Press release
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Antiphospholipid syndrome: discovery of a promising route to improving patient care

Teams of the Nephrology–Adult Transplant department of the Necker Hospital-Sick Children (AP-HP, department led by Prof Christophe Legendre, Paris Descartes University) and of Dr Fabiola Terzi, Inserm research director of the 'Therapeutic mechanisms and strategies for chronic renal diseases' team, have just discovered, in part, the molecular mechanisms underlying the development of vascular lesions in the course of antiphospholipid syndrome. By combining fundamental research and monitoring a single cohort of kidney-transplant patients with antiphospholipid syndrome, the researchers have highlighted a beneficial effect of sirolimus, commonly used as an immunosuppressor in organ transplants, to prevent recurrence of vascular lesions on the transplanted kidney. **This study was published in the *New England Journal of Medicine* on Thursday 24 July.**

A rare and still poorly-described disease.

Antiphospholipid syndrome is a rare auto-immune disease with an estimated prevalence between 2% to 5% of the general population. It is characterised by the presence of clots that form repeatedly in the arteries or veins, and in pregnant women is accompanied by repeated episodes of miscarriage. Making the diagnosis requires, in addition to clinical signs, identifying the presence of antiphospholipid antibodies in the blood.

Alongside clinical signs, there is a still poorly-described form of this disease characterised by thickening of the intima[1], the wall of blood vessels, and resulting in a problem of the vessels supplying downstream organs (vessel problem called vasculopathy). These lesions are particularly well described in the kidneys where they lead progressively to terminal kidney failure. The physiopathological mechanisms of this thickening were unknown until now and anticoagulant treatments are ineffective against this phenomenon.

"*Nephrologists know this syndrome well and find themselves powerless against the rapid advance of the disease and the development of terminal kidney failure requiring dialysis. In*

[1] The tunica intima is the inner layer of blood vessels, corresponding to the endothelial cells and the underlying connective tissue.

an initial study we had shown that, unfortunately, these vascular lesions associated with antiphospholipid syndromes reappeared rapidly on the grafted kidney when these patients were transplanted and very significantly reduced the survival of the grafts. This observation was the basis for our thoughts" explains Dr Guillaume Canaud (Necker Hospital-Sick Children, AP-HP, Inserm Unit 1151, Paris Descartes University)

The origin of this advance: the role of the AKT/mTORC pathway

Work done by the teams Nephrology–Adult Transplant department of the Necker Hospital-Sick Children (AP-HP, department led by Prof Christophe Legendre) and Inserm research unit 1151 shows that the development of vascular lesions during antiphospholipid syndrome is largely associated with activation of the AKT/mTORC pathway in endothelial cells by antiphospholipid antibodies.

"*When this pathway is activated, whatever the cell type, it induces proliferation and growth of the cell*" explains Dr Canaud. "*First of all we observed in man that this pathway was highly activated in the vessels of patients with a kidney disorder linked to antiphospholipid syndrome and in vessels of the kidney graft after transplant in patients affected by this syndrome. It is also activated in other vascular regions for an extremely severe form of this syndrome*".

The researchers confirmed *in vitro* that antiphospholipid antibodies were capable of activating the AKT/mTORC pathway in endothelial cells in cultures. They were later able to test *in vitro* the impact of different AKT/mTORC pathway inhibitors, including sirolimus, on endothelial cells exposed to antiphospholipid antibodies.

Backed by these laboratory results, the researchers observed the impact of sirolimus treatment in a group of transplant patients with antiphospholipid syndrome. Among 37 patients with antiphospholipid syndrome, transplanted at the Necker Hospital from 2001 to 2009, 10 received sirolimus as an immunosuppressor. These ten patients, compared with the 27 patients that did not receive sirolimus but another class of immunosuppressor, were spared the recurrence of vascular lesions and saw the survival of their transplant very significantly improved.

For Dr Canaud, "*For the first time, this study describes the mechanisms that lead to thickening of vessel walls in these patients. Inhibition of the AKT/mTORC pathway, using sirolimus, makes it possible to prevent the reappearance of vascular lesions after the graft and so improve renal survival (12 years post-transplant). This observation opens a promising therapeutic route in transplant patients with antiphospholipid syndrome, or even in patients carrying this syndrome but not transplanted".*

References

Inhibition of the mTORC Pathway in the Antiphospholipid Syndrome
Guillaume Canaud, Frank Bienaimé, Fanny Tabarin, Guillaume Bataillon, Danielle Seilhean, Laure-Hélène Noël, Marie-Agnès Dragon-Durey, Renaud Snanoudj, Gérard Friedlander, Lise Halbwachs-Mecarelli, Christophe Legendre and Fabiola Terzi.
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