Cells with a tight rein on the immune system

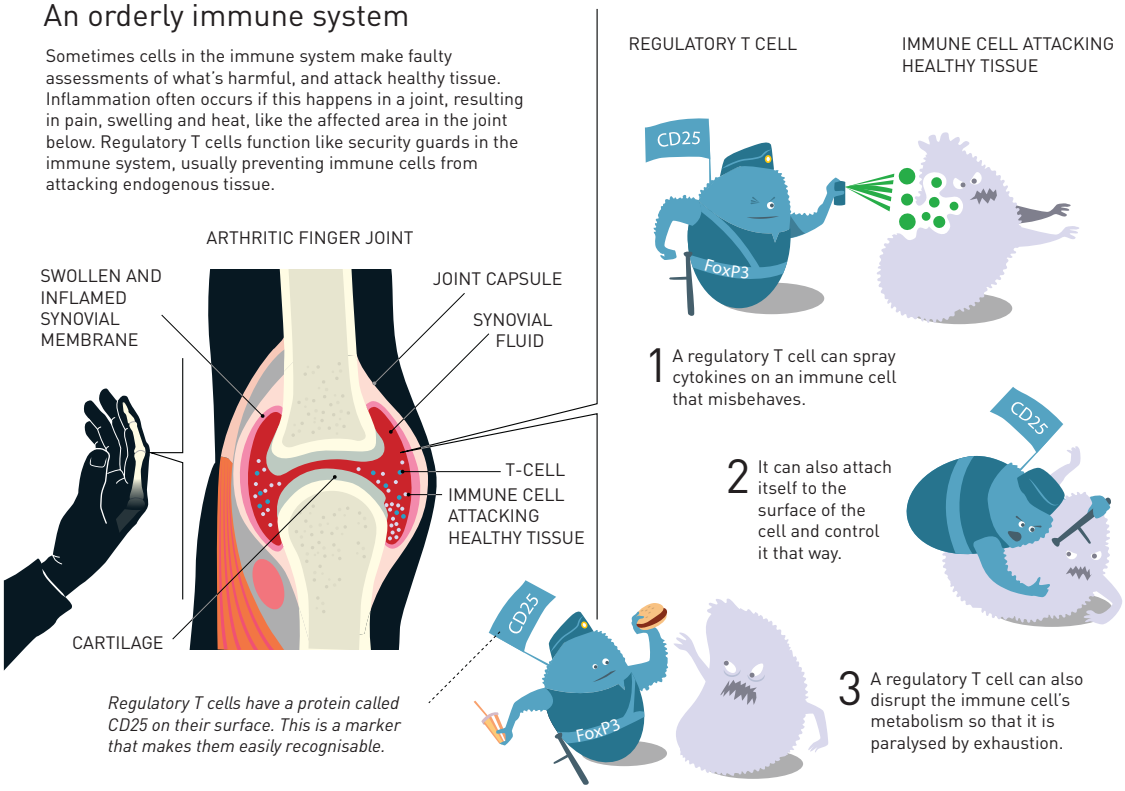
Scientific perseverance and a tiny sick mouse. These are central to the story of how important knowledge about the immune system was discovered. It tells of regulatory T cells that suppress overactive immune cells and so prevent them from attacking healthy tissue. These regulatory T cells are the bearers of great hopes, as they are thought to have the potential to be used in effective treatment for autoimmune diseases. For their fundamental discoveries relating to regulatory T cells, three researchers share 2017's Crafoord Prize in Polyarthritis: Shimon Sakaguchi, Japan; Fred Ramsdell, USA; and Alexander Rudensky, USA.

The task of our immune system is to protect us from various kinds of infection, but sometimes it can become overzealous and start to attack normal tissues. Diseases that occur when the immune system destroys healthy cells are called autoimmune diseases, which include type 1 diabetes, multiple sclerosis (MS), as well as rheumatoid arthritis, one of several diseases that can cause polyarthritis. Autoimmune diseases can affect many organs, such as the thyroid, adrenal gland or the skin, causing suffering and premature death for millions of people globally. There are no cures. That said, there are numerous suppressive treatments for diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Previously, patients with these diseases were often severely disabled, but thanks to suppressive treatments they are now able to enjoy healthy lives.

The Laureates' discoveries concern a specific type of cell in the immune system – regulatory T cells, also called Treg. These cells can be described as security guards who keep watch over other cells in the immune system, namely those that attack the body's own healthy tissue. These security guards can both attack and overpower temperamental colleagues that randomly react with aggression towards both dangerous intruders and healthy cells. They can react to these potential troublemakers by releasing modulatory immune hormones, known as cytokines, to paralyse them by disrupting their metabolism. They can also attach themselves to the cells' surface and then signal to them how they should behave. The result is that white blood cells that want to attack healthy tissue are prevented from continuing their rampage – they cannot multiply, nor can they continue behaving aggressively towards normal cells.

Safety checks in the immune system

The immune system has a variety of ways to prevent or interrupt attacks on healthy cells. Autoimmune diseases can occur when one or more of these security systems fails. One problem found in many, but not all, people with autoimmune diseases, is that they have too few suppressing security guards, or those they do have are not doing their job properly. The anomalies in these suppressive cells vary with different autoimmune diseases and they may even be different for the same disease in different people. More knowledge is needed before the dream of new pharmaceutical treatments comes true, but the general outline has been convincingly drawn. Everything indicates that the immune system's own security guards can be used to maintain order among the immune system's harmful cells. This means that, in the future, it may well be possible to use a mechanism normally found in the body to prevent autoimmune reactions. This year's Crafoord Laureates have played decisive roles in this field.



Aggressive cells are good – overly aggressive cells are bad

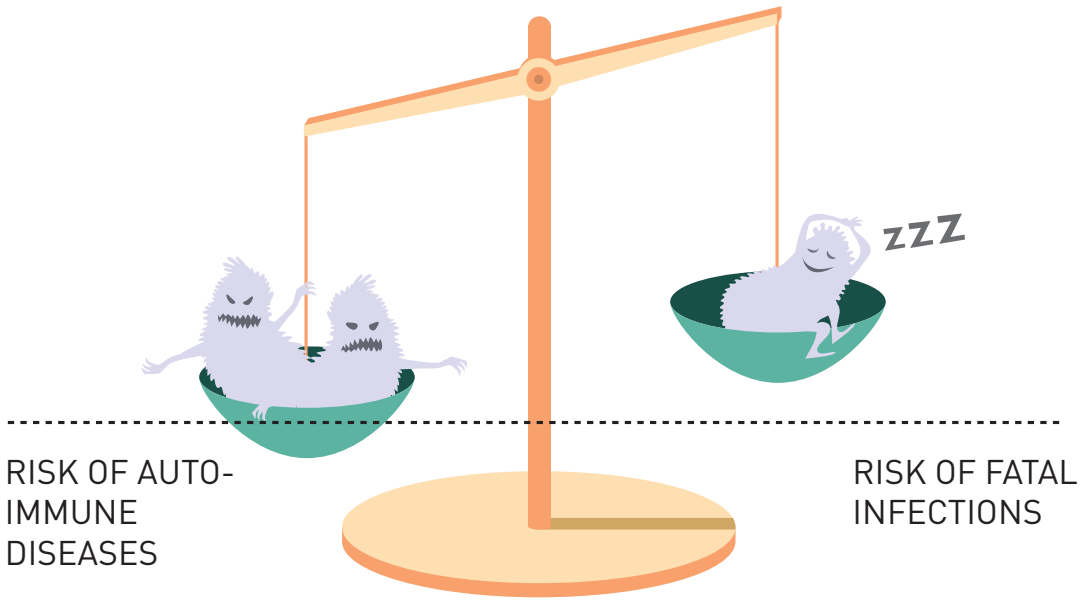
Throughout history, some infectious diseases, such as the plague and the Spanish flu, have killed vast numbers of people in a short period. This means that it is vital for us to have an immune system that reacts quickly and aggressively. However, the immune system must also be tolerant and gentle towards our own healthy tissue and friendly gut bacteria. Our health depends upon the immune system's cells doing the right thing and being aggressive or tolerant at the appropriate time. Autoimmune diseases can arise if there is too much aggression toward endogenous tissue, whereas bacteria and viruses can take over if there is too much tolerance.

It has been known for many years that T cells are separated out and instructed to die if they are too aggressive or too tolerant, and that this selection takes place in the thymus, an organ located in the chest, close to the heart, which is particularly active in young children. Potentially harmful T cells sometimes escape into the body, despite supposedly having been destroyed following an inspection in the thymus. These T cells may be overzealous in their desire to protect the body from dangerous intruders and, if they are activated and start to multiply, they can cause problems. They are short-tempered and lash out at healthy tissue with the same force as against bacteria and viruses, thus harming the body.

Tenacious researcher worked against the tide

Even in the 1960s, there were theories that the immune system might have suppressor cells to rein in overzealous cells that attack endogenous tissue. Some studies indicated that these theories were correct, but they were later dismissed as being exaggerated or poorly executed. This led to the entire research area becoming neglected. An aura of ridicule surrounded the hunt for the immune system's suppressor cells; no researchers who wanted to be taken seriously could dedicate themselves to this

field. However, Japanese immunologist Shimon Sakaguchi was convinced the theories were correct. He struggled alone in his attempts to identify these suppressor immune cells, which he finally succeeded in finding in a cell population that previous researchers had neglected.



The right balance: Cells in the immune system should be aggressive and attack dangerous intruders, but if they are too aggressive they may start to attack healthy tissue, perhaps causing an autoimmune disease. However, if the cells are too passive they may be overly lenient on dangerous bacteria and viruses. A good immune cell senses the right balance and is aggressive or tolerant on the right occasions.

Sakaguchi made his first find at the start of the 1980s, when he surgically removed the thymus from new-born mice. The thymus has an important function in the immune system because this is where T cells, which first develop in the bone marrow, mature. T cells is an abbreviation of thymus dependent cells. As they mature, the T cells are given various special functions. Some become killer cells, destroying cells that have been infected by viruses or bacteria. Others become helper cells, commanders that are vital to the immune system's defences. Helper cells can produce cytokines, which activate other cells in the immune system, allowing them to perform the correct actions to disarm intruders.

Sakaguchi removed the thymus from three-day-old mice and discovered that they developed severe autoimmune diseases that fatally attacked the ovaries. However, if, immediately after the thymus was removed, the mice received T cells transplanted from other mice, ones that still had a thymus, they did not develop an autoimmune disease. Sakaguchi drew the correct conclusion: there are T cells that should restrain the cells that mistakenly attack endogenous tissue. He also determined that these suppressive T cells develop in the thymus in the first three days of a mouse's life. This contradicted the current dogma; only a few researchers paid attention to his results and conducted their own studies of the phenomenon.

Sakaguchi continued to methodically transplant different types of T cells into diseased mice. This was how, ten years later – in 1995 – he succeeded in isolating the cells now known as regulatory T cells. These are recognisable by the protein they carry on their surface, a "flag", called CD25. Other

researchers became more interested in suppressor T cells after these discoveries were published, but many were still doubtful and highlighted how the CD25 "flag" could also be found on the surface of T cells with completely different functions. Was there really a unique group of T cells that only suppress immune reactions and, if so, which mysterious cellular machinery governed their actions?

The importance of a small diseased mouse in solving the riddle

American immunologist Fred Ramsdell approached this field of research from an entirely different direction. He was interested in mice that are born with a severe autoimmune disease that attacks the skin, pancreas, kidneys and bowels, which means they die soon after birth. These mice are called scurfy mice and it was known that the disease is X chromosome-linked. Ramsdell decided to identify exactly which gene had mutated. He also wanted to find out how the gene worked.

Ramsdell proceeded methodically. He bred and cross-bred a great many mice with changes in the genome, gradually narrowing down his search. Finally, he closed in on the gene now called FOXP3. This gene has mutated in scurfy mice and thus cannot produce the protein for which the gene codes. This protein, also called FOXP3, turned out to be a transcription factor, a protein that binds in proximity to other genes in the DNA and can thus govern whether these genes should produce various proteins.

When Ramsdell was in the final stage of his research, he asked paediatricians around the world to examine tissue samples from their patients to see whether any of them had faults in the human equivalent of the FOXP3 gene. The results were almost immediate – children with a congenital disease called IPEX, which is short for immune dysregulation, polyendocrinopathy, enteropathy and X chromosome, had changes in exactly that gene. Children with IPEX are usually born with diabetes and autoimmune attacks to their skin and small intestine, and urgently require stem cell transplants to ensure survival. Identification of the faulty gene in IPEX in 2001 was a breakthrough for the understanding of other autoimmune diseases. However, the central issue was still shrouded in mystery: why does a lack of FOXP3 protein cause autoimmune disease – exactly how is the immune system affected by this protein?

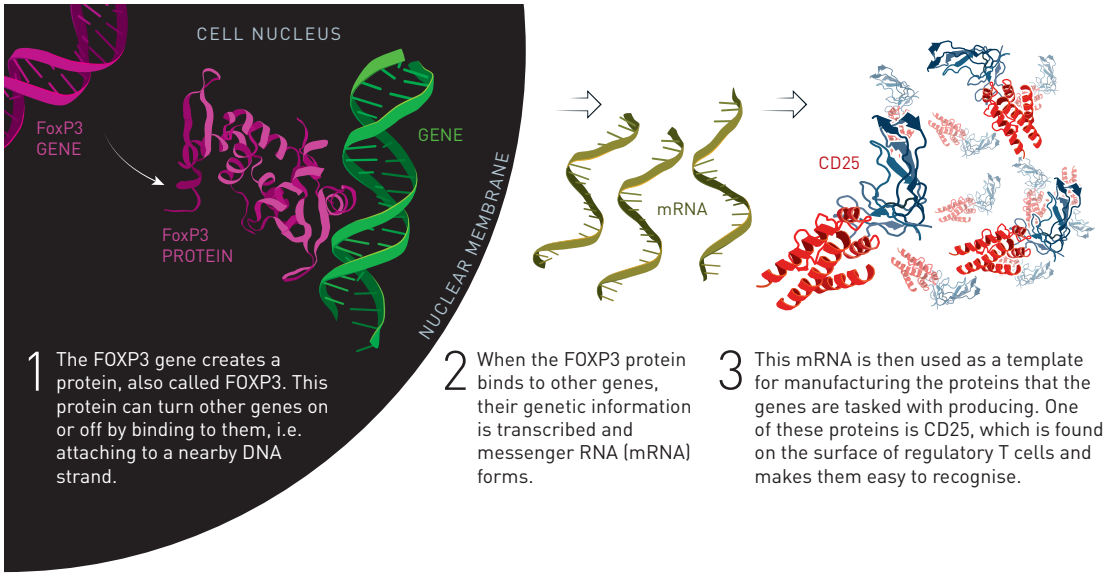
Everything is tied together and starts making sense

There was a two-year wait until the answer came from the three Laureates working independently of each other, but whose separate threads now entwined to make a sturdy rope: Shimon Sakaguchi, Fred Ramsdell and Alexander Rudensky. The latter created FOXP3 deficient mice, in which the genome has been manipulated in order to investigate the function of single genes. The experiment showed that mice that cannot manufacture the FOXP3 protein are unable to form regulatory T cells and therefore suffer from severe congenital autoimmune diseases. Sakaguchi and Ramsdell arrived at the same conclusion in their studies, namely that the FOXP3 gene is a start button for a major gene programme that results in some T cells becoming security guards, trained to keep an eye on misguided colleagues that attack the body they were supposed to protect. Sakaguchi's and Ramsdell's previous discoveries could be linked, opening up an entirely new field of research that has undergone rapid development.

Subsequently, more pieces of the puzzle have been put into place, one by one, due to further dynamic advances led by Rudensky and Sakaguchi, who have contributed important additional discoveries. We now know how regulatory T cells develop, how they work and how they can be controlled. It's also known that these cells are often dysfunctional in patients with arthritis or other autoimmune diseases. A great number of clinical trials are now being conducted globally, with research teams testing various methods of controlling regulatory T cells, in order to understand and

use the immune system's own mechanisms to protect the body from autoimmune attacks.

Pressing the immune system's brake



The aim is to use the mechanism normally found in the body and subdue an overactive immune system that is attacking endogenous tissue. The vision is that this will lead to more effective treatments and, in the best case, a cure for polyarthritis and other autoimmune diseases.

LINKS AND FURTHER READING

Mer information om årets pris finns på Kungl. Vetenskapsakademiens webbplats, *http://kva.se/crafoordpriset* och *www.crafoordprize.se*

Scientific articles

www.nature.com/ni/focus/regulatory_tcells/classics/pheno.html
www.nature.com/nri/journal/v14/n5/fig_tab/nri3650_F1.html

Interview

Alexander Rudensky: www.youtube.com/watch?v=4kgNr9ecF2Y

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