What essential function do regulatory T cells (Tregs) serve in the immune system?

Tregs do just what their name implies – they regulate immune responses. As most people are aware, the immune system is one of the body’s defences against infection. The main function of Tregs is to stop the immune system from going overboard. In other words, they prevent unwanted immune responses to substances that the immune system needs to ignore, such as the components of the body itself (including our microbiome) and harmless external substances such as allergens.

The importance of Tregs is clear from what happens when they are seriously defective or absent, as in some rare genetic syndromes, such as severe forms of immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX). If these babies are not given bone marrow transplants from healthy donors, they develop multiple life-threatening autoimmune and allergic diseases in early infancy.

Improved health practices may have led to a reduction in our exposure to harmless infectious agents, microorganisms and parasites, thereby suppressing the development of our immune system.
How has your professional background contributed to your research developments?

I trained in clinical medicine, where the emphasis is on looking at the big picture. A good diagnostician has to integrate many different findings – the patient’s history, their symptoms and any abnormal signs noted on physical examination – to come up with a provisional diagnosis to test.

Learning this skill has taught me to avoid a trap that is common in basic biomedical science, which is to base entire experimental programmes on the published interpretations of other basic scientists without considering alternative interpretations of the data itself. This is akin to a diagnostician basing treatment on the patient’s notes without examining the patient.

In what ways is your approach to studying the fundamentals of the immune system unique?

As far as I am aware, my lab is the only one to study the direct interactions between Tregs and dendritic cells in mouse models in which there are no other immune cells to confuse the picture. I have been using complex mouse models for a long time. When I first worked in a lab as a student, the results from mouse models were very hard to interpret. I was one of the first to develop a transgenic mouse to study CD4 T lymphocytes, which is still one of the best mouse lines available for performing experiments that give clear, relevant results.

Does your research have the potential to be translated into the clinic?

There are many areas in which our research could be translated into the clinic. At the moment, we are very excited about our recent results showing that establishing a normal-sized population of Tregs early after stem cell transplantation prevents graft versus host disease – one of the most serious complications of therapy for leukaemia. This finding came from our very basic studies into how Tregs work, but it could radically change the way stem cell transplantation is performed in the near future. We are looking to take this into the clinic using our human Treg cell isolation procedure. Graft versus host disease is not only life-threatening and a drain on health resources, it also makes life miserable for those who suffer from it.

Finally, as this is International Innovation’s ‘Women in Science’ issue, can you outline some of the difficulties women in scientific disciplines face?

The first and most obvious problem is balancing work and family when you have children. When I had young children, there was simply no consideration at all. We can never make up for the lost opportunities associated with the effects of pregnancy, childbirth, breastfeeding and childcare on our careers. From that time onwards, we are awarded fewer grants and have less research money – an issue that is often not factored into assessments of productivity in Australia.

Quite aside from the practicalities of motherhood, women always have to be significantly better than male colleagues to be considered as good. For men, a major discovery is always associated with their name; for women, the question ‘What else have you done?’ is routine.

Moreover, there is the straightforward problem of gender bias in funding in Australia. In National Health and Medical Research Council (NHMRC) funding, women only have 85 per cent of the chance of men to be successful in project grants and fellowships. This disparity has achieved exactly two one-line mentions in the national press in the past two years!

Reboots the microbiome, resetting the threshold

The epidemic of autoimmune, allergic and inflammatory diseases skyrocketing in the Western world could soon be curbed thanks to a laboratory at University of Sydney’s Centenary Institute that is investigating ways of preventing immune system dysfunctions.

The immune system is a highly complex network of biological structures and processes that protects against disease. It works by detecting infectious agents capable of producing disease and then neutralising them. However, there is a dark side to the immune system. Despite its multiple benefits, when the system falls into disorder it can result in a range of inflammatory diseases, autoimmune diseases and even cancer. Indeed, autoimmunity – where the immune system confuses healthy tissue for foreign organisms and attacks it – can cause many chronic diseases such as type 1 diabetes.

Novel models for studying the immune system

It is not clear why the immune system malfunctions and attacks its host; however, there are researchers around the world who are investigating this issue. One such team of scientists is based at the Centenary Institute, University of Sydney, Australia. Led by Professor Barbara Fazekas de St Groth, the researchers have adopted an unusual approach to studying the fundamentals of the immune system – complex mouse models. One of their main foci with these models has been on the role of regulatory T cells (Tregs) – a component of the immune system that suppresses the immune response of other cells.

Initially, Fazekas de St Groth was struck by the commonly held belief that it is an abnormal ratio of Tregs to conventional CD4 T cells that causes autoimmunity. “I noticed that within CD4 T lymphocytes, the ratio of Tregs to conventional CD4 T cells was always normal; this commonly held view just did not seem to fit the data,” she notes. “Also, we noticed that the molecules that turn on Tregs are not expressed by other CD4 T cells in the mouse, indicating that another target of Tregs was likely to be involved.”

Because of this, Fazekas de St Groth and her team chose to study dendritic cells, which are known to turn on both Tregs and conventional CD4 T cells. They found that dendritic cells overexpressed a number of stimulatory molecules when there were no Tregs present. Hypothesising that real-time cross-talk between Tregs and dendritic cells was occurring, the researchers went on to show that autoimmunity arose due to only a few conventional CD4 T cells, which normally remained dormant when enough Tregs were
CHRONIC DISEASES AND THE IMMUNE SYSTEM

OBJECTIVE

To understand why the immune system causes so many chronic diseases using mouse models and patient samples to study the fundamentals of the immune system, particularly regulatory T cells.

KEY COLLABORATORS

Professor Derek Hart, Anzac Research Institute, Australia • Professor Wolfgang Weninger, Centenary Institute, Australia • Professor Stephen Aderstein, Royal Prince Alfred Hospital, Australia • Professor Ranjeny Thomas, Diamantina Institute, Australia • Professor Bart Lambrecht, VIB Ghent, Belgium

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Centenary Institute • University of Sydney • Royal Prince Alfred Hospital • Anzac Medical Research Institute

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PROFESSOR BARBARA FAZEKAS DE ST GROTH

trained in medicine, left to earn a PhD in Immunology at the Walter and Eliza Hall Institute and returned back to working with patients 20 years later. She is very interested in applying big data techniques to get the most out of the intersection between clinical medicine and basic science (some of this probably stems from her interest in maths, which she trained in before she moved into medicine).

present. “Ultimately, this line of research has led to the idea that it is relatively minor, short-lived drops in Treg numbers that could be responsible for the majority of autoimmune disease in humans,” Fazekas de St Groth enthuses.

UNDERCUTTING GRAFT VERSUS HOST DISEASE

Moreover, her research cracked a nut that researchers around the world struggled for many years to open: finding a reliable way to identify human Tregs without killing the cells. “In the mouse, most cells bound by antibodies to two molecules, CD4 and CD25, are Tregs. However, in humans, most cells in this category are not T cells,” she explains. “We discovered a third molecule that was expressed by all the cells expressing CD4 and CD25 except for Tregs, so we now use this to reliably distinguish Tregs from other cells.”

While important to a broad range of immune system malfunctions, one area where this finding has the potential for real impact is in curbing instances of graft versus host disease (GVHD) following treatment for blood cancers such as leukaemia and lymphoma.

Often, patients who have such cancers receive a bone marrow or stem cell transplant together with T cells from the stem cell donor. The T cells are highly effective in killing off any remaining cancer cells, but can also cause GVHD. “We discovered that Tregs are highly effective in preventing GVHD, but only when they are present in high numbers before any GVHD-causing cells are transplanted,” she said. “If Treg populations fall too low, the donated cells can attack patient’s tissues, causing GVHD.”

Using her novel breakthrough method to identify Tregs, Fazekas de St Groth and her team are facilitating the design of protocols that could someday give far better outcomes for those suffering from blood cancer by preventing the unwanted immune responses responsible for GVHD. “We are developing new ways to help donor Tregs to survive and proliferate in transplanted animals,” she shares. “This could someday be applied to humans.”

ARE WE TOO CLEAN? THE HYGIENE HYPOTHESIS

A major question for Fazekas de St Groth and her team is: why is the number of people with autoimmune and allergic diseases growing? While the possible reasons for the onset of these diseases is vast, much evidence supports the ‘hygiene hypothesis’.

Essentially, the theory goes that as living standards rise, so too do levels of hygiene. The ‘good’ bacteria we have inside of us are likely to be acquired early in our lives, from all those we come into contact with, especially our mothers. However, improved health practices may be leading to a reduction in our exposure to harmless infectious agents, microorganisms and parasites, thereby suppressing the development of our immune system.

Fazekas de St Groth has postulated that the lack of microbial information available to Tregs – the cells responsible for setting the ‘immune threshold’ (that is, what our immune system should consider as good and bad) – has led to the threshold being set too low, so the immune system reacts to harmless substances such as allergens (in the case of allergies) or the body’s own organs (in the case of autoimmune diseases).

THE FUTURE FEELS GUT

While it is important to acknowledge that reducing transmission of disease-causing infections as a result of public health measures and medical care has saved countless lives, it is essential to consider the potentially catastrophic consequences of a population devoid of good bacteria. “Once the good bacteria are gone, we won’t get them back without having contact with people who still have them. One way to do this is via early childcare, but only in circumstances where this is a mix of children including those born in countries that do not yet have Western levels of autoimmune disease and allergy,” explains Fazekas de St Groth.

If she is correct in thinking that the rapid increase of allergies and diseases associated with the immune system (including lifestyle diseases such as vascular disease, diabetes and obesity) is affected by the microbiome, then the solution is sobering – we need to save the microbiome before essential bacteria are lost forever. With the team’s continuing research, this is a distinct possibility, as she explains: “I’m hoping that we can get some compelling evidence showing how we could reconstitute the microbiome to reboot Western immune responses – getting them back to the point where autoimmune disease and allergy are things of the past”.

INTERNATIONAL INNOVATION