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Long-term prevention of organ rejection

University of Konstanz biologists use immunoproteasome inhibition to prevent chronic antibody-mediated allograft rejection

The Konstanz immunologist Professor Marcus Groettrup and his team have developed a procedure for preventing organ rejection in rats after renal transplantation, and for suppressing the creation of antibodies in the recipients' immune systems. Immunoproteasome inhibition, which suppresses the production of antibodies, is crucial to this process. The research results were published in "Kidney International". The title of the original publication is: "Immunoproteasome inhibition prevents chronic antibody-mediated allograft rejection in renal transplantation".

Approximately one half of all organ recipients experience antibody-mediated organ rejection within ten years of the transplantation. Currently, pharmacological agents for the suppression of chronic rejection are lacking. Non-selective proteasome inhibitors can suppress antibody-mediated allograft rejection. However, their extensive adverse side effects severely limit their application. Immunoproteasome inhibition, in contrast, has proved effective in preclinical models of autoimmune diseases and was applied over weeks without obvious adverse side effects. Using a rat model, the researchers, led by Marcus Groettrup, were able to show that immunoproteasome inhibition kills the activated plasma cells that produce allo-antibodies against the transplanted kidneys and lead to organ rejection. Selective immunoproteasome inhibition using the inhibitor ONX 0914 reduced the number of B cells and plasma cells and suppressed donor-specific allo-antibody production. The transplantations were performed by Dr Jun Li, a urological surgeon from the Cancer Institute Chongqing in China, who is an international expert for microsurgery and currently works at the University of Konstanz thanks to a scholarship awarded by the Chinese Scholarship Council.

"These results are a huge success. We can completely prevent organ rejection in all animals, also observing that allo-antibodies are virtually absent. The inflammation parameters in the transplanted kidneys decreased significantly and renal function in all recipients is excellent", summarises Marcus Groettrup, adding that these results suggest immunoproteasome inhibition as a promising therapeutic approach to suppress chronic antibody-mediated rejection.

Groettrup's structural model of the immunoproteasome is considered a milestone in the development of new agents in the fight against autoimmune diseases like diabetes, rheumatoid arthritis and multiple sclerosis. As early as the 2000s, Groettrup was able to define the immunoproteasome as a regulator of cytokines that are responsible for triggering autoimmune diseases. Pharmaceutical immunoproteasome inhibitors, which are presently tested in a first

clinical trial, might allow us to fight autoimmune diseases and prevent the chronic rejection of transplant organs without compromising the patients' entire immune system.

Original publication:
Li, J., Basler, M., Alvarez, G., Brunner, T., Kirk, C. J., and Groettrup, M. Immunoproteasome inhibition prevents chronic antibody-mediated allograft rejection in renal transplantation. Kidney Int. in the press.

DOI: 10.1016/j.kint.2017.09.023

Facts:

- Li, J., Basler, M., Alvarez, G., Brunner, T., Kirk, C. J., and Groettrup, M. Immunoproteasome inhibition prevents chronic antibody-mediated allograft rejection in renal transplantation. Kidney Int. in the press.
- Immunoproteasome inhibition using the immunoproteasome subunit LMP7 (β5i)-selective inhibitor ONX 0914 kills the activated plasma cells that produce allo-antibodies and lead to organ rejection.
- The infiltration of T cells, B cells and macrophages as well as interferon-γ, interleukin-17, IgG and complement deposition were reduced in renal allografts of ONX 0914-treated recipients. Chronic nephropathy was ameliorated and renal allograft function preserved, ensuring the long-term survival of the recipients.
- Funding provided by: Else Kröner-Fresenius-Stiftung (www.ekfs.de)
- Research partners: Kezar Life Sciences (www.kezarlifesciences.com) Biotechnology Institute Thurgau at the University of Konstanz (www.bitg.ch).

Note to editors:
You can download a photo here:
https://cms.uni-konstanz.de/fileadmin/pi/fileserver/2017/Bilder/UniKN_Bio_Groettrup_0930_2017.jpg

Caption: Prof. Dr. Marcus Groettrup (left) and Dr. Jun Li

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