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Non-invasive screening for sub-clinical antibody-mediated rejection as a new tool for indication of kidney allograft biopsy

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Antibody-mediated rejection (ABMR) is nowadays the major problem for long-term kidney allograft survival. ABMR frequently takes a continuous and fluctuating course. It often occurs sub-clinically, and abnormal serum creatinine levels or the detection of proteinuria is only detectable at stages with already advanced graft injury. Frequent follow-up controls to uncover the rise of known pre-transplant donor-specific antibodies (DSA) or their de novo formation, that might trigger diagnostic biopsies for detection of earlier stages of graft injury, or the implementation of protocol biopsies are not always possible in transplant centres. However, a timely treatment of ABMR would enhance significantly graft outcome [1–4].

Efforts to develop better measures that allow early detection of rejection before any clinically obvious, irreversible damage has accumulated and range from protocol biopsies to less invasive approaches such as metabolomics, proteomics or mRNA profiling of single or multiple markers in urine or serum. These latter techniques aim at detecting active injury, due to acute rejection, T-cell mediated rejection (TCMR) in particular, and, to a lesser extent, ABMR [5–8]. Although innovative, none of these approaches has been widely adopted for routine clinical procedures, mainly due to the lack of confirmation of these often small to medium-sized studies.

Owing to these nonetheless encouraging data, Van Loon et al. sought to assess the transcriptome from peripheral blood prospectively and, if possible, renal allograft tissue, in 630 renal allograft recipients from multiple European centres [9]. They split the study into three distinct parts: into a discovery, a derivation and a validation phase, and correlated blood mRNA levels to clinical, serological, and histological data. The authors first tested blood and tissue samples in a genome-wide expression assay on an RNA microarray. They computed with five different statistical approaches a multivariate score for each transcript, which could separate four pre-defined and centrally confirmed diagnostic situations (no rejection, pure ABMR, pure TCMR and mixed rejection but excluding glomerulonephritis, BK-virus nephropathy and unclear diagnosis) and inspected arbitrarily chosen thresholds, which could suitably classify cases into these scenarios. In doing so they importantly demonstrated parallel variations of mRNA levels in both compartments when ABMR occurs. They then explored candidate transcripts in further samples through a targeted evaluation of blood samples by reverse transcription polymerase chain reaction (RT-PCR) to detect the best performing diagnostic combination of transcripts. Finally, they assessed the locked 8-gene marker most precisely hallmarking ABMR in a third additional cohort by RT-PCR on blood samples and tested different thresholds for diagnosis accuracy. It allowed independent validation of the combination of eight transcripts, which discriminate cases with or without ABMR with a high negative predictive value regardless of the current graft function or the timing of the evaluation. The identified transcripts are members of documented signal pathways of ABMR (natural killer cell, interactions between innate and adaptive immunity or antigen presentation).

These valuable data raise some questions mostly related to the application and interpretation of this method utilised in single individuals. Does the clinical context influence the validity of the combination of transcripts (i.e., subtypes and binding strength of donor-specific antibodies, ABO-incompatible transplantation, type of immunosuppression, synchronous inflammation such as infections or autoimmunity)? Has the assay the capacity to distinguish rejection subtypes (C4d-positivity or not, ABMR-related thrombotic microangiopathy (TMA) from other causes of TMA, isolated acute tubular injury, intimal arteritis, mixed rejection)? What is the kinetics of the mRNA levels (including baseline pre-transplant data, after intervention therapy, and their long term evolution)? What is the potential predictive value for up-to-come ABMR, or graft and patient outcomes? A thorough evaluation of this approach in various clinical scenarios, possibly pre-setting the interpretation of transcript levels, such as the presence of DSA (de novo or not) or proteinuria, will be essential too. One last stimulating consideration would be the correlation of these transcripts with early histological modifications only detectable by ultrastructural examination (endothelial cell modifications or early multilayering of glomerular or peritubular capillary basal membranes for instance).

These results could, if further validated, support the indication to perform diagnostic renal allograft biopsy with a reasonable amount of proof when clinicians suspect ABMR in its early form or patients are undergoing subclinical rejection. The early diagnosis of this deleterious

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process and its rapid suppression could subsequently ameliorate the allograft outcome significantly. It is not anticipated that such non-invasive procedures will be able to replace standard histology soon, as clinicians will still need valuable information on the activity of ABMR, on signs of chronicity and separate it from potential supplementary diseases but this study could be a milestone for the timely detection of ABMR.

Declaration of Competing Interest

The author declares no conflict of interest.

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