CESTI IHU: innovative strategies of tolerance induction in the transplanted patient
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This research program, led by Dr. Sophie Conchon (CRTI - Inserm 1064 - ITUN) uses the specific immunological properties of the liver to induce tolerance in the recipient patient of an organ ...

The liver is a vital organ that is the site of many metabolic functions.
It is nourished by arterial blood but also portal venous blood, which is directly stemming from the digestive system and thus laden with food and bacterial antigens. The hepatic immune system is thus more inclined to tolerance, and better able to avoid a chronic inflammatory condition that would interfere with metabolic functions.

"Our work focuses on understanding the basics of liver tolerance, studying, for example, from an immunological point of view, patients in whom the liver's immune system is disrupted (autoimmune hepatitis).

Our project is also to capitalize on liver tolerogenic properties for a therapeutic purpose: to induce tolerance to allogeneic transplantation. ", says Sophie Conchon. The allogeneic organ transplantation is the preferred treatment for many terminal stage diseases. Long-term non-specific immunosuppressive treatments are needed to prevent graft rejection, but they have toxic side effects in transplanted patients. Finding innovative approaches to induce specific allogeneic tolerance is therefore a major goal.

Gene therapy studies have shown that gene transfer in the liver induces tolerance to the transgene product. This was confirmed for various transgene, model (GFP) or therapeutic (Factor IX).
"Our project is to induce the alloantigen's hepatic expression in order to induce tolerance to an allograft. We tested this strategy in a graft model of allogeneic islet cells in diabetic mice. Thus, we showed that the expression of a single alloantigen from the donor mouse strain of islets in the liver of diabetic recipient mice increases the graft survival in all transplanted mice. In addition, over 40% of these mice remained normoglycemic without time limit, and without immunosuppressive therapy.

We have identified a specific population of T regulatory cells which is responsible for this allogeneic tolerance. We are currently pursuing their phenotypic and functional characterization, and are studying the robustness and stability of the induced tolerance, after various nonspecific pro inflammatory stimuli. ".

"In conclusion, we have established the proof of concept of an innovative strategy of allogeneic tolerance induction, that could be beneficial in clinical situations in which alloreactivity constitutes an obstacle to the effectiveness of a treatment.", she concluded.