CROSSING THE RUBICON:
HAS GENE EDITING GONE TOO FAR, TOO FAST?
Dear Reader,

Shortly, we will welcome about 560 young men and women of the Medicine and Nursing classes of 2024 and 2022 respectively. They will undergo a transformative educational experience over the next three to five years, one that will equip them with medical and nursing skills and knowledge to be effective healthcare providers. They will in time to come, join other NUS Medicine alumni in providing care for our community.

As the School cycles through a new academic year, our biomedical research work continues apace. This issue, we present a discussion on gene editing. It is a science that has come under a cloud caused by the controversial editing of the genomes of two babies born in China. In another marvellous piece of research work, our colleagues have found the reason for chronic rejection of transplanted organs. This opens 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. A third story that we are pleased to share with readers is about the speed at which the human brain processes and manages information: their finding gives new meaning to the phrase, quick thinking.

We have been turning out doctors for Singapore since 1905, and the work of our scientists has helped to influence and shape the practice of medicine here. That has and will always remain our mission. But the ways in which we work, teach and train and conduct biomedical science are changing, shaped by new technological advances in telemedicine, artificial intelligence, big data, to name just three of the revolutionary, disruptive global forces that are transforming the way we all live, work and play. The NUS medical school will harness the power of these advances to seek, exploit and harvest the new and exciting opportunities that will enable us to contribute even more meaningfully to health education and healthcare.

Wishing you an enjoyable read.

Yap Seng
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NO MERE GUT FEELING

Blastocystis unmasked as a killer of good bacteria
Since most of the microbes in our gut are bacteria, they tend to hog much of the microbiome research limelight. But, lurking amongst the bacteria are other microbes such as single-cell eukaryotes (SCE) and viruses, which have been largely ignored until now. If doctors and scientists think of Blastocystis (one of the most common gut SCEs) at all, they often regard it as a harmless commensal organism, peacefully co-existing with its bacterial neighbours. However, that could change with the publication of a new study from NUS Medicine (online in Microbiome on 11 March 2019), which shows that a subtype of Blastocystis isolated from the stools of a hospital patient with gastrointestinal problems in Singapore can actually harm its neighbours and its home in an insidious way.

In fact, Associate Professor Kevin Tan and Associate Professor Zhang Yongliang from the Department of Microbiology and Immunology at NUS Yong Loo Lin School of Medicine (NUS Medicine), together with postdoctoral research associates John Yason and Chin Wen Png, demonstrated that Blastocystis subtype 7 (ST7) selectively caused the death of Bifidobacterium (one of the “good” bacteria in the body) in cell culture and in vivo. The ST7 strain of Blastocystis appeared to induce oxidative stress mechanisms, which involve the release of reactive oxygen species (ROS). These killer molecules caused the death of the good Bifidobacteria. Interestingly, the Blastocystis ST7 organisms also reduced the population of Lactobacillus (another good bacteria) in vivo, although the mechanism of killing is still unknown.

Bifidobacterium and Lactobacillus are considered good bacteria because they maintain the integrity of the intestinal lining by supporting tight junctions, which act like cement between the cells that make up the lining. They are also commonly used as probiotics to promote gut health. Besides killing Bifidobacterium directly, Blastocystis ST7 can also gang up with E. coli in the gut to kill even more of these protectors. The researchers also found that ironically, Bifidobacterium and E. coli both help Blastocystis grow better. In other words, Bifidobacterium promotes the growth of its own killer.

To make matters worse, Blastocystis ST7 injures the gut lining directly as well as indirectly by triggering an inflammatory response, causing lesions (ulcers) and a disordered structure of the intestinal lining in vivo.
Add to this the loss of the protective good bacteria, an infection with Blastocystis ST7 could be a recipe for long-term damage to the gut lining, possibly contributing to inflammatory bowel disease, irritable bowel syndrome, as well as gastrointestinal and colon cancers.

Part of the reason for the unclear role of Blastocystis in disease is that previous studies did not consider the Blastocystis subtype that was being investigated. Some subtypes are likely to be harmless, but this study shows that ST7 is uniquely different. Not only does ST7 have harmful effects, it is also resistant to metronidazole, the typical treatment for Blastocystis. Like other Blastocystis subtypes, ST7 is transmitted through eating food that has been contaminated with faeces from infected animals, especially birds. Although ST7 has been reported mainly in Singapore, it has also been described in Japan and in at least one Danish study. Thus, this pathogenic Blastocystis subtype could be found in other ethnicities and geographic locations as it becomes more widely studied.

Assoc Prof Tan is already developing tools to study the mechanisms by which Blastocystis causes disease in greater depth. He and his team have established a genetic modification system for Blastocystis, whereby foreign genes can be introduced into and expressed in Blastocystis and the effects of these changes can be studied. They hope to use this system to illuminate how Blastocystis interacts with its host to cause disease and to explore ways to combat the microbe.

“This is the first detailed study to show a causal link between Blastocystis, a common single cell eukaryote of the human gut, and the host microbiota. We reveal how it reduces the numbers of beneficial bacteria, which may in turn lead to an unbalanced gut microbiome and poorer gut health,” he said.

The detrimental effects of Blastocystis on Bifidobacterium and Lactobacillus could facilitate the development of inflammatory bowel disease and irritable bowel syndrome, in which the good bacteria play a protective role. Based on these results, doctors may want to consider excluding faecal transplants that contain specific subtypes of Blastocystis during faecal microbiota transplantation.
Rejection of any kind is always hard to deal with, but when one’s body rejects a precious organ transplant, the consequences can be devastating. Professor A. Vathsala, Co-director of the National University Centre for Organ Transplantation at the National University Hospital (NUH) and Professor of Medicine, shared that between 30% to 40% of kidney transplants are lost over time to rejection. She, together with Associate Professor Paul MacAry of the Department of Microbiology and Immunology at NUS Medicine, decided to collaborate on addressing one major clinical problem at NUH’s NUCOT: How 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 can be categorised into two main types: cell-mediated rejection and antibody-mediated rejection. Cell-mediated rejection, which occurs more commonly within the first year after a transplant, is caused by immune cells called T cells attacking the transplant. This type of rejection responds well to treatment with non-specific immunosuppressants such as steroids.

The particularly thorny issue for transplant patients is antibody-mediated rejection, which causes chronic rejection. Antibodies in the transplant patient bind to a molecule called human leukocyte antigen (HLA) on the transplanted donor organ and stimulate an inflammatory response involving either immune cells or the complement pathway. One major problem in transplantation is the difficulty in diagnosing and predicting antibody-mediated rejection. Moreover, doctors only find out that rejection has occurred when a graft starts to fail and they perform a biopsy.

“We found that up to twenty percent of patients had antibodies against their donors. 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.

Another, bigger problem is that there are no effective treatments for antibody-mediated rejection. Such patients with antibody-mediated rejection end up needing re-transplantation with a fresh organ, which is challenging given the shortage of donor organs. Hence, antibody-mediated rejection is a major challenge in organ
transplantation and presents an ideal target for pushing the envelope on transplant outcomes.

A critical step in antibody-mediated rejection is the binding of antibodies in a transplant recipient to the donor HLA molecule. These antibodies are called alloantibodies. However, until now, the mechanism by which these antibodies bind to HLA was not known. In a paper published online in Nature Communications on 21 February 2019, Assoc Prof MacAry, Prof Vathsala, along with collaborators from Nanyang Technological University and Oxford University, announced the first high-resolution crystal structure of the alloantibody-HLA interaction.

At this resolution (2.4 angstroms), the researchers were able to glean several important insights. Firstly, they identified two amino acids in HLA (aspartic acid at position 90 and arginine at position 14) that were critical for the antibody-HLA binding. Secondly, they found that the antibody bound to a site at the bottom of the HLA protein, some distance away from the sites at which peptides, T cells and natural killer cells bind to HLA. This finding was surprising because it indicated that the inflammatory response stimulated by the antibody was independent of the interactions of peptides or immune cells 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.”

In fact, the team showed that one form of the antibody (a subclass called IgG4) 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 antibody subclasses from binding, they could be developed as therapies for prevention or treatment of antibody-mediated rejection.

According to Professor Kathryn Wood, Emeritus Professor of Immunology at the University of Oxford and the Khoo Oon Teik Professor of Surgery at NUS Medicine, who was an advisor for the project and a co-author on the Nature Communications paper, this is a “landmark study that all groups around the world will take note of. It’s really a first in this field.”

The crystal structure is of just one type of HLA called HLA-A*11:01, which is common amongst Chinese and the most common type in Singaporeans. In the next three to five years, the team hopes to solve the structures of all other HLA molecules that are common in Asians.

Prof Vathsala described the project as a serendipitous collaboration of basic science and clinical research to solve a longstanding problem in the clinic. “We [at NUH] have a wonderful campus in our backyard where we can meet with experts from Microbiology and Immunology. The project grew out of a chance tea where Paul and I met and said, ‘Let’s solve this problem and look at the structural aspects of antibody and antigen.’”
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*Details are subject to change.*
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