

Unravelling calcineurin inhibitor-induced hypertension after transplantation

Clinical relevance

Annually over 96,000 transplantations of vital organs are carried out worldwide and to prevent rejection of transplanted organs immunosuppressive drugs, calcineurin inhibitors (CNIs), like cyclosporine A (CsA) and tacrolimus (Tac) are widely used. The efficacy of CNIs in reducing rejection rates after transplantation is unquestionable. This benefit, however, comes at the cost of serious side effects, like the induction of hypertension accompanied by hyperkalemia, hypercalciuria and metabolic acidosis. Hypertension is clinically important because it is an independent risk factor for cardiovascular disease and impairs the graft survival after transplantation.

Background

Kidneys play an essential role in blood pressure maintenance by adjusting blood volume that is achieved, in part, by amending the urinary excretion of NaCl. Possibly CsA and Tac directly, but with different efficacy, stimulate thiazide-sensitive NaCl cotransporter (NCC) activity present in the distal convoluted tubule (DCT) of the kidney. This will cause renal Na⁺ retention leading to volume expansion and hypertension.

Goals

The aim is to address molecular, functional and clinical implications of CsA and Tac treatment on NCC activity and blood pressure. The network of signaling proteins connected to the mechanism of NaCl reabsorption in DCT will be dissected using cell models as well as human urinary samples in a collaborative study involving the departments of Nephrology and Physiology. The following key objectives will be investigated:

- I) Molecular mechanism of NCC stimulation by CsA and Tac using *mDCT* cells.
- II) Role of NCC in CsA and Tac-induced hypertension in renal transplant recipients measuring the response to a thiazide diuretic and analysing their urinary exosomes

The results of our study will enable us to formulate a rational guideline for the treatment of hypertension in organ transplant recipients treated with CNIs. Ultimately, this information will translate into improved patient care and graft survival.

Techniques

This internship will allow you to learn and apply several techniques, such as:

- Molecular cloning
- Cell culture
- Immunohistochemistry
- Fluorescence microscopy
- Exosome isolation
- Western Blot

Contact

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