones and complex immunological processes. Renal hemodynamics, immune responses and susceptibility to reperfusion injury is also different according to donor sex.	11-13
Donor source	In deceased organ transplantation, increased inflammation (in donor brain death) and also prolonged ischemia times, that increase the occurrence of DGF, contribute to decreased function of graft compared to living donors.	14
Donor-specific antihuman leukocyte antigen antibodies	Donor-specific antihuman leukocyte antigen antibodies are largely responsible for the chronic deterioration of allografts.	15
Ethnicity	Due to differences in immunologic responsiveness, acute rejection episodes happen more common in black than in white recipients.	16
Klotho	Klotho, an anti-aging protein, hinders profibrotic effects of TGF-β1 and Wnt/β-catenin and ameliorates renal fibrosis. Therefore, loss of Klotho contributes to kidney injury and fibrosis.	17-19
Cytokines IFN-γ IL-1 IL-6 TNF-α TGF-β	Interferon-γ has antifibrogenic effects due to its inhibitory effects on myofibroblasts and on collagen gene expression. Tumor necrosis factor-α is known to be mitogenic and chemotactic for fibroblasts, but it also has effects that could be antifibrotic such as enhancing collagenase activity and inhibiting collagen gene expression.	20
Growth factors	Increased excretion of CTGF is associated with interstitial fibrosis/tubular atrophy in the graft. TGF-β and IL-6 are involved in the proper induction of CTGF in allograft fibrosis. PDGF has implicated in renal IF due to its ability to transform fibroblasts into myofibroblasts. bFGF has role in angiogenesis and for its mitogenic effect on several cells including resident kidney cells. EGFR may mediate renal fibrogenesis by promoting transition of renal epithelial cells to a profibrotic phenotype, increased production of inflammatory factors, and activation of renal interstitial fibroblasts. Inhibition of EGFR may have therapeutic potential for fibrotic kidney disease.	20, 21
Hormones	Estrogens have nephron-protective effects on kidney and the progression of CAD. Likewise, attenuate glomerulosclerosis and tubulo-interstitial fibrosis. Estrogens play an important part in disturbances of the phosphorus-calcium metabolism beside other factors like parathormone, vitamin D and FGF-23. Sex hormone action may be mediated via gene-specific epigenetic modifications of DNA and histones. FGF23 plays a key role in the regulation of calcium phosphate metabolism. Serum calcium, phosphorus and PTH levels are risk factors for DGF A low pretransplantation serum T3 concentration in patients with uremia may have protective effects against reperfusion injury and the hypercatabolic state early after transplantation. Donor use of dopamine is resulted in less AR episodes, a lower incidence of DGF and improved renal function and long-term graft survival.	13, 22-26
Infection	A global state of immunosuppressive therapies makes a significant increased risk for opportunistic infections in recipients. Releasing of cytokines, chemokines, and GFs in response to viral infection, altered expression of surface antigens (eg, histocompatibility antigens), increased risk of secondary infection by bacteria, fungi and viruses, dysregulated cellular proliferation and allograft fibrosis are some of viral infection effects.	27-33
Body mass index	Elevated body mass is strongly linked with worse graft survival	34
Proteinuria Albuminuria Hypertention Hyperglucoma Hyperlipidemia Hyperuricemia Anemia	An excessive amount of protein resorption causes inflammatory mediators releasing from tubular cells and consequent interstitial injury. Albuminuria contributes to progressive glomerulosclerosis through inhibition of the differentiation of renal progenitor cells into podocytes. Hypertension increases expression of growth factors and MHC II in CAD. Excessive uric acid is associated with insulin resistance, dyslipidemia and with interstitial fibrosis/tubular atrophy.	35-37
Diet	High protein intake exacerbates glomerular injury.	
Microbiome	The population of microbes (microbiome) in the intestine have numerous bidirectional interactions with the host, influencing immunity, resistance to infection, inflammation and metabolism; therefore, its composition may be involved in CAD development.	38, 39

*TNF-α indicates tumor necrosis factor alpha-α; TGF-β1, transforming growth factor-β1; CTGF, connective tissue growth factor; BMP, bone morphogenetic protein; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; PTH, parathyroid hormone; FGF, fibroblast growth factor 23; CMV, cytomegalovirus; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; AR, acute rejection; DGF, delayed graft function; CAD, chronic allograft dysfunction; and IFTA, interstitial fibrosis and tubular atrophy.

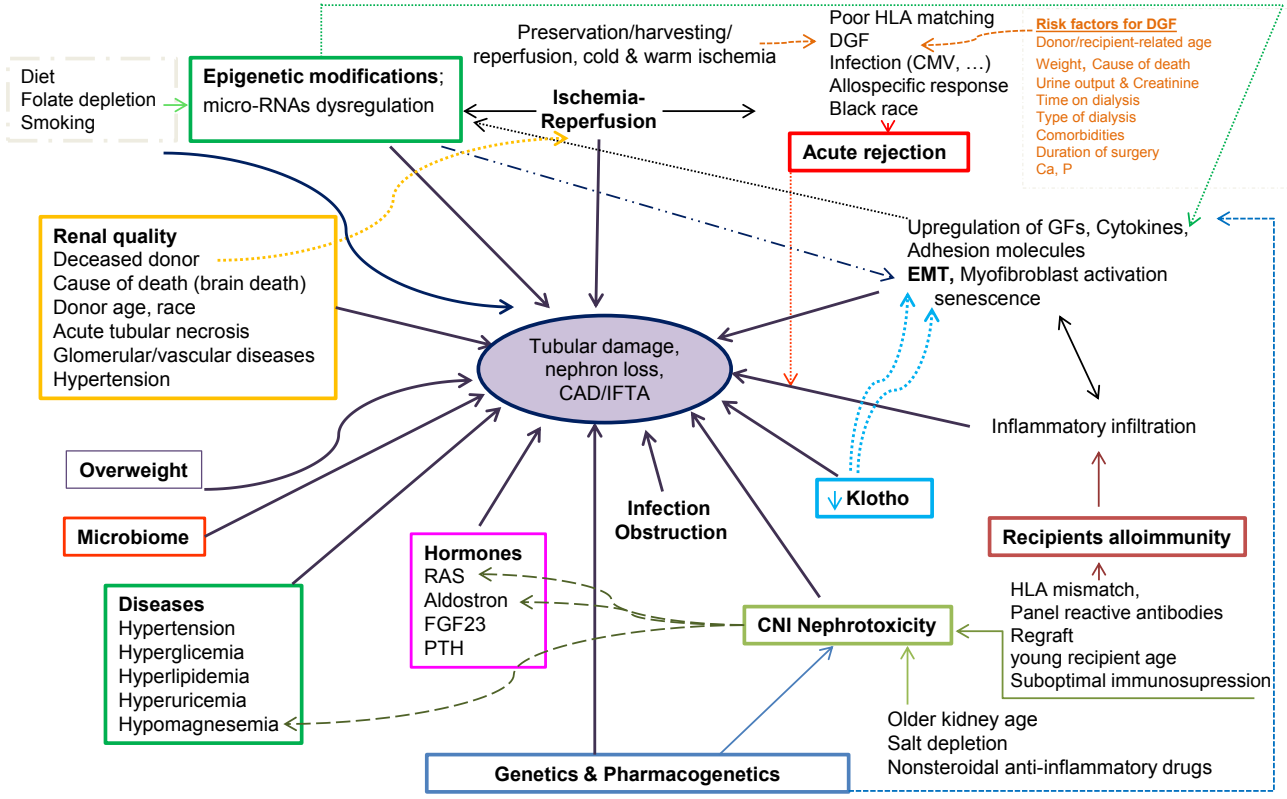

Figure 1. Chronic allograft dysfunction rises from different genetic, epigenetic, and environmental factors. Allelic variation in cytokines, chemokines, growth factors (GF), drug transporter, and metabolizing enzymes genes causes different immune and drug responses that are correlated with clinical outcome of kidney allograft. Early allograft damage causes by acute peritransplantation injuries, donor/recipient-related risk factors, hormones, and episodes of acute rejection. DGF indicates delayed graft function; CMV, cytomegalovirus; EMT, epithelial-mesenchymal transition; RAS, renin-angiotensin system; PTH, parathyroid hormone; FGF, fibroblast growth factor 23; CAD, chronic allograft dysfunction; and IFTA, interstitial fibrosis and tubular atrophy.

the PubMed for English-language articles using the search terms "interstitial fibrosis/tubular atrophy," "chronic allograft dysfunction," "chronic allograft nephropathy," alone and in combination with "hormones," "infection," "donor/recipient-related risk factors," "genetics," "polymorphism," "epigenetics," "microRNA," and "microRNA polymorphism.'' We focused on articles published in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of identified articles for further relevant papers, and also we included additional papers suggested by the authors.

INTERSTITIAL FIBROSIS/TUBULAR ATROPHY

Interstitial fibrosis/tubular atrophy results from the combination of tubular injury and healing responses. Interstitial fibrosis/tubular atrophy is orchestrated by a complex combination of cytokines, chemokines, growth factors, signaling pathways, toxins, and stress molecules[4,49-54]; transforming growth factor (TGF)-β1 is a the central mediator.[50,55] Activation and proliferation of fibroblasts/myofibroblasts, epithelial-mesenchymal transition, and extracellular matrix accumulation all happens in this condition.[49,55,56] Suppression of matrix metalloproteinases leads to matrix accumulation and glomerulosclerosis.[49-54,57] This process is exacerbated by immunosuppressants.

GENETICS

Overview

Genetic variants in the donors and recipients and their interactions can influence the allograft outcome.[58-60] Genetic polymorphisms in cytokines, chemokines, growth factors, drug transporter, and metabolizing enzymes all influence the allograft outcome. Immunosuppressive drug metabolism is also influenced by genetic factors.[60-62] Genotype of kidney donor's nephropathy susceptibility genes and recipient's immune response genes impact

the allograft.[63] Donor polymorphisms in cytokines and chemokines influence the recipient's immune response as these genes are expressed in tubular epithelial cells.[58]

Genetic Variants

Single nucleotide polymorphisms affect the expression and activities of various genes, including human leukocyte antigens and related allo-immunity.[60,62] Cytokine gene polymorphism can influence the expression of genes and their products,[64] and also modify the strength of environmental and traditional risk factors. Nikolova and colleagues found that high production of TGF-β1 and tumor necrosis factor-α and low production of interleukin-6 in the kidney of recipients might be risk factors for development of CAD.[65] Genetic polymorphisms of TGF-β1, angiotensin II receptor type 1, and vascular endothelial growth factor are also associated with different susceptibility to CAD.[66] Tumor necrosis factor-α, TGF-β1, and interleukin-10 high producer haplotype are associated with poorer graft survival and a higher risk of acute rejection.[67] However, the carriage of interleukin-6 high producer Fas low producer genotype has a protective effect against kidney graft function loss.[68]

There is an association between recipient's cytokine genotype and acute rejection after deceased kidney transplantation.[69] However, in another study, donor-derived cytokines were found to play a major role in allograft outcome.[70] In another study, donor-derived but not recipient-derived allelic variant of stromal-derived factor-1, a ligand for chemokine CXC receptor 4, influenced the graft outcome.[71] Caveolin-1 is a caveolate-enriched protein in the cell membrane in the vicinity of TGF-β, epidermal growth factor, and platelet-derived growth factor receptors that hinder TGF-β signaling.[72,73] Caveolin-1 risk variants are significantly associated with allograft failure and influence the risk of kidney allograft infection with Polyoma virus nephropathy.[63,74]

Allelic variation of the following genes also influence the kidney allograft outcome: complement component C3, cytotoxic T-lymphocyte antigen, endothelial nitric oxide synthase, regulated upon activation normal T-cell expressed and secreted, platelet glycoprotein III type A, inducible T-cell costimulator, monocyte chemoattractant protein-1, plasminogen activator inhibitor, vitamin D receptor, angiotensin-converting enzyme, and apolipoprotein L1.[59,62,63]

Complement C4 is a central component of the classical and the lectin pathways and has an active role in organ rejection,[75] and low C4 gene copy number is associated with better graft survival in some studies, while some other studies found the contrary result.[75,76]

EPIGENETICS

There is a tenuous link between genes and epigenetic factors as posttranscriptional modifications can regulate the gene translation and transcript ion. Epigenetics refers to a heritable change in the pattern of gene expression without actual changes in DNA sequence.[77] Major epigenetic mechanisms include DNA methylation, histone modifications, and the action of methylation of the DNA that occurs in CpG islands (cytosine and guanine separated by phosphate) located in the first exons or near the promoters of genes that are conserved across species. DNA methylation is an important mechanism that silences the gene expression through altering the chromatin arrangement and blocking the binding of transcription factors. Histone proteins play a major role in DNA condensation into chromatin, and regulation of expression and replication of the DNA histone proteins play a major role in regulation of expression and replication of the DNA. Epigenetic modifications including acetylation, phosphorylation, methylation, and ubiquitination occur in the histone's amino acids and affect the histones DNA affinity and the accessibility of DNA to transcription factors.[78]

Epigenetic changes are adjustable in response to environmental signals, such as diet, inflammation, oxidative stress, metabolic changes, and toxin.[57] For example, folate depletion can lead to loss of methylation and genetic instability[79,80]; hypomethylation, in turn, leads to re-expression and re-insertion of viral genes that normally were silenced. Viral infections and tobacco exposure are known triggers of DNA methylation.[81,82] Aberrant methylation and demethylation of specific genes and histone modifications can lead to hastening the course of diabetic nephropathy, aging nephropathy, and other causes of chronic kidney disease.[30,32,33] Gene methylation and epigenetic modifications

influence the activation, proliferation and differentiation of the immune cells, and cytokines production that are involved in allograft rejection.[64] Uremia-induced inflammation and metabolic could induce the epigenetic changes.[83] Uremic toxins increase the DNA methyltransferase that silences the Klotho gene through its hypermethylation. Loss of Klotho function exacerbates the kidney injury and fibrosis progression (Figure 2).[84,85]

Epigenetic changes during transplantation contribute to posttransplant gene dysregulation that influences the transplantation outcome.[86,87] Cold ischemia-induced epigenetic changes influence the transplantation outcome.[87-89] During the reperfusion phase, oxygen and hydroxyl radicals release. Reperfusion injury-induced C3 complement aberrant demethylation also influences the allograft survival.[44] During the ischemic phase, upregulation of hypoxia-inducible factor controls the expression of downstream target genes by histone demethylation.[90] Aberrant hypermethylation of the calcitonin gene promoter also happens during the acute tubular necrosis and acute rejection. It could be a good urine biomarker for early detection of acute ischemic injury.[91]

Hypermethylation of the renin-angiotensin system protein activator like-1, which encodes an inhibitor of the Ras oncoprotein, is associated with prolonged fibroblast activation and fibrogenesis in the kidney.[92] Transforming growth factor-β1 and high-glucose concentration can promote histone lysine gene methylation in glomerular mesangial cells that correlates with extracellular matrix accumulation and diabetic nephropathy progression.[89] Histone's lysine methylation is a metabolic memory and persists even with later normal control of glucose. Recently, cytosine methylation in enhancer regions of profibrotic genes in epithelial cells could influence the downstream transcript events.[88]

It is possible that other immunological molecules like major histocompatibility complex molecules, intercellular adhesion molecule 1, co-stimulatory molecules, cytokines, and transcription factors be affected by epigenetic changes during the transplantation process.[57,87] The methylation pattern in the graft may become stable and heritable upon cell division. Cells that are involved fibrosis process gain a heritable-altered phenotype that promotes excessive fibrotic tissue accumulation. Epigenetic modifications could activate the fibrotic genes; enhance the TGF-β signaling, inflammation, and epithelial-mesenchymal transition changes in the expression of different microRNAs; and decrease the expression of Klotho gene.[57,93] The reversible nature of the epigenetic changes make it possible to pause or even reverse the fibrosis process through targeted therapeutic strategies in allografts or other fibrotic related kidney diseases.

MICRO-RNA

Micro-RNAs are a class of small endogenous noncoding RNAs, and 30% to 80% of human genes are predicted to be influenced by micro-RNAs.[94] The micro-RNA gene is transcribed by RNA polymerase II and processed into a primary micro-RNA, which is processed in the nucleus to generate primary micro-RNA by the microprocessor complex, and then primary micro-RNA is transported to the cytoplasm by exportin-5 and further processed

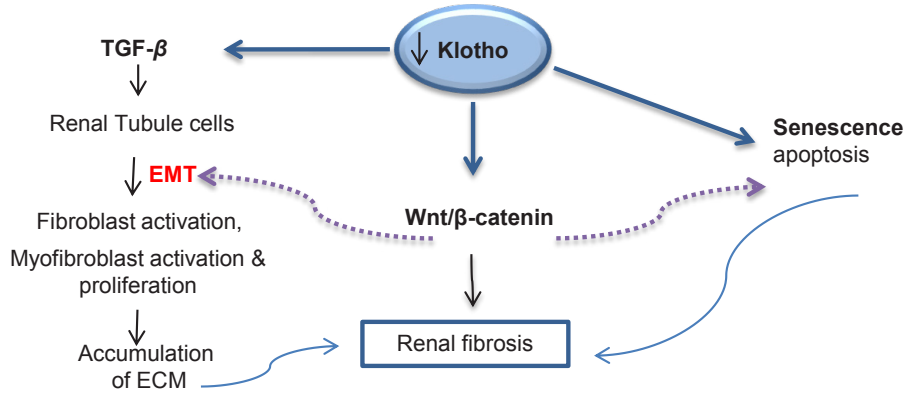

Figure 2. Klotho acts as an endogenous antifibrotic and anti-aging factor by inhibiting multiple growth factor such as TGF-β1, and Wnt. Klotho also inhibits the activation of renal β-catenin, myofibroblast activation, and epithelial-mesenchymal transition (EMT) responses and ameliorates renal fibrosis. Loss of Klotho contributes to kidney injury and fibrosis.

by dicer complex into a mature micro-RNA. Single-stranded form of mature micro-RNA is incorporated into the RNA-induced silencing complex to recognize target mRNA and cause cleavage or translational repression of targeted mRNAs and gene silencing.

Cellular micro-RNAs are tightly controlled by multiple mechanisms, at both the transcriptional and posttranscriptional levels. The micro-RNAs transcription is regulated by epigenetic modifications through histone methylation, and histone de-acetylation micro-RNAs control their own expression via an indirect regulation of transcriptional activation and or repression.[95-97] The posttranscriptional regulation of micro-RNAs can be controlled by factors that influence the endonuclease activity.[98,99] Some pseudogene mRNAs can act as micro-RNA decoy.[100,101]

Micro-RNAs are critical in the maintenance of glomerular homeostasis and their aberrant expression is associated with kidney disease. In the field of kidney transplantation, the accumulative effects of inflammatory cytokines, high blood pressure, proteinuria, hypoxia, and hyperglycemia result in the alteration of micro-RNAs expression profiles. Expression of micro-RNAs (-200s, -29s, -30s, -192, and -215) enhances the endothelial-to-mesenchymal transition. Expression of miR-21, miR-23, and let-7b enhances the extracellular matrix accumulation, and expression of miR-21, miR-216, miR-377, miR-382, miR-200, miR-205, and miR-192 enhances fibrogenesis.[102]

MICRO-RNA-RELATED POLYMORPHISM

Gene polymorphism and copy number variations in micro-RNAs are demonstrated in different studies.[103-105] Despite a target-specific polymorphism in micro-RNA, they could affect the expressions of multiple genes and lead to serious consequences. Micro-RNA gene polymorphisms can be present in different stages of micro-RNA processing.[106] The functional consequences of genetic polymorphisms, which reside at both 5′ and 3′ ends of primary or mature micro-RNAs, generate a large range of sequence variants, called micro-RNA isoforms. These polymorphisms and mutations could affect epigenetic regulation of micro-RNA genes that could affect the regulated cell death, cell proliferation, stress resistance, immune responses, and drug response.[106-108]

CONCLUSIONS

The biocomplexity of CAD and tubulointerstitial fibrosis arises from complex orchestration of molecular and cellular mediators; genetic and epigenetic differences explain the intra- and individual variability in susceptibility to CAD/interstitial fibrosis and tubular atrophy. Genetic and epigenetic datasets could be a tool to understand and identify the risk factors for such conditions. In this context, targeting the epigenetic factors could be considered as therapeutic strategies. Micro-RNAs have critical regulatory roles in a variety of cellular activities and has a significant role in pharmacogenetics and pharmacokinetics of immunosuppressive drugs.

CONFLICT OF INTEREST

None declared.

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