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Editorial

Is Neutrophil Gelatinase Associated Lipocalin the Best Troponin-Like Biomarker to Predict the Need for Dialysis and Graft Recovery Afterrenal Transplant?

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In the last decade, several research efforts have been directed at finding early, accurate and predictive biomarkers of graft recovery after kidney transplant. In the immediate post-transplant period, large inter individual differences can be observed among kidney transplant recipients: allograft function after transplantation varies from early recovery, characterized from a rapid increase in GFR, to primary allograft failure. However, acute kidney injury leading to Delayed Graft Function (DGF) occurs on 5-50% of deceased donor kidney transplants and 4-10% of live donor transplants [1].

Unfortunately, long-established methods to evaluate graft function, using serum creatinine and urine output are unreliable and slow indicators for DGF, since they their changes may require several days and are not able to timely reflect acute kidney injury [2].

DGF mostly results from ischemia-reperfusion injury [3] and is defined as the need for dialysis within the first postoperative week [4,5]. Besides the immediate detrimental effects associated with DGF, such as lengthening of hospital stays and higher costs due to the necessity of dialysis, it has been shown that patients with delayed or slower graft function recovery have a 40% higher risk of graft loss at 1 year post-transplant [6], increased susceptibility to acute and chronic rejection [7] and poorer long-term outcomes [8].

Current studies of diagnosing DGF have screened some candidate biomarkers, in the search of a troponin-like molecule for an early and sensitive reflection of graft function.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) has emerged as promising biomarker for the prediction of kidney injury and damage in the immediate post-transplant period: several hours before the rise of serum creatinine, kidney epithelia express and excrete large quantities of NGAL into urine following stress by ischemia-reperfusion injury [9,10].

NGAL also known as lipocalin 2, uterocalin, siderocalin, or oncogene 24p3, was firstly isolated from the supernatant of human activated neutrophils [11].

A great interest on NGAL arose several years ago from the studies by a young graduate student David Goetz who, under the supervision of Professor Roland Strong at the University of California in San Francisco, investigated the three-dimensional structure of NGAL, finding a great sequence similarity to a super family of proteins called lipocalins. Prof. Strong defined lipocalins as "small proteins that cells send out to bind things and carry them back" [12].

Later it was shown that NGAL binds with high affinity bacterial siderophores or endogenous compounds in mammals [13,14] and it has a key role in iron transport into cells, where the iron is released inducing downstream cellular responses. NGAL is implicated in different mechanisms, including bacteriostasis, control of apoptosis, and induction ofproliferation of renal tubules, which constitute possible pathways of NGAL-mediated kidney protection in acute injury [15,16].

Afterwards, many other cell types, including kidney tubular cells, have been proven to produce NGAL in response to various insults. Different levels of NGAL gene expression have been demonstrated in several human tissues, including uterus, prostate, salivary glands, lung, trachea, stomach, colon and kidney [17,18], highlighting NGAL potential multifaceted role in a variety of renal and non-renal clinical settings [19,20].

A milestone in the research on NGAL in renal transplantation is a study by Mishra et al. who, using immunochemical staining of protocol biopsy specimens from renal allografts, demonstrated a correlation between an increased expression of NGAL and prolonged cold ischemia time, elevated serum creatinine levels, and dialysis requirement [21]. These important findings suggested that increased local production of NGAL by the tubular epithelium of DGF kidneys contributes to the high circulating and urine levels, reflecting the ischemia/reperfusion stress applied to the transplanted kidney before organ withdrawal, during the storage period and successive reperfusion. The advantage of NGAL as a biomarker for predicting kidney injury in the early post-transplant period lies in its potential applicability for a timely detection of the beginning of kidney injury, with respect the rise in serum creatinine which does not appear until 48-72 hours after initial insult [22,23]. In contrast, NGAL expression shows a rapid and significant rise following renal ischemia/reperfusion injury, the major determinant of DGF. This up-regulation of NGAL gene occurs in the proximal tubules during the regeneration process of damaged kidney.

However, the underlying mechanisms for NGAL increase in urine and plasma are different. The main fraction of urinary NGAL during acute kidney injury is the result of an impaired absorption of the filtered NGAL by the proximal tubule together with the increased synthesis of NGAL by the distal nephron. In contrast, the injured

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kidney is not the main source of plasma NGAL, but other distant organs, principally the liver and the lungs, display higher NGAL mRNA expression, giving the most substantial contribution to the plasma pool [23].

It is still debated whether urinary NGAL or plasma NGAL provide the most reliable biomarker for graft outcome.

The most recent study on serum NGAL is that by Hollmen et al. who analysed its performance to predict DGF and recovery of kidney function in 176 deceased-donor kidney recipients. The authors observed patients with DGF had a significant increase of serum NGAL in the first postoperative day, compared to those with early graft function and this difference persisted until the 14th day. In multivariate analysis, the serum levels of NGAL at day 1 emerged as an independent predictor of DGF. Moreover, the best predictive ability of serum NGAL for DGF was found in the subgroup of patients with a timeframe of six hours or less from reperfusion to blood sampling [24].

Current research has also focused on the urine medium, integrating clinical studies on biomarkers and proteomics: the transplanted kidney, through its urinary output, represents an ideal model to reflect the molecular constitution of the graft, providing insight into either the healthy function or developing dysfunction of a newly transplanted organ [25].

In an observational cohort study of 91 deceased-donor kidney transplant patients, Hall et al. investigated urinary NGAL as biomarker to predict dialysis within first week post-transplant. The authors found significant differences in the levels of urinary NGAL from serial urine samples collected 3 days after transplant between patients with delayed, slow or immediate graft function. Multivariate analysis revealed that the ability of NGAL to predict dialysis requirement during the first week after transplantation was moderately accurate when measured on the first postoperative day, whereas the decline in serum creatinine was not predictive [22].

Nevertheless, the main limit of NGAL is its poor specificity, because several non-renal diseases can also induce NGAL. So urinary exosome content has been proposed as a better source to examine candidate biomarkers of renal dysfunction. Exosomes are small vesicles released into the urine from the kidney epithelium and their molecular composition mirrors the physiological or pathological condition of the kidney.

Alvarez et al. used Western blot analysis to determine NGAL in the cellular and exosomal fraction of urine samples from 15 kidney allografts, 11 of them living donor recipients and 4 deceased donor recipients. The authors reported that the exosomes expressed higher levels of NGAL than the cellular fraction, as soon as 24 hours after transplantation. While in the cellular fraction NGAL levels were similar between patients, regardless of the type of donation, NGAL expression in the exosomes fraction was significantly higher in deceased donor recipients from the first day postoperative day. Moreover, NGAL expression in exosomes remained increased in the patients with DGF compared with those who had an immediate recovery of their graft function. Considering the highest abundance of NGAL in the urinary exosomes and its correlation with DGF patients, these findings seem to indicate the exosomal fraction as a more sensitive substrate to evaluate early biomarkers of DGF in renal transplant recipients [26].

Recently Peake et al. analysed mRNA for biomarkers of kidney injury extracted from urinary exosomes isolated from renal transplant recipients, patients with Chronic Kidney Disease (CKD) and healthy controls. They compared exosomal mRNA expression of for the injury biomarkers NGAL, Interleukin-18 (IL-18), Kidney Injury Molecule-1 (KIM-1), and cystatin C with the concentrations of corresponding urinary proteins, 18S RNA and serum creatinine. The study revealed that exosomal mRNA for NGAL, IL-18 and cystatin C did not correlate with the creatinine reduction ratio at day 7, or urinary biomarker concentrations at any time after transplantation. Exosomal NGAL mRNA was lower 4 hours after transplantation than in control exosomes. These results suggest that urinary NGAL and IL-18 levels are associated with creatinine reduction ratio at day 7 after renal transplant, but even if mRNA for these biomarkers is present in exosomes, their levels do not reflect or predict urinary biomarker levels or the creatinine reduction ratio. So it is feasible that the incorporation of mRNA into exosomes is a selective mechanism, not necessarily representative of mRNA in the parent cells responsible for biomarker production [27].

In conclusion, even if NGAL seems to emerge as an intriguing troponin-like biomarker in the plasma and urine in predicting DGF after renal transplant, there are still some limitations mainly related to its poor specificity.

So the challenge is currently open for ongoing biomarker discovery studies in the fields of proteomics and metabolomics, aimed at the identification of patterns of reliable markers rather than a single standalone molecule.

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