NEPHROTIC SYNDROME

NPC mutations cause SRNS

Mutations in four genes that encode components of the outer ring subunits of the nuclear pore complex (NPC) are associated with steroid-resistant nephrotic syndrome (SRNS), say researchers.

Podocytes are the critical site of injury in SRNS and although >50 monogenic causes have been identified, many cases are unexplained. Previous studies have shown that mutations in *NUP93* and *NUP205*, which encode proteins of the inner ring subunit of the NPC, cause SRNS. "NPC proteins are ubiquitously expressed and play an essential role in every eukaryotic cell, so it was surprising that germline mutations in genes that are expressed in every cell of the human body give rise to a cell-specific phenotype," says Friedhelm Hildebrandt, an author on the new paper.

In their latest study, Braun et al. further investigated the functional link between alterations in NPC proteins and podocyte injury. They performed whole-exome sequencing in 160 families with SRNS. They excluded mutations in known SRNS genes and used homozygosity mapping in consanguineous families to identify mutations in four genes encoding components of the outer ring subunits of the NPC — *NUP107*, *NUP85*, *NUP133* and *NUP160* — that cause SRNS.

The researchers used co-immunoprecipitation experiments to show that particular pathogenic alleles of *NUP107*, *NUP85*, *NUP160* and *NUP133* weaken the protein–protein interactions between components of the NPC.

The researchers used the CRISPR–Cas9 system to generate stable zebrafish lines carrying different alleles of *NUP107* and *NUP85* and found that fish with two null mutations died early in development, while fish with at least one hypomorphic mutation did not.

> "it was surprising that germline mutations in genes that are expressed in every cell of the human body give rise to a cell-specific phenotype"

Using *Xenopus tropicalis* as a model system, the researchers showed that knockdown of *NUP107*, *NUP85* or *NUP133* disrupted glomerulogenesis. Hildebrandt and co-workers also found that CRISPR–Cas9 knockout of *NUP107*, *NUP85* or *NUP133* in podocytes increased the level of active Cdc42, which is an important effector of SRNS pathogenesis.

"Our genetic data provide strong evidence for a functional link between alterations in different structural components of the NPC and development of podocyte injury," notes Hildebrandt. "However, the specific molecular pathogenesis is yet to be fully understood. We seek to investigate which distinct properties of podocytes convey the specific vulnerability to alterations in NPC proteins as compared to other cell types."

Rebecca Kelsey

ORIGINAL ARTICLE Braun, D. A. et al. Mutations in multiple components of the nuclear pore complex cause nephrotic syndrome. *J. Clin. Invest.* https://doi.org/10.1172/JCI98688 (2018)

TRANSPLANTATION

Blocking CD122 might improve outcomes

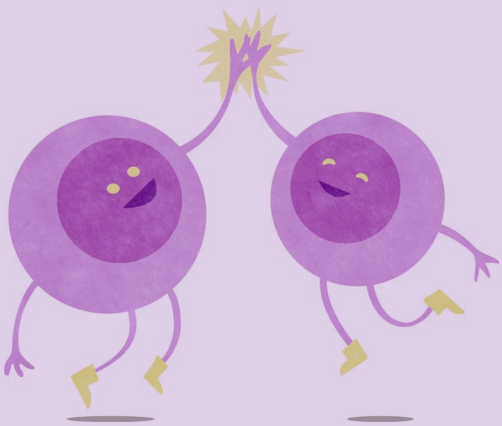
Targeting CD122, which has an important role in both primary and secondary immune responses, has the potential to reduce transplant rejection, say researchers.

Immunosuppressive therapies are effective at preventing early rejection in transplant recipients, but late rejection and adverse effects are common. Blocking T cell-co-stimulatory pathways is a more targeted approach and belatacept, a high-affinity version of cytotoxic T lymphocyte antigen 4–immunoglobulin (CTLA4–Ig), which blocks ligand ligation to CD28, is approved in kidney transplant recipients. However, belatacept is associated with increased early rejection in some patients.

"Our work has been to determine which pathways are important for T cell-mediated rejection in the absence of co-stimulatory signals — so-called co-stimulation-independent rejection," says Andrew Adams, an author on the new paper. "CD122 is an important component of the IL-2–IL-15 receptor complex. Both IL-2 and IL-15 are critical cytokines for T cell development and function. We hypothesized that co-stimulation-independent T cells may rely on signals from these cytokines."

Using a mouse model of transplantation, the researchers showed that CD122 was important for both naive T cell function and for memory T cells. Adams and colleagues also investigated the CD122 pathway in rhesus macaques.

"We were able to show that in the absence of traditional co-stimulatory signals, IL-2 was important for naive T cell responses whereas IL-15 played a critical role in memory-dependent rejection," notes Adams. "As CD122 is required for both IL-2 and IL-15 signalling, treatment with an antibody specific for CD122 was able to prevent co-stimulation-independent rejection.



Credit: Lara Crow/Springer Nature Limited

> "treatment with an antibody specific for CD122 was able to prevent co-stimulation-independent rejection"

Currently, many kidney transplant recipients only receive therapy directed against the IL-2 specific receptor (CD25) and when used in conjunction with belatacept results in high rejection rates. Our data suggest that by blocking both naive and memory T cells (IL-2 and IL-15), anti-CD122 therapy may be combined with belatacept to provide improved survival with low rejection rates."

Rebecca Kelsey

ORIGINAL ARTICLE Mathews, D. V. et al. CD122 signaling in $CD8^+$ memory T cells drives costimulation-independent rejection. *J. Clin. Invest.* https://doi.org/10.1172/JCI95914 (2018)