Mechanisms and signatures of immune tolerance in combined kidney and hematopoietic stem cell transplantation

Investigators: Yves Zurbuchen, Kerstin Hübel, Thomas Fehr

For many patients with end-organ failure solid-organ transplantation is the treatment of choice. Currently in Switzerland around 350 kidneys are transplanted every year to patients with end-stage kidney disease. Despite this success, several challenges remain. Patients undergoing a kidney transplant require lifelong immune suppression, which puts them at a high risk of a variety of infections, as well as an increased cancer risk. This immune suppression has allowed a better control of acute rejection of the organ, but over time chronic rejection processes can occur, which are not adequately controlled and lead over time to a failure of the kidney graft.

A transplantation of a donor kidney triggers an immune response whereby the recipients' immune system recognizes the transplanted organ and initiates a rejection process, thereby leading to the need for an immune suppression. The ultimate goal in transplant immunology is the ability to induce tolerance to the donor organ i.e. that the recipient's immune system no longer recognizes the organ as 'foreign' and thus does not mount an immune response against it. This aim has over the last decades lead to many investigations, but so far only one approach has proved effective in human studies[1,2]. This successful approach combines the kidney transplantation with a hematopoietic stem cell transplantation, in such a way that the recipient's immune system consists of donor and recipient immune cells, termed mixed chimerism, which leads to tolerance towards the transplanted kidney graft. This clinical strategy was established by research groups in Stanford and in Boston. The protocols these groups developed require an initial induction protocol leading to an immune suppressed state to allow the stem cell and kidney transplantation. Remarkably, within 1 year all the immune suppressive medication can be stopped, and the patients acquire a tolerance towards their kidney transplant. At the Department of Nephrology at the University Hospital of Zurich the first trial in Europa was launched in 2016 established the Stanford protocol. Currently, six patients have been transplanted and are weaned off immune suppression without any rejection episodes and maintaining kidney function[3].

The main limitation with the protocol that has been established in Zurich is that it only works in patients which are genetically very similar, called HLA-matched, which occurs with a 1 in 4 chance in siblings, therefore making this a therapeutic strategy that currently can only be offered to few patients. To improve the protocol and allow translation of this approach clinical routine, we plan to investigate the mechanisms that are essential for the generation of the transplantation tolerance. We have generated a biobank with blood samples from patients before the transplantation, during the tolerance acquisition 6 and 12 months after the transplantation and once the tolerance has been achieved. By applying novel state of the art technologies, we plan to investigate the changes within the different donor and host immune cell subsets comprehensively over the course of the tolerance acquisition. Subsequently, we will use an assay that allow us to quantify and investigate the very rare alloreactive T cells, which are responsible for the organ rejection, and track these over the clinical course, to understand how these can be controlled in this protocol.

Overall, we propose that with this study we will identify the mechanisms leading to immune tolerance in combined kidney and hematopoietic stem cell transplantation protocols, which will help to improve and foster translation these protocols to clinical routine. We hope that this study helps in the final goal to achieve kidney transplantation without the need of lifelong immune suppression.

Key References

1. Kawai, T. *et al.* HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression. *New England Journal of Medicine* **358**, 353–361 (2008).
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