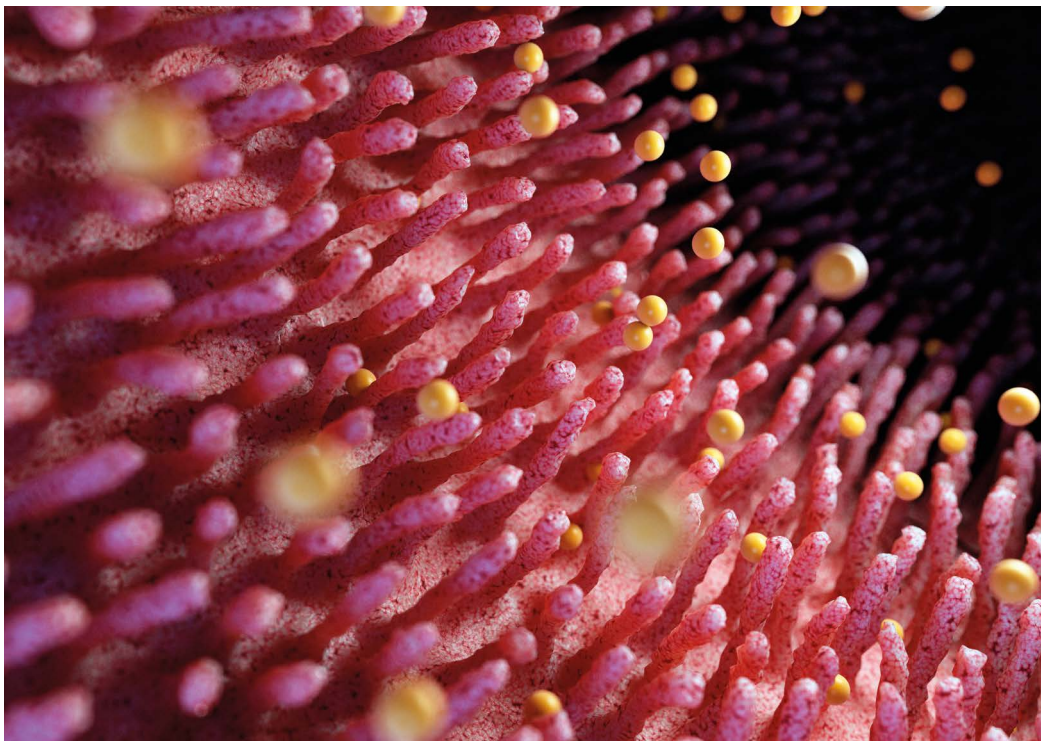
Research round-up

Highlights from research. By Laura Vargas-Parada



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Gluten, a protein found in cereals, damages the intestinal villi in people with coeliac disease.

Autoimmunity on the rise

For decades, clinical observations have suggested that the prevalence of autoimmune disease is increasing. However, studies based on systematic data are limited, so it has been unclear whether the apparent rise is simply due to changes in diagnosis and reporting. Now, a team of researchers has shown that antinuclear antibodies – a type of autoantibody that is a common biomarker of autoimmune disease – have become increasingly prevalent in the US population over the past 25 years.

The team, led by Frederick Miller at the National Institute of Environmental Health Sciences in Durham, North Carolina, analysed serum samples from more than 14,000 people, collected as part of the US National Health and Nutrition Examination Survey between 1988 and 2012. The researchers used indirect immunofluorescence, a technique that stains antibodies with a fluorescent dye, to identify the antinuclear antibodies present in each sample. They then compared the prevalence across three time periods; 1988–91, 1992–2004, and 2011–12. The researchers also looked for correlations between antinuclear antibody prevalence and other variables such as sex, age, ethnicity, weight, smoking history and alcohol consumption.

The analysis showed that antinuclear antibody prevalence increased over the 25-year span, from 11% in the earliest samples to almost 16% in the most recent. The increase was most obvious in men, in non-Hispanic white people and, most significantly, in adolescents; the prevalence of antinuclear antibodies in teenagers nearly tripled over the period assessed by the study.

Weight, smoking history and alcohol consumption had little impact on the increase in the prevalence of antinuclear antibodies, suggesting that other changes in lifestyle or the environment might be driving the rise in autoimmunity.

Arthritis Rheumatol. **72**, 1026–1035 (2020)

Accurate model of coeliac disease

For the first time, a mouse model of coeliac disease reproduces the genetic and immune characteristics of the human condition, providing a powerful tool for developing treatments.

In coeliac disease, exposure to dietary gluten – a protein found in cereals such as wheat, barley and rye – causes the immune system to attack a person's own tissues. It occurs in genetically susceptible individuals who have particular DNA sequences known as HLA-DQ8 or HLA-DQ2, and produces hallmark damage to the small, finger-like protrusions in the small intestine known as villi, which help to absorb nutrients.

The mouse model, engineered by Bana Jabri and her team at the University of Chicago in Illinois, has the DNA sequence HLA-DQ8 and reproduces the villous atrophy caused by eating gluten by producing a compound called IL-15 in the gut, which is characteristic of active coeliac disease. Moreover, the disease can be reversed when the mouse receives a gluten-free diet, just as in people. The researchers think this unique model will provide a much-sought tool for trying new non-dietary treatments or preventive strategies in those with high-risk genetic profiles.

Nature **578**, 600–604 (2020)

Tissues' shared response to attack

Type 1 diabetes, lupus, multiple sclerosis and rheumatoid arthritis can all be characterized as the immune system attacking a person's own tissues. There are also commonalities in the way this attack is launched, with several shared mediators of tissue damage. The tissues affected in each disease are

different. But researchers led by Decio Eizirik at the Indiana Biosciences Research Institute in Indianapolis have shown that how these tissues respond to immune assault in each disease is remarkably similar – although the target cells vary considerably, the path to destruction is shared.

The team used gene-expression data sets from each of the affected tissues – the pancreas, kidneys, optic chiasm and joints – and looked for similarities and differences during the inflammatory response in people with and without disease. They found changes in the expression of major common sets of genes in the target tissues of all four diseases. One of the shared molecular signatures is the gene that codes for TYK2, a protein involved in the regulation of a key immune modulator, interferon.

The activation of common molecular signatures suggests drugs already in use to treat one autoimmune disease could be equally beneficial for another. In separate studies, it has been found that TYK2 inhibitors have a protective effect against immune-mediated damage in psoriasis and type 1 diabetes. The authors say that their work demonstrates the benefit of focusing not only on the immune attack, but also on how the target tissues respond to immune cells.

Sci. Adv. **7**, eabd7600 (2021)

COVID-19 linked to autoimmunity

People infected with SARS-CoV-2 generate large numbers of autoantibodies capable of attacking their own immune system and tissues, according to research conducted at Yale University in New Haven, Connecticut. The study suggests that autoimmunity could explain why some people experience symptoms of COVID-19 more severely than others, or for a longer time after infection.

Aaron Ring and his colleagues screened 172 people who were hospitalized owing to COVID-19, as well as 22 people with the SARS-CoV-2 infection who had mild or no symptoms and 30 uninfected individuals, for antibodies against a collection of almost 3,000 human proteins. They found that people with the infection had many more of these autoantibodies than did uninfected people, and that levels were highest in those with severe disease. This latter finding was further probed in a mouse model of COVID-19, which suggested that autoantibodies against certain immune targets could severely exacerbate the disease.

"The persistence of these autoantibodies could be behind long COVID."

The researchers identified numerous autoantibodies in people with COVID-19 that impair the immune system, either by attacking B cells – the cellular factories that produce antibodies to fight the virus – or by destroying proteins known as interferons that are key to defending against viruses. They also found that people with COVID-19 developed autoantibodies against proteins in their blood vessels, connective tissue and brain – tissues and organs that can be affected by the disease.

The persistence of these autoantibodies could be behind long COVID, which causes people to continue experiencing symptoms for months after infection, according to the authors. They also suggest that people with pre-existing autoantibodies at time of infection with SARS-CoV-2 could be at greater risk of severe disease. Together, pre-existing and induced autoantibodies might explain the different clinical outcomes observed in people with COVID-19.

Nature https://doi.org/gj39vh (2021)

Microbial role in multiple sclerosis

Two groups of researchers have each found evidence of how the gut microbiota composition might affect the symptoms of multiple sclerosis (MS), the most common autoimmune disease affecting the central nervous system in adults.

In MS, the immune system attacks the insulating sheath covering the nerve fibres of the brain and spinal cord, made up of a lipid–protein mix known as myelin. Although accumulating evidence suggests that gut microbiota play a part in the condition, a mechanism by which the microbiota can influence a disease that affects another part of the body has eluded researchers.

In the first study, Hiroshi Ohno and his colleagues at the RIKEN Center for Integrative Medical Sciences in Yokohama, Japan, found that when the antibiotic ampicillin was administered to a mouse model of MS, demyelination was reduced. Further analysis revealed that a strain of bacteria from the family *Erysipelotrichaceae*, named OTU0002, which was cleared by ampicillin, combines with *Lactobacillus reuteri* bacteria to exacerbate demyelination and inflammation in mice.

Researchers identified proteins in *L. reuteri* that mimic a region of a protein known as myelin oligodendrocyte glycoprotein (MOG), which is important for the myelin sheath to adhere to neurons. But this alone is not enough to cause damage: OTU0002 also needs to be present. It acts as an adjuvant, activating a particular kind of T cell in the small intestine that targets MOG. Because only the mice that harboured both types of bacterium showed more severe symptoms, the authors concluded that understanding microbes' synergistic interactions might help to identify preventive strategies.

Meanwhile, an international team led by Anne-Katrin Pröbstel at the University of Basel in Switzerland and Sergio Baranzini at the University of California, San Francisco, uncovered the first evidence that during MS flare-ups, immune cells activated by certain bacteria living in the gut can travel to the brain, where they help to reduce inflammation.

The researchers wanted to know whether gut microbiota composition affects the production of immunoglobulin A (IgA) B cells – a type of immune cell specialized in producing IgA – and if these antibody-producing cells had a role in MS symptoms. By sequencing intestinal microbiota from people with active disease, as well as those in remission and healthy controls, the researchers found that IgA B cells specific for certain gut bacteria commonly present in people with MS but not in the controls, such as *Akkermansia muciniphila* and *Eggerthella lenta*, travelled to the brain. They also showed that these B cells secreted proteins in the brain that helped to reduce inflammation, and that IgA antibodies produced by the cells did not recognize brain proteins – only gut microbiota. The authors suggest these bacterium-specific IgA antibodies could be used as biomarkers for MS, whereas the cells producing them could be a target for therapeutic interventions (see page S54).

Nature **585**, 102–106 (2020); *Sci. Immunol.* **5**, eabc7191 (2020)

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