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Commentary

Exploring Biomarkers for Graft Dysfunction in Kidney Transplant Recipients: Insights and Prospects

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DESCRIPTION

Kidney Transplantation (KT) is the best therapeutic choice for patients with End-Stage Renal Disease (ESRD) and is associated with a higher quality of life and decreased mortality when compared to patients on chronic dialysis. However, these patients frequently experienced short- and long-term complications, and about 10% of Kidney Transplant Recipients (KTRs) presented life-threatening conditions requiring Intensive Care Unit (ICU) admission, mainly related to acute ventilatory failure and anaemia. As a result, there has been an increase in the number of transplantations performed at high immunological risk. Acute Kidney Injury (AKI) is increasingly recognised as a primary cause of short-term outcomes among critically ill patients, as its start and progression is associated with a high risk of mortality and chronic comorbidities such as Chronic Kidney Disease (CKD) and cardiovascular disease. An increased risk of graft loss exists in KTRs who develop AKI; renal outcomes in these patients are a result of the interaction between pre-existing CKD (i.e., baseline renal function), the use of nephrotoxic drugs, and episodes of hemodynamic instability during ICU stay.

De Novo Donor-Specific Antibodies (DSA), which develop during or after an ICU stay and cause graft dysfunction, may develop as a result of the need to reduce or discontinue immunosuppressive medications, which could result in additional immunological injuries and a decreased chance of graft survival in ICU survivors. Classical AKI criteria are known to have numerous limitations when assessing renal disease in the acute situation. The standard for identifying renal dysfunction is still serum creatinine, but it is a late measure that cannot detect kidney injury at an early stage. Additionally, a number of variables might impact creatinine levels, particularly in the acute situation for ICU patients; the rate at which creatinine is produced varies depending on age, gender, muscle mass, food, and nutritional status. Additionally, a protracted ICU hospitalisation has a considerable impact on muscle mass, which therefore has an impact on creatinine levels. Some of the most researched AKI biomarkers include Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule 1 (KIM-1), Tissue Inhibitor of Metalloproteinase 2 (*TIMP-2*), Insulin-Like Growth Factor-Binding Protein 7 (IGFBP7) and cystatin C. The only Food and Drug Administration (FDA)-approved AKI biomarkers among them are *TIMP-2* and *IGFBP7*, which target the G1 cell cycle cessation of tubular epithelial cells and their subsequent release at the urine level after noxious stimuli in a variety of clinical situations.

TIMP-2 performed better than *IGFBP7* at detecting Delayed Graft Function (DGF) patients. Although its specificity is limited because elevated urinary levels are also observed in patients with Urinary Tract Infections (UTIs) and sepsis, Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a protein that is produced in the urine and functions as a biomarker of distal tubular injury. This molecule has also been examined in the context of DGF. After kidney damage, the type 1 transmembrane protein Kidney Injury Molecule-1 (KIM-1) is quickly produced in the proximal tubules. Klotho levels were considerably lower in DGF patients, implying that Klotho deficiency may play a significant role in DGF-associated chronic allograft dysfunction due to its pleiotropic activities. Plasma levels of Corin are decreased in Kidney Transplant Recipients (KTRs) with DGF and may be used as a measure of renal ischemia-reperfusion injury. Corin is a serine protease implicated in the generation of Atrial Natriuretic Peptide (ANP) and performing a protective role against renal damage. MicroRNAs (MiRNA) dysregulation caused by genetic events or the suppression of regulatory enzymes has been linked to the development of numerous diseases, including kidney illness. They serve an important intracellular function in addition to being typically secreted in extracellular vesicles, where they operate as hormones and have paracrine actions. Additionally, miRNAs control post-transcriptional gene expression, and because of their stability in biofluids (such as urine and plasma), they are promising possibilities for biomarkers.

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Several miRNAs are important in the treatment of AKI patients. For instance, elevated levels of *miR-494* in the urine, which prevents the Nuclear Factor Kappa B (NF-kB) pathway's Activating Transcription Factor 3 (*ATF3*) gene from being expressed, have been observed in patients with AKI prior to an increase in serum creatinine. Additionally, elevated levels of miR-107 have been observed in septic individuals with AKI, which causes endothelial cells to secrete more Tumor Necrosis Factor (TNF) and results in tubular damage. *MiR-21* suppression also inhibits apoptosis and controls inflammation in renal tissue. Inhibition of this miRNA has been shown to correlate with the death of tubular cells, increasing the severity of AKI; in addition, miR-21 is linked to an increase in tissue fibrosis and the development of chronic kidney disease. *MiR-146* a has been shown to be upregulated in urine samples from kidney transplant recipients who received kidneys from deceased donors as opposed to surviving donors, suggesting that it may serve as a diagnostic marker for ischemia-reperfusion injury. Through their influence on several pathways Transforming Growth Factor-Beta (TGF-b), endothelin, vascular endothelial growth factor and Platelet-Derived Growth Factor (PDGF) signalling, microRNAs are implicated in the angiogenetic and apoptotic processes, providing a chance to distinguish between different graft injuries.

An improved understanding of this condition might result in the discovery of new molecules that, in addition to being able to specifically diagnose acute kidney damage and distinguish its various origins in the context of transplantation, could also be used as possible therapeutic targets.