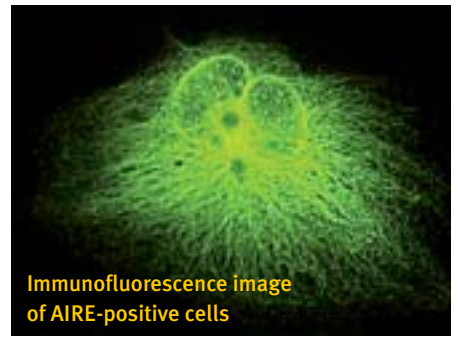
Autoimmune disease in Tartu/Estonia

Working on AIRE

In the thymus, young T cells are eliminated that are not able to differentiate between self and foreign antigens. Pärt Peterson *et al.* are studying a key player in this crucial control that safeguards the body against overly aggressive autoimmune reactions.



Immunofluorescence image of AIRE-positive cells

A very important property of the immune system is flexibility. It defends the organism against a great variety of attackers: bacteria, viruses, parasites – and it also has to combat degeneration of tissues, for instance during cancer development. There are hundreds of multifaceted antigens to deal with. The immune system is well equipped with a just as multifaceted repertoire of immune cells – each one specifically recognizing one special antigen. It is able do to battle against all imaginable kinds of different antigen variations.

However, lashing about and fighting against everything that crosses your path is not necessarily a good defence strategy, as you can hurt yourself. Also if you are not able to differentiate between friends and enemies there may be losses in your own ranks.

Friend or foe?

If the immune system is over aggressive this may lead to autoimmune reactions against the body's own structures. Then immune cells attack self-tissues in error, which are in consequence destroyed.

The autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, shortly APECED, is a disease caused by a broad breakdown of self-tolerance and an immuno-attack on multiple tissues. Mostly, endocrine organs like the adrenal cortex and the parathyroid gland are affected – thus typical symptoms are combinations of different endocrine autoimmune syndromes such as Addison's disease, hypoparathyroidism, and type 1 diabetes.

"It is a kind of general failure of immune tolerance," says Pärt Peterson from the Laboratory for Molecular Pathology at the University of Tartu, Estonia. He has dealt with this disease, also known as autoimmune polyglandular syndrome type I or APS I for quite a long time. The biologist has been studying its basics since the early 1990s first during his PhD and later as a postdoc in the lab of Kai Krohn at the University of Tampere in Finland.

Friendly fire

Since Finland has historically been quite isolated, the monogenic autosomal recessive syndrome is greater in the Finnish population with an incidence of 1:25,000. This is not good for the people affected, but good for the people who study the disease. "We had good opportunities to get patient's material for our research," Peterson remembers.

He first started to identify the target proteins of this autoimmune attack. "In the adrenocortex we found the enzymes 17α-hydroxylase and 21-hydroxylase, which are essential in steroidogenesis, act as autoantigens," he says. In consequence, the adrenal gland is destroyed.

Pärt Peterson (center) and his T cell maturation experts

Subsequently, Pärt Peterson and his colleagues looked at the gene behind this disease using positional cloning, as the human genome sequence was not yet available at that time. They were successful: they know today that APECED is caused by knock-out mutations in the gene for the autoimmune regulator called AIRE. Moreover, the researchers found that this transcriptional activator usually – when functional – prevents the development of the autoimmune disease (*Nat Genet.* 17:393-8). This was already implied by the name they had given to the protein – but how does the regulator perform its job?

Under control

At the end of 2003, Pärt Peterson returned to the University of Tartu as a senior fellow supported by the Wellcome Trust programme. With his group, which numbers 15 people today, he still continues to elucidate the molecular background behind AIRE's function.

Pärt Peterson explains that to avoid autoimmune reactions the immune system has to be able to differentiate between self and foreign antigens and has to establish tolerance for self-antigens. In this regard, the thymus has been known for a long time to be the essential teacher of the immune cells, rather T-cells. This primary immune organ checks if a T-cell aspirant recognizes specifically a body's self-antigen. If so, this "harmful" T-cell needs to be selected and eliminated through apoptosis or functional inactivation. Only non-autoreactive T-cells are al-

lowed to go outside the thymus to the periphery, where they do their work in the defence against infections.

Enter epigenetics

This negative selection is organized by the thymic medullary epithelium expressing a huge number of promiscuous self-antigen genes. Pärt Peterson describes how AIRE enters here. Itself expressed in the thymic medulla, AIRE was found to be the key player in regulating the expression of these highly diverse self-antigens. A special task, if one bears in mind that many of those antigens are usually restricted to special tissues and not expressed in other tissues. "For instance, AIRE makes tissue-specific genes such as insulin, which is usually only expressed in pancreatic β-cells in the islets of Langerhans, activating it in untypical tissue, the thymic medullary epithelium," explains Peterson.

AIRE was shown to control genes in genomic clusters, indicating its role in epigenetic regulation. In addition, Peterson and his team found that the AIRE protein contains so called plant homeodomain or PHD fingers. These small zinc-binding domains are often found in chromatin-associated proteins. "The PHD fingers came out to recognize lysine methylation events at the N-terminal end of the histone H3," explains Pärt Peterson. Very often, trimethylation of lysine 4 (K4) in H3, especially located in promoter regions, serves as an active gene mark transcription activators can recognize. A gene that should be expressed in a specific cell is assigned in this way. On the other hand, in tissues where it is inactive the referring H3K4 is not methylated or is single-methylated.

So far so good! However, in self-antigen presentation in the thymus, something must work in a crucially different way, as the potpourri of normally tissue-restricted antigens are present here. What allows the transcriptional controller AIRE to realise this unusual gene expression?

Sticky fingers

Pärt Peterson and his co-workers very recently came closer to what distinguishes normal gene activation from that in the thymic medulla and where AIRE is silhouetted against other transcription modulators (*EMBO Rep.* 9:370-6). "We found that AIRE also binds to H3 histones through its PHD finger, but preferentially to non-methylated ones at lysine 4," summarizes the 42-year old. Thus, in the thymic medulla, AIRE is able to read the unmethylated form of H3K4 in promoters and nevertheless activates gene expression of antigens to be presented to a developing T-cell.

"We now have an idea of how AIRE works sensing epigenetic chromatin modifications," says Pärt Peterson. This understanding might finally be useful to develop therapeutic strategies to treat autoimmune diseases.

Many autoimmune diseases develop during the second decade of life, as thymus activity decreases after puberty. Peterson says, "If we could regenerate the activity of the thymus and stimulate the expression of self-antigens thereby modulating AIRE expression or function, we would be able to block autoimmunity!" Dreams of the far future fascinate Pärt Peterson.

With a little help from...

However, there is still a lot of work to do, the biologist states realistically. "We first have to study exactly, how the immune tolerance in the thymus is formed and, for example, how AIRE selects and activates the tissue specific genes," says Peterson. However, he does not want to do that with his group alone. "We work together with collaborators from all over the world and especially as part of the EU framework program 6, THYMAIDE and EurAPS, to get more insight into this."

Of course, he still has good contacts with Finland, not only because the disease he is studying is so frequent there but also because it is just a step across the Gulf of Finland. "I made a lot of friends in the more than ten years I lived there," he laughs.

Finnish connections

For researchers in a small country like Estonia, working in collaboration and with networks is essential and improves the level of science a lot. "It is obvious that we cannot cover all aspects of contemporary science! However, research conditions are very good in Estonia.These days, laboratory facilities, for example, are as up to date as in Scandinavia." Therefore he sees no reason to go abroad again.

The one thing Pärt Peterson wishes for the future is more investment in science on a national level. The current percentage of the gross national product for research and development in Estonia is less than 1%, compared to more than 3.5% in Finland and Sweden. He considers that "this is too little!"

Maybe somebodyin the Estonian government will read this article?

SUSANNE DORN