Tissue samples analysed with Sensitive Data (SD) services provide new information on celiac disease and other autoimmune diseases

Celiac disease is a condition in which gluten in cereal-containing food products containing rye, wheat and barley cause inflammation and damage to the small intestinal mucosa. Because of the damage, nutrients are not properly absorbed. RNA sequencing of patient tissue samples and cells makes it possible to study the immune system, and whether it's functioning properly.

Celiac disease is considered an autoimmune disease, in which the body's defence system mistakenly targets its own tissues. Although the exact causal mechanism of celiac disease is not yet known, there is a hereditary predisposition to its onset.

Immunologist **Helka Kaunisto** from the Celiac Disease Research Center at Tampere University studies dermatitis herpetiformis, the skin manifestation of celiac disease.

"I have always been interested in autoimmune diseases. People who get them are at risk of developing other autoimmune diseases."

How disease becomes systemic

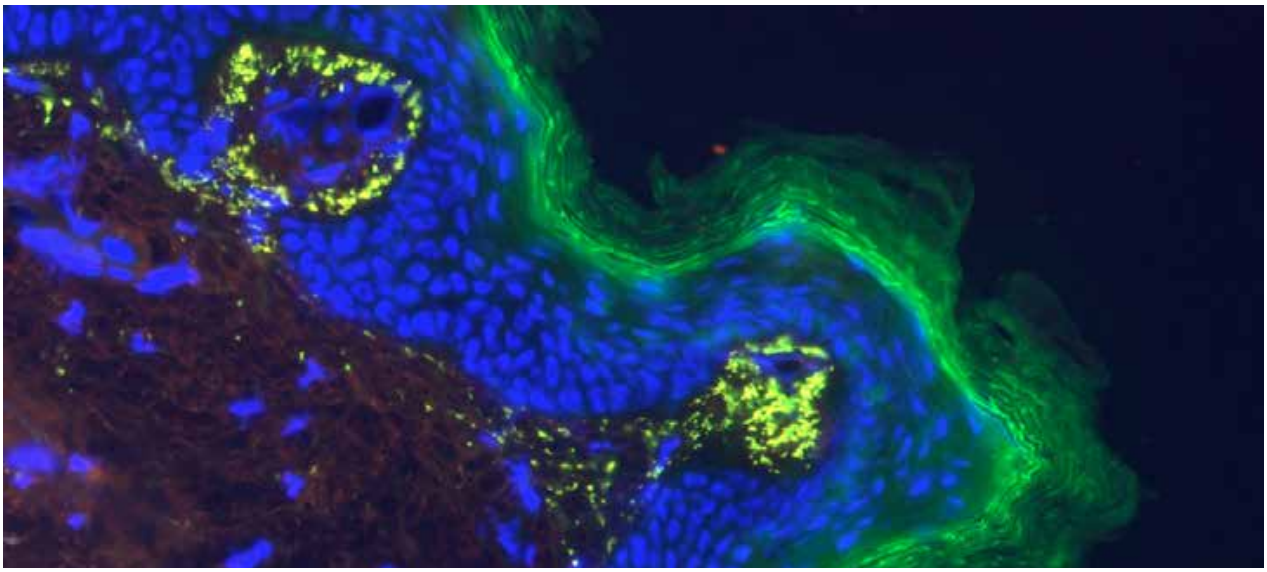
Dermatitis herpetiformis is a common extra-intestinal manifestation of celiac disease, causing an itchy rash with small blisters due to intake of wheat, rye and barley -derived gluten. Both celiac disease and dermatitis herpetiformis are associated with a strong hereditary predisposition.

"Half of my thesis work is RNA sequencing. We are not looking for a specific gene or protein in the sequencing, but want to investigate what types of changes gluten intake causes in the RNA profile of people with dermatitis herpetiformis."

According to Kaunisto, it is possible that gluten intake leads to altered expression of certain RNA molecules in people with dermatitis herpetiformis. It shows the effect of gluten on the immune system, for example on cellular metabolism or inflammation.

At the same time, it is possible to explore how in celiac disease the immune response can spread from a local reaction in the gut to a systemic reaction that spreads to the skin or other organs. In other words, the disease is complex, and this complexity includes immunological abnormalities.

In the Nordic countries in general, and in Finland in particular, there is a high level of awareness of celiac disease. It is widely screened, and doctors know when to suspect it. In Finland, almost 2 per cent of the population has celiac disease. There are good gluten-free food options available in Finland.



Fluorescent image of a skin sample, where the nuclei are blue, transglutaminse 3 is green, and IgA antibodies (immunoglobulins) are red. Yellow areas indicate overlapping location of IgA and transglutaminase 3 in the skin.

Kaunisto studies immune cells and the immune response to find out why some people with celiac disease develop dermatitis herpetiformis.

"It should be remembered that the gut and the skin have different layers that function in different immunological ways. Dermatitis herpetiformis is a really good target for studying the extra-intestinal symptoms of celiac disease. This information can then also be used to investigate other autoimmune diseases. For example, how can rheumatism start in one place and then spread elsewhere and become systemic?"

Around 10 per cent of people with celiac disease have dermatitis herpetiformis. Celiac disease and dermatitis herpetiformis can be investigated by measuring antibodies in the blood. In people with celiac disease and those with dermatitis herpetiformis, gluten triggers the formation of tissue antibodies.

"Celiac disease is known as an intestinal disease, but it has many other symptoms that are not related to the intestines at all. There may be neurological and skin problems too. Is there a difference in immunity between people with celiac disease and people with dermatitis herpetiformis? How can an immune response spread from the gut to the skin – and why does a rash develop?"

The diagnosis of celiac disease exploits the analysis of antibody levels. Transglutaminases are enzymes that bind proteins together in tissues. High levels of antibodies to transglutaminase 2 (S-tGAbA) suggest the person has celiac disease. Transglutaminase 2 modifies the structure of gluten in the body. This causes the lining of the small intestine to become inflamed and damaged.

The Celiac Disease Research Center in Tampere has conducted a study in which patients with dermatitis herpetiformis who were on a gluten-free diet were exposed to gluten for a short period. Before and during exposure, samples were taken from the small intestine and blood. These samples are studied to find out how gluten affects the expression of RNA in blood cells and the small intestine.

"Although some people with celiac disease have the same serum-based antibodies as people with dermatitis herpetiformis, not everyone will get dermatitis herpetiformis", says Kaunisto.

"Patients with dermatitis herpetiformis have antibodies to transglutaminase 2, but they also have antibodies to a related enzyme, transglutaminase 3. Transglutaminase 3 (TG3) antibodies are also found in the skin, close to the rash, and are thought

CSC can install new software on CSC's computing environment SD Desktop at the researcher's request.

to be involved in its development. TG3 antibodies are also found in the bloodstream of patients with dermatitis herpetiformis. Although some people with celiac disease also have antibodies to transglutaminase 3 in the bloodstream, not all people with celiac disease develop dermatitis herpetiformis. Why this is so is what we want to solve."

According to Kaunisto, the research is of great benefit to clinical science.

"For example, if celiac disease is not well managed – the person doesn't stick to a strict gluten-free diet, say – is there a greater chance of developing extra-intestinal symptoms?"

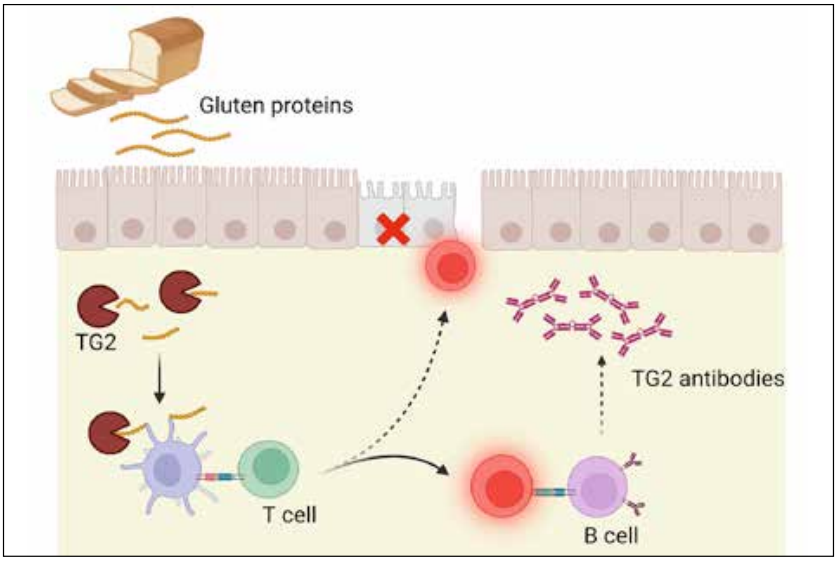
CSC's sensitive data services

The study involves analysis of sensitive data obtained from patient's tissue samples. Patients consented to participate in the study. As this is information subject to the European Union's General Data Protection Regulation (GDPR), the data will be processed and used in CSC's sensitive data services (SD Desktop and SD Connect).

The sequencing has been done in collaboration with the University of Helsinki, and the data is stored encrypted in SD Connect and analysed with SD Desktop.

Kaunisto did not have previous experience of the high-performance computing or sensitive data services.

"I started using the Sensitive Data Services because I needed more computational power than what was available for me through the university, and I needed a secure environment for this computational power. I find the services very easy to use as the online guides are very thorough. If I have a problem I can't solve myself the helpdesk is always very helpful."



The inflammatory reaction in the small intestine. Transglutaminase 2 (TG2) modifies gluten proteins, which are presented to the T-cells. T-cells cause inflammation that leads to the dysregulation and apoptosis of the epithelial cells. T-cells also activate antibody-producing B-cells to produce the antibodies targeting to TG2. In the picture the red X indicates changes in the gut that leads to the damage or destruction of intestinal cells.

To avoid the long-term effects of gluten, treatment can begin as soon as possible when celiac disease is detected early. However, since gluten is present in many foods, gluten-free diets are difficult to maintain.

"At the moment, the only treatment is a strict gluten-free diet, but there is also a lot of research underway into pharmaceuticals as possible future treatments. The Celiac Disease Research Center also collaborates extensively with companies developing new potential drugs. Drugs may be able to prevent intestinal and other damage in patients in the future, but initially they will likely be adjunctive therapies alongside gluten-free dietery treatment. A preliminary study carried out in Tampere University found that the experimental-phase drug ZED1227 inhibited transglutaminase 2 activity, and its use reduced gluten-induced intestinal damage in patients."

12.4.2023 | ***Ari Turunen***

MORE INFORMATION:

Celiac Disease Research Center, University of Tampere
https://www.tuni.fi/en/research/celiac-disease-research-center

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