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INVITED COMMENTARY

Spontaneous tolerance in kidney transplantation – an instructive, but very rare paradigm*

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Recognition and induction of donor-specific immune tolerance have been a major focus of interest in transplantation immunology even before immunosuppressive treatment became available [1]. Several decades of research resulted in reliable protocols for induction of donor-specific tolerance in rodents, but translation of those to nonhuman primates and to patients was extremely challenging [2]. So far only the mixed chimerism approach, which is based on a combined transplantation of bone marrow and kidney from the same living donor, was successful in the clinical setting [3,4]. However, also in these protocols a long and intense conditioning including myelosuppressive treatment limits its routine clinical application.

Despite the difficulty in inducing tolerance in humans, anecdotal cases of patients, who have removed themselves from immunosuppression without experiencing graft rejection, have been repeatedly described in the literature. Whether these cases are associated with a state of microchimerism remains a matter of debate [5,6]. Nonetheless, spontaneously tolerant patients represent a unique opportunity to the transplant community: on one hand a better characterization of these patients may provide fundamental knowledge about the immunological regulation of tolerance in humans, on the other hand it might help us to optimize immunosuppressive therapy after transplantation. For these reasons, a large international collaboration was initiated aiming at characterization of this rare group of patients. It was possible to identify a 'tolerance footprint' based on gene expression profiles in peripheral blood of spontaneously tolerant kidney and liver recipients [7,8]. However, it is currently unknown how frequently this situation occurs and how such patients should be managed. Obviously, nowadays most spontaneously tolerant patients undergo unnecessary immunosuppressive therapy with potentially deleterious side effects but no benefit, and they could profit from immunosuppression weaning.

In this issue of *Transplant International*, Brouard *et al.* [9] present their results of the next logical step toward clinical application of tolerance profiling with the intention of identifying patients for an immunosuppression weaning protocol. A particular cohort of long-term stable kidney allograft recipients under cyclosporine-based

immunosuppression was screened using the mentioned gene expression profile for operational tolerance. The main finding of this study was that this 'tolerance footprint' was very rare among stable kidney transplant recipients under maintenance immunosuppression: only 5 of 144 highly selected patients (3.5%) presented the profile previously observed in spontaneously tolerant patients. The low percentage of kidney recipients expressing the operational tolerance profile contrasts with similar studies previously performed in liver transplant recipients using different genes [8]. Liver recipients more frequently expressed a tolerance profile, suggesting that liver grafts are more tolerogenic than kidney grafts. This observation, which is supported by the clinical experience that liver grafts usually require less immunosuppression compared with kidney grafts, also points to the hypothetical role of solid-organ grafts not only as the target of the allogeneic immune response, but also as important immunomodulators. According to Starzl and Zinkernagel, this phenomenon might be explained by a more pronounced clonal exhaustion after transplantation of leukocyte-rich liver grafts [10]. Moreover, an anti-tolerogenic effect of immunosuppressive drugs and particularly of calcineurin inhibitors might be involved. Although the 'tolerance footprint' could be detected under immunosuppressive therapy in a few patients in this study, the negative effect of immunosuppressants on clonal exhaustion and tolerance after transplantation has been confirmed in several experimental models [11,12].

But where should we aim with respect to long-term immunosuppression for the majority of kidney recipients? The disappointingly low frequency of the 'tolerance footprint' in even highly stable kidney recipients certainly tempers the enthusiasm for a broader use of immunosuppression minimization or weaning. On the other hand, deleterious consequences of long-term immunosuppression also raise 'caveats'. Thus, a triple strategy may result form the study of Brouard *et al.* [9]: (i) As patients presenting with the tolerance profile also displayed other clinical, immunological and inflammatory markers associated with a favorable outcome, it seems reasonable to proceed to a controlled protocol for immunosuppression weaning in this small group of patients; this could provide definite proof for the validity of their tolerance profile and help understanding donor-specific tolerance in humans. (ii) As the occurrence of spontaneous tolerance seems to be a very rare phenomenon, the search for a clinically applicable protocol to induce donor-specific tolerance should be reinforced, as it probably remains the only possibility to completely avoid long-term toxicity of immunosuppression. (iii) In the meantime, implementation of strategies aiming at a personalized immunosuppressive therapy are crucial to further ameliorate outcome [13]; so far most efforts have been put in identifying markers of *under*immunosuppression (e.g. detection of donor-specific antibodies, protocol biopsy programs to detect subclinical rejection episodes, urinary biomarkers for rejection), whereas no parameters to characterize *over*immunosuppression are available. In this context, data such as those presented by Brouard *et al.* may assume a more generalized role as a part of a set of biomarkers that could help to optimize immunosuppression particularly by recognizing a state of overimmunosuppression.

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