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A ray of hope for organ transplant patients

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Study of organ recipient immune system interaction with transplanted organ offers new insights into chronic organ rejection

The holy grail of organ transplantation is getting the recipient's immune system to accept the transplanted organ. Despite an initial period of successful function, between 30% to 40% of kidney transplants worldwide are lost over time to rejection, according to Professor A. Vathsala, Co-director of the National University Centre for Organ Transplantation at the National University Hospital (NUH) and Professor of Medicine at the NUS Yong Loo Lin School of Medicine (NUS Medicine). NUH and NUS Medicine are members of the National University Health System (NUHS).

In 2015, she initiated a comprehensive research plan in collaboration with various teams to understand why some kidney grafts survive while others do not. The aim was to make each transplanted organ last longer.

Introducing an organ from a donor into a recipient almost always leads to the recipient's immune system recognising the new organ as foreign and mounting an immune response. Transplant (or graft) rejection is categorised as acute rejection and chronic rejection. Acute rejection, which occurs more commonly within the first year after a transplant, is caused by immune cells called T cells attacking the implanted organ. This type of rejection responds well to treatment with non-specific immunosuppressants such as steroids.

Chronic rejection a poser

The particularly thorny issue for transplant patients is chronic rejection, which is caused by antibodies. One major problem in transplantation is the difficulty in diagnosing and predicting chronic rejection. "We found that up to 20 percent of patients had antibodies against their donated organs. Just because a patient has antibodies doesn't mean they are going to have a rejection. Although many transplant patients have antibodies, not all antibodies are harmful and to date, there is not a good way to predict which antibodies are actually harmful," said Prof Vathsala.

Moreover, doctors only learn that rejection has occurred when a graft starts to fail and a biopsy is done. A bigger problem is that there are no effective treatments for chronic rejection. Patients with chronic rejection need re-transplantation with a fresh

organ, which is challenging given the shortage of donor organs. Hence, chronic rejection is a major challenge in organ transplantation. It is one that doctors and scientists are working to overcome.

A meeting between Prof Vathsala and Associate Professor Paul MacAry of the Department of Microbiology and Immunology at NUS Medicine resulted in both deciding to collaborate to gain insights into chronic rejection. They looked at the structural aspects of how antibodies in the transplant patient bind to a molecule called human leukocyte antigen (HLA) on the transplanted donor organ, stimulating an inflammatory response.

Found – inflammation-causing antibody

Until now, the mechanism by which these antibodies bind to HLA was not known. The research team, led by Prof Vathsala and Assoc Prof MacAry, comprising NUH and NUS Medicine staff, as well as collaborators from Nanyang Technological University and Oxford University, was able to glean several important insights through a first highresolution crystal structure of the antibody-HLA interaction. The study was published online in the scientific journal Nature Communications on 21 February 2019. Amongst other things, the researchers found that the antibody which they studied bound to a site at the bottom of the HLA protein, some distance away from the sites at which other cells bind to HLA. This suggested that the inflammatory response stimulated by the antibody was independent of other cell interactions with HLA.

“What was interesting is that the antibody binds to the side of the [HLA] molecule,” explained Assoc Prof MacAry. “What this allows you to do is design inhibitors that are going to obstruct the interface because if you stop the antibodies binding, you stop those antibodies from engendering the immune attack.”

The team also showed that one form of the antibody bound to the HLA protein without causing an inflammatory response. Since these antibodies are able to reduce inflammation by binding to HLA and preventing other forms of antibody from binding, they could be developed as therapies for the prevention or treatment of chronic rejection.

Professor Kathryn Wood, Emeritus Professor of Immunology at the University of Oxford and Visiting Khoo Oon Teik Professor in Nephrology at NUS Medicine, was an advisor for the project. She described it as a “landmark study that all groups around the world will take note of. It’s really a first in this field.”

Identifying harmless antibodies from the bad

The crystal structure is of just one type of HLA, which is common amongst Chinese and the most common type in Singaporeans. In the next three to five years, the team hopes to map the structures of all other HLA molecules that are common in Asians. In addition, they will also look at discriminating harmful antibodies from the harmless ones, using transplant patient-derived antibodies and donor tissue proteins.

The project is a serendipitous collaboration of basic science and clinical research to solve a longstanding problem in the clinic, added Prof Vathsala. “We have a wonderful campus in our backyard where we are able to engage and work together with basic scientists to solve issues we face at the clinical front. We hope that this will pave the way for precision medicine in transplant, where specific immunosuppressive strategies can be devised to minimise transplant failure and reduce transplant patients’ risk of getting infections and cancer.”