Serological and Urine Biomarkers in Organ Transplant

Subjects: Transplantation

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The process and evolution of an organ transplant procedure has evolved in terms of the prevention of immunological rejection with the improvement in the determination of immune response genes. Some serological biomarkers are non-commercial and economical, depending on having an immunology laboratory with experience in their implementation and standardization. The commercials show affordable prices. Regarding the cost of cellular methods, one must be aware that it will depend on the number of these monoclonal antibody markers (CDs) for flow cytometry.

human leukocyte antigen (HLA) donor-specific antibody (DSA) monitoring biomarkers kidney transplantation

1. Classical Markers

Aside from physical examination, we have traditionally used routine serological or urinary markers such as urine volume, evaluation of albuminuria or proteinuria, determination of serum creatinine, estimation of glomerular filtration rate (eGFR) based on serum creatinine and HLA antibody profiling to assess the absence or presence of DSA when a kidney is transplanted. Serum creatinine levels, which rise late in the lesion and are unrelated to the type of lesion, are the most commonly used biochemical parameter [1]. However, serum levels of this parameter are neither sensitive nor specific for determining graft status [2]. Furthermore, serum creatinine levels are neither specific nor predictive when predicting or evaluating the progression of chronic lesions [1]. The gold standard diagnostic test for determining transplanted kidney rejection is a kidney biopsy, which can reveal chronic immune injury, interstitial fibrosis and tubular atrophy [3]. Because of the heterogeneity of processes underlying the same lesion, biopsies have low sensitivity and specificity, a lack of standardization and quantitative thresholds, and even sampling errors [4]. Due to the procedure's high invasiveness, researchers are looking for more effective immune monitoring or imaging techniques for accurate diagnosis [5][6][7].

For several years, attempts have been made to reduce rejection rates by meticulously serologically monitoring the specificities and titers (via mean fluorescence intensity (MFI)) of anti-HLA antibodies, including their identification with high-resolution tests (single antigens) or the ability to fix complements (C1q and C3d assays) in conjunction

with other non-HLA antibodies (ETAr, ATR1,...), and, more recently, new biomarkers for potential use in clinical practice [8].

2. New Markers

New serological and urinary markers may seem essential for evaluating renal function post-transplant. Among these, several can indicate damage or renal graft function.

Neutrophil gelatinase-associated lipocalin (NGAL). Neutrophils secrete NGAL during an inflammatory response and it functions as an acute-phase protein. NGAL levels in urine (uNGAL) can also be measured; siderophores and metalloproteinase 9 are its primary ligands and markers of acute tubular cell injury [9]. NGAL can also be used to detect kidney damage [10]. The creatinine concentration in urine and plasma rises about 2 h after renal cell destruction [11]. In contrast, NGAL can assess the transplant status a few hours after surgery. Other researchers have discovered that uNGAL was lower in renal recipients who did not have reperfusion injury on the first day after implantation [12]. A decrease in these protein levels on day three was also a good predictor of renal function one month later. Another study [9] concludes that uNGAL may be more helpful in assessing renal function in the first week after KT when combined with other markers. Another study found that NGAL levels in urine and serum could be used to predict kidney damage and as a biomarker of acute kidney injury after transplantation [13]. According to the researchers, patients with acute kidney injury had higher uNGAL levels than patients without acute kidney injury, with a 2 h post-transplant increase. A different group of researchers [14] discovered a significant increase in sNGAL levels on day one in HLA-incompatible KT recipients who developed rejection within a month, demonstrating that uNGAL was the most sensitive marker to detect acute KT dysfunction in a living donor. Finally, according to other authors [15], sNGAL and NGAL/creatinine can be used to estimate kidney and transplant function change.

Kidney injury molecule-1 (KIM-1). KIM-1, also known as T cell immunoglobulin mucin receptor 1 (TIM-1) and found in pathology in the kidney, liver, liver and spleen [16], is involved in T and B cell biology. KIM-1 is thought to aid in diagnosing kidney disease because its extracellular domain is cleaved by metalloproteinases and secreted in urine [17]. According to the FDA [18], the protein is a biomarker of kidney damage caused by nephrotoxic drugs. KIM-1, like NGAL, is found in urine 24 h after exposure to various induced nephrotoxic factors, and its concentration has been shown to influence eGFR values and thus predict kidney damage [19], though other authors disagree [19]. KIM-1 seems to be a good predictor of KT rejection [10]. As a result, another study [20] suggests that sKIM-1 could be used to predict renal failure early in the rejection process. They also discovered that osteopontin (OPN) and sKIM-1 improved the prediction accuracy. Other researchers [21] studied uKIM-1 mRNA expression and urinary and serum KIM-1 proteins in renal recipients with rejection and chronic dysfunction and concluded that KIM-1 could be used to monitor renal recipients, which can help diagnose AR and chronic dysfunction and be an independent factor for predicting transplant loss.

CXCL-10. It is a chemokine secreted by renal graft leukocytes that regulate angiogenesis in conditions such as wound healing, ischemia and neoplasia [22]. It is also a sign of inflammation. CXCL-10 (uCXCL-10) in urine

appears to be more sensitive and specific than creatinine in serum [22]. Its levels can aid in the detection of early signs of acute renal failure as well as the diagnosis of noninvasive kidney disease [23]. Many studies on the role of CXCL-10 in renal rejection have been conducted worldwide. According to some authors [11], uCXCL-10 is well-identified in ACR and correlates with plasma creatinine levels. Other studies [24] found that measuring urinary CXCL-10 and creatinine levels, then calculating the ratio of these two parameters, can accurately predict the risk of AMR. Other researchers [25] think children's CXCL-10/creatinine ratio is a promising biomarker of acute cellular rejection. CXCL-10 mRNA detection in urine [26] has also been proposed as an ideal biomarker of biopsy-confirmed rejection. Other authors believe that measuring these chemokine levels prior to transplantation is critical because high levels in the serum pre-transplant indicate a high risk of rejection and transplant failure [8]. Another study discovered that CXCL-10 serum levels greater than 150 pg/mL prior to transplantation predispose to severe rejection [27], and others discovered that CXCL-10 levels in urine could rise in acute rejection and BK virus infection. This chemokine is unable to differentiate between these conditions [28]. According to another group, CXCL-10 levels rise with BK virus replication and infection-related nephropathy [29].

Cystatin C (CysC). It is a cystatin superfamily proteinase inhibitor or cysteine protease inhibitor that primarily inhibits cathepsins L, B and H and is required for intracellular protein and peptide catabolism [30]. The glomeruli freely filter this protein, reabsorption occurs through reflux and catabolism occurs in the renal tubules [31]. When the renal tubules are damaged, cystatin appears in the urine [32]. It is thought to occur two days before elevated creatinine levels in patients with end-stage renal disease [33]. In acute renal failure, CysC is an excellent marker of renal function, especially as renal function deteriorates and rejection occurs. Other authors [34] have found that determining CysC 14 days after transplantation outperforms creatinine in terms of sensitivity and specificity.

Osteopontin (OPN). BSP-1 (bone sialoprotein) and SPP-1 (secreted phosphoprotein 1) are other names for OPN. OPN, like cytokines, regulates the immune system and is involved in tissue and bone remodeling, inflammation, atherogenesis, cell survival and kidney damage [35]. It is crucial in the development of chronic inflammatory diseases and cancer. Based on plasma, the highest urinary OPN can predict renal function deterioration and estimate the risk of cardiovascular death [36]. Urinary OPN, like NGAL and KIM-1, is a promising biomarker for detecting renal damage in neonates, according to other researchers [37]. It appears to be a promising biomarker in KT rejection because of its critical role in the inflammatory process [38]. Other studies have found higher levels of this protein in KT with AR biopsies [39], and one group believes that OPN levels in plasma predict the severity of ACR in renal recipients. The diagnostic findings corroborated the changes in biopsy age [40].

Clusterin (CLU). Low levels of CLU impair renal function in ischemia–reperfusion disorders by destroying kidney tissue and increasing cell apoptosis [41]. CLU is involved in both the apoptotic and antiapoptotic processes. Other authors [42] argue that it adds nothing new to the discussion. Another study [43] found that urinary CLU could be a useful noninvasive marker for detecting renal damage in children with systemic lupus erythematosus, which predisposes them to end-stage organ failure. CLU was discovered to be a marker of sublethal kidney damage in another study of children undergoing allogeneic stem cell transplantation [44]. Finally, CLU may be an important biomarker when KT function is delayed, with levels rising as early as 4 h after surgery [45].

CXCL13. It is a chemoattractant necessary for forming the germinal center (GC) and alloantibodies. Serum CXCL13 levels can be correlated with HLA antibody formation post-transplantation. With a murine skin graft model, an author co-cultured in vitro follicular helper T cells (Tfh): human B cells to assess CXCL13 production by human lymphocytes in recipients with and without de novo DSA. They found that CXCL13 was detectable in the blood of allografted mice and correlated with B, Tfh and GC cell responses [6] and also observed increased expression of CXCL13 in the draining lymph nodes of allografted mice compared with recipients of syngeneic grafts or without previous treatment. The serum levels also preceded the detection of post-transplant DSA. Similarly, Tfh–human-B-cell interactions, which are very important in plasmablast differentiation and IgG formation, also showed CXCL13 expression. CXCL13 levels in recipients with de novo DSA were higher than in stable recipients, presenting CXCL13 as a potential biomarker for HLA antibodies.

In the same way, another chemokine, CXCL9, has also been implicated in AMR in KT [13].

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