Ischemia Reperfusion Injury in Kidney Transplantation

Subjects: Transplantation

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Cardiovascular disease (CVD) remains one of the leading causes for increased morbidity and mortality in chronic kidney disease (CKD). Kidney transplantation is the preferred treatment option for CKD G5. Improved perioperative and postoperative care, personalized immunosuppressive regimes, and refined matching procedures of kidney transplants improves cardiovascular health in the early posttransplant period. However, the long-term burden of CVD is considerable.

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1. The Role of Thrombo-Inflammation

Ischemia Reperfusion Injury (IRI) is an inevitable part of kidney transplantation. The processes of ischemia and reperfusion in transplanted kidneys are distinct and have different consequences on kidney cells and their environment [1].

The kidney graft is exposed to ischemia during organ preservation and transportation. Ischemia induced anaerobic metabolism causes intracellular accumulation of lactate and, therefore, a decrease in intracellular pH. Acidosis induces the release of lysosomal enzymes that damage intracellular structures. Simultaneously, the adenosine triphosphate (ATP) depletion leads to the Ca^{2+} ion overload in the cells, which increase protease activity and prepares for mitochondrial release of reactive oxygen species (ROS) after reperfusion [1][2].

Ischemia sets off a phenotype change in the endothelial cells (EC) and parenchymal cells. As EC starts to express heparan sulphate, hyaluronan, syndecan-1, CD44, and metalloproteinases, the uncontrollable shedding of the glycocalyx begins [3]. This change of phenotype is recognized by innate immunity response. The endothelium becomes vulnerable and unprotected from the attacks of the contact, the coagulation, and the complement systems [4].

The reperfusion phase restores normoxemia and pH. The normoxemia boosts oxidative stress by releasing and furtherly hyperproducing ROS. Meanwhile, normal pH drives the protease-induced damage of intracellular structures [5]. These changes in homeostasis are unfavorable for ischemia-altered endothelial, tubular, and perivascular cells and thereby launches cell death through necrosis and apoptosis [1]. As a result, the released cellular fragments behave as damage-associated molecular patterns (DAMPs), which are recognized by innate and adaptive immunity response [6], and this sets in motion the thrombo-inflammatory cascade [7]. Although the

reperfusion process aims to heal the ischemia-damaged cells, the activation of DAMPs deepens kidney transplant injury and contributes to delayed graft function (DGF) [8].

Additionally, the recognition of phenotypically altered cells is controlled by mannose-binding lectin, collectin, ficolin, C1q receptors, and C3b [9]. During the ischemia, collectin-11 (CL-11) binds L-fucose that is largely expressed on renal tubular cells [10], and marginally expressed on epithelial cells and glomerular mesangium [11]. During the reperfusion, CL-11 forms a complex with mannan-binding lectin serine protease 1 (MASP1) and MASP2 and activates the lectin pathway of the complement system, consequently leading to production of membrane attack complex (MAC). Simultaneously, ficolin 2 and natural antibodies (IgM, IgG) contribute to the formation of leucocyte-platelet complexes. Activated neutrophiles fuel further tissue damage by migrating into parenchyma [7]. In the end, all the three pathways of the complement system—a part of the thrombo-inflammatory cascade—are activated.

2. Links to Cardiovascular Continuum

IRI in kidney allograft affects different kidney cells, including the renal endothelium, and may cause the dysfunction of endothelial cells in other organs such as the cardiovascular system.

The endothelium forms one of the biggest cellular layers in the human body [10]. The heterogeneity of the endothelial cell (EC) properties along the vascular tree is determined by the endothelial glycocalyx [6][12], which is responsible for vascular permeability and protection, aside from leukocyte and platelet adhesion to ECs [13]. The endothelium expresses a diversity in appearance ranging from continuous cell layers with dense glycocalyx in the brain and heart [14][15] to significantly less compact glycocalyx in lung capillaries [16]. The fenestrated glycocalyx has been found in the kidneys and endocrine glands, whilst sinusoid glycocalyx has been found in liver, spleen, and bone marrow [17]. Nevertheless, the endothelial glycocalyx has a role in the development of albuminuria, which is an early marker of cardiovascular disease both in diabetes [18] and in the general population, and it also provides evidence of microvascular dysfunction in the kidneys [19][20].

The importance of endothelial dysfunction, i.e., endotheliopathy [4], has recently been recognized in kidney transplantation. The ECs and endothelial glycocalyx are the targets of the thrombo-inflammation that engages the complement, the contact, and the coagulation systems [21]. It has been hypothesized that kidney transplantation itself can improve endothelial glycocalyx stability in the early posttransplant period by reducing vascular injury, modifying syndecan-1 concentration [22], and retaining EC function up to 24-month posttransplant [23]. However, the role of endothelial injury in a transplanted kidney caused by IRI and allograft rejections could further contribute to the unfavorable cardiorenal outcomes and needs further investigation.

Injured ECs release less nitric oxide (NO) that, under normal circumstances, inhibits thrombosis by reducing the expression of chemokine and P-selectin, in addition to regulating transcription of the adhesion molecules [7], e.g., the intracellular cell adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1). Enhanced expression of ICAM-1 and VCAM-1 have been linked to pretransplant atherosclerotic burden and posttransplant

outcomes [24]. Moreover, VCAM-1 induces vascular smooth cell (VSMC) function switching to the synthetic phenotype [24], and thereby contributes to inflammation. As for ICAM-1, it may induce aortic valve calcification [25].

Beyond the effect on adhesion molecules, IRI activates matrix metalloproteinases (MMP). MMP-9 is activated through different pathogenetic pathways, which amplifies cardiovascular risk and upregulates transforming growth factor beta (TGF-β), leading to vascular remodeling and, thus, vascular calcification [26][27]. Unfortunately, vascular calcification is not reversible after kidney transplantation and tends to progress in the 5-year posttransplant period [22], further contributing to CVD. Moreover, increased urinary MMP-9 was correlated with tubular atrophy and interstitial fibrosis in kidney transplant and could predict early and long-term graft function [28].

Higher CV morbidity and mortality both in subjects on hemodialysis and peritoneal dialysis could be linked to stimulation of the complement system and low-grade systemic inflammation that damages ECs [29][30]. The uncontrolled activation of the complement system by the pretransplant kidney replacement modality, together with posttransplant IRI, contributes to the remaining increased risk for CVD. Activation of the lectin pathway might even lead to myocardial infarction (MI). The highest tertile of ficolin 2 concentration was associated with early MI (OR 1.55, $p = 0.03$) in the adults [31]. The same report showed that pentraxin-3 (PTX-3)—a possible histological marker of acute kidney transplant rejection [32] —in combination with MBL/ficolin/collectin-associated serine protease-3 (MASP-3) added credibility to the Framingham score in predicting MI. Notably, ficolin 2 rs7851696 gene polymorphism has been shown to be associated with DGF in deceased kidney transplant recipients [33].

The alternative pathway of the complement system, and thus dysregulation of factor B and C3bBbP, impacts adverse outcomes in heart failure [34]. However, the role of this pathway in kidney transplant has been regarded as borderline significant [4]. Altered expression of some other complement components, including factor B, C1, C3, C4, and C5a, are involved in coronary artery disease as compared to healthy controls. Moreover, circulating C1q levels were associated with arterial stiffness in the middle-aged and older healthy subjects [35]. Although the inhibition of C5 in animals can preserve endothelial glycocalyx and kidney graft function [36], the applicability of these findings in humans is debatable.

Finally, thrombo-inflammation is the driving force for chronic allograft rejection that histologically is defined by interstitial fibrosis and tubular atrophy (IFTA) [37] and remains one of the challenges in transplantology. Despite improvement in immunosuppressive treatment, better posttransplant care, and lower rate of acute rejection, IFTA is one of the leading causes of allograft loss in kidney transplants [38]. Supposedly, the same signaling pathways drive the progress of atherosclerosis and arteriosclerosis in the posttransplant period [39]. Additionally, deteriorating kidney transplant function worsens molecule permeability in glomeruli and exposes the cardiovascular system to uremic toxins. Hence, chronic allograft rejection plays an important role here by contributing to the uremic milieu and inflammaging.

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