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Predicting an allograft's fate

Thomas Fehr[1] and Clemens D. Cohen[1,2]

Renal allografts inevitably develop progressive morphological and functional deterioration. Naesens *et al.* now report on a transcriptomic approach to identify transcriptional markers that might predict rapid development of chronic damage even in histologically unremarkable allografts. The data indicate that processes similar to those seen in overt acute rejection are also involved in chronic allograft nephropathy. Identifying such 'sub-morphological' markers should help us to better understand biological processes leading to chronic allograft failure.

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Destiny—our cultural heritage is rich in stories telling about humans who struggle with the foreseen and attempt to change their fate. Greek legends, Shakespeare's drama, and even modern science fiction movies deal with the dilemma of being unable to outmaneuver the prediction. Currently, we are experiencing an era of 'predictive medicine.' Modern techniques have been successful in predicting the outcome of disease for specific cohorts. In parallel, they help to focus on candidate molecules and biological processes centrally involved in disease processes. Hence molecular markers might lead to novel therapeutic concepts. However, until a potential intervention is achieved, any molecular prediction appears as inexorable as destiny.

One example of a currently inevitable destiny in medicine is chronic allograft failure. Most renal allografts have an inescapable fate of interstitial fibrosis and tubular atrophy accompanied by progressive loss of allograft function.[1] The introduction of potent immunosuppressant therapy did not change this course fundamentally. The burden of failing allografts is growing. It leads to medical complications in the individual patient and challenges to the transplant physician facing a growing number of sensitized patients awaiting retransplantation, increasing organ shortage, and rising costs.

Allograft fibrosis may have multiple origins, including acute and chronic rejection, infection, drug toxicity, and progression of donor-derived diseases such as hypertensive damage. Many of these factors are directly or indirectly linked to alloimmunity, as evidenced by the fact that these processes do not occur in isografts or tolerant patients. Thus it would be of utmost interest to identify the causative, damaging process as early as possible. In the case of a clinically acute rejection we are able to identify and treat it successfully, although often not without scarring and a permanent loss of function. By contrast, we can barely influence the course of histopathologically identifiable chronic transplant alterations, such as transplant glomerulopathy, glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Recent prospective studies on immunosuppressive treatment of subclinical morphological alterations failed to show a benefit.[2,3] A next logical step could be to look even earlier for markers indicating the future development of chronic damage in histologically normal allografts. Transcriptomic analysis might be a promising tool to develop molecular classifiers to predict future allograft dysfunction[4] by detecting even 'sub-morphological' alterations ('transcriptomic window,' Figure 1).

Now the group of Minnie Sarwal (Naesens *et al.*,[5] this issue) has taken this step by generating a comprehensive set of genome-wide expression data from allograft biopsies of a pediatric transplant cohort. Biopsies with chronic allograft damage but without obvious inflammatory alteration showed altered expression levels of genes known to be linked to immunological processes. The authors confirmed this transcriptomic fingerprint in an independent set of protocol biopsies taken two years after transplantation. Interestingly, they could also demonstrate that a smaller set of transcripts, again mainly indicating activation of immune responses, were more prominently altered in biopsies of patients who progressed to histological chronic allograft damage 18 months later compared with individuals with no such progression. These data from protocol biopsies taken 6 months after transplantation suggest a continuous induction of immunological processes in allografts prone to develop chronic damage more rapidly. In transplant

[1]*Division of Nephrology, University Hospital Zurich, Zurich, Switzerland and* [2]*Institute of Physiology, University of Zurich, Zurich, Switzerland*
Correspondence: *Clemens D. Cohen, Division of Nephrology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. E-mail: clemens.cohen@usz.ch*

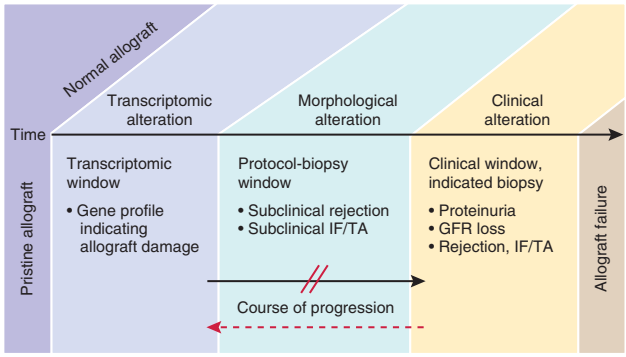

Figure 1 | Progression of chronic allograft damage. A 'transcriptomic window,' as suggested by the study by Naesens *et al.*,[5] may indicate which histologically unremarkable allografts will rapidly progress to morphological and functional alterations. A future therapeutic intervention should halt this progression or even lead to a regression of established damage (both indicated in red). GFR, glomerular filtration rate; IF/TA, interstitial fibrosis/tubular atrophy.

medicine it is self-evident to compare a given 'immune gene set' with transcripts induced in acute allograft rejection. Hence this was performed as a fourth sub-project in the study. Clinically indicated allograft biopsies with acute cellular rejection and tubulitis showed a much more prominent but 'functionally' similar expression pattern compared with protocol biopsies with histological chronic allograft damage. This suggests that similar immunological processes are involved in both settings—that is, acute rejection and chronic allograft nephropathy without obvious inflammatory alterations—but are of a more subtle and smoldering nature in the latter.

The authors must be congratulated for this extensive study. For the identification of marker molecules it is advantageous to have homogenous sample groups. However, this favors a positive outcome of such a marker-set definition. The authors applied rigorous inclusion and exclusion criteria for both biopsy and patient selection. Patients with delayed graft function or post-transplantation complications, as well as biopsy samples with preexisting chronic damage, recurrence of disease, or even potential sample bias, were excluded from the study. Obviously this is quite different from the mixture of patients seen in routine clinical transplantation, making the translation of the findings to a diagnostic application a long journey. Despite the careful selection of samples, biopsies of 'progressors' still showed a slightly higher histological chronic allograft damage score (at month 6) than biopsies of 'non-progressors.' This may limit to some extent the specificity of the transcriptomic predictors but is good news for all friends of morphology—as is the fact that all the end points of the study by Naesens *et al.*[5] were histology-based surrogate parameters for chronic allograft nephropathy and dysfunction. Hence it appears difficult to judge the results in a real-life perspective, where glomerular filtration rate or even allograft survival is the end point of immediate impact. The limitations of such histology-based criteria in protocol biopsies are also highlighted by the fact that biopsies with the highest chronic allograft index had the best glomerular filtration rate (at month 6). This counterintuitive finding appears to be explained by the ratio of allograft mass to body size of the recipient, a finding specific to pediatric transplantation.[6]

The study is a beautiful example of how sensitive screening techniques can help to decipher biological mechanisms involved in smoldering disease processes. As the data are now in the public domain, anybody working in the field can mine the data and thereby build hypotheses that are urgently needed to test new interventions designed to prevent chronic allograft nephropathy. Although the gene pattern seen in acute allograft rejection was similar to that seen in chronic damage in this study, it would be an oversimplification to conclude that intensified immunosuppressive therapy should be used for patients with normal transplant histology but 'immune gene expression.' This is apparent in the study, as there was no correlation between steroid dosage and degree of intrarenal immune gene expression. More importantly, two recent studies failed to show improvement of clinical and morphological outcome when immunosuppressive treatment was intensified in patients with subclinical rejection identified in protocol, rather than clinically indicated, biopsies.[2,3] While cellular infiltrates are associated with the development of chronic allograft dysfunction,[7,8] intensified routine immunosuppressive therapy can apparently not alter the course of this deleterious condition.

In short, the study by Naesens *et al.*[5] is an important step toward identifying molecular markers for the development of chronic allograft damage. However, there remains a long way to go to decipher the transcripts with predictive value for routine daily practice—let alone for the identification of therapeutic interventions. Until such suitable interventions are available, any predictive marker set may just indicate allograft's fate and patient's destiny.

DISCLOSURE

The authors declared no competing interests.

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