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The hunt for clues to immune-system disorders

EU researchers are taking fresh approaches to understanding a growing group of illnesses in a bid for more effective treatments.

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In mid-2015 and early 2016 in Finland, a group of scientists became interested in inspecting doormats.

The pursuit, while seemingly unusual, had a serious aim: to determine whether a higher mix of microbes typically found in rural environments might protect against the development of type 1 diabetes, an immune-system disorder.

Microbe mixes

The study is part of a research project that received EU funding to examine links between immune-system illnesses and external environmental factors. These factors, grouped as the “exposome”, include microbes as well as air quality, chemicals, diet and urbanisation.

The researchers found that the risk of developing diabetes was higher in urban locations than rural ones – but that not all rural areas can be regarded the same way.

Rural areas in Finland with relatively little snow on the ground have a greater diversity of environmental microbes. A large mix of such organisms, known collectively as the microbiome, in an area is often linked to better human health. These microbes may, for example, protect against pathogenic microorganisms and toxins when a person is exposed to them in the environment or digests them in food.

‘Snow cover seemed to reduce the microbiome a lot,’ said Professor Heikki Hyöty, a researcher in virology at Tampere University in Finland.

Hyöty leads the EU project, which is called HEDIMED – an acronym for Human Exposomic Determinants of Immune Mediated Diseases.

It runs for five years until the end of 2024 and brings together universities, research centres and companies in countries that range from Austria and the Czech Republic to Switzerland and the US.

Finnish footprints

The study of rural and urban environments in Finland highlights the complexities involved in such research and the difficulties of drawing simple lessons.

But it also signals potentially big benefits for public healthcare from the effort.

The immune system is a network of cells, tissues and organs that work together to protect the body against infections. Multiple disorders ranging from allergies and asthma to diabetes and rheumatoid arthritis can result when the system fails to function properly.

In their study, the researchers in Finland took samples in August 2015 and February 2016 from special doormats placed in the entrances of homes of children in their first year of life.

Doormats were chosen as the way to collect information because they absorb a wide range of organisms when people enter the home. The months of August and February were picked because they ensured specimens from both summer and winter.

The homes were located in rural and urban locations around Turku on Finland's southern coast, in Tampere farther north and in Oulu just south of the Arctic Circle.

Only rural areas showed the sort of higher bacterial richness often associated with health benefits, according to Hyöty.

He said the development of immune-system disorders may be influenced by multiple external factors – for instance, not only whether a location is rural or urban but what the local climatic conditions are.

Network forces

HEDIMED is part of the European Human Exposome Network (EHEN), nine EU research projects that together create the world's largest collaboration on the exposome.

The goal is to deepen understanding of the impact of environmental exposure on health, including immune-system disorders.

As a whole, such disorders are widespread. Allergies, for example, are estimated to affect around a third of people worldwide.

Nonetheless, many immune disorders are poorly understood.

Hyöty said he recognised earlier in his career that more research was needed into the effects of the exposome, with genetics alone unable to explain rapid increases in immune diseases.

'Everybody was studying genes and their relationship to the immune response in type 1 diabetes, but there seemed not too many who were interested in the exposome,' he said. 'I realised that, if we could find environmental factors that explain the increase in these conditions, we may also find a way to prevent them.'

High hopes

In another study, HEDIMED researchers found that different agricultural methods and locations strongly affect microbial diversity in apples and blueberries.

Fruits grown in the wild and in home gardens generally had greater diversity, while commercial horticulture made the microbiome less varied.

This finding highlights how the method and location of food production may play a role in gut health and should be explored in future research on immune disorders, according to Hyöty.

Meanwhile, he said the HEDIMED team has plenty of numbers to crunch.

Researchers are analysing data from large cohorts including altogether 350 000 pregnant women and 28 000 children tracked from birth.

Because the process of contracting an immune disorder begins early in life, the focus is on the foetal and childhood exposome.

Hyöty thinks uncovering even a single factor behind various immune disorders would make it easier to prevent them.

‘I hope that we find at least one common determinant in these diseases,’ he said. ‘That would be a huge breakthrough.’

Molecular markers

Improving the treatment of immune-system disorders is something that Dr Marta Alarcón-Riquelme, scientific director at genomics centre GENYO in Spain, has in her sights.

She leads an EU-funded project taking a new approach: looking at the molecular mechanisms behind patients’ individual responses to treatments rather than classifying the diseases by their final effect on organs.

Called 3TR, the seven-year project is due to run until the end of August 2026. As a public-private partnership under Europe’s Innovative Medicines Initiative, 3TR also receives industry funding and includes pharmaceutical companies such as AstraZeneca and Sanofi.

The research focuses on seven illnesses: asthma, Crohn’s disease, chronic obstructive pulmonary disease, inflammatory bowel disease, lupus, multiple sclerosis and rheumatoid arthritis.

They can be severe and require lifelong management. Lupus, for example, creates joint pain, fatigue and rashes.

‘Diseases like lupus can be life-threatening,’ Alarcón-Riquelme said.

She said that treatments for immune disorders are often a case of trial and error. Patients frequently fail to respond to medication, even if they have the same diagnosis as someone who gets better with the same treatment.

‘They’re also insidious diseases, which means they start earlier than can clinically be seen,’ said Alarcón-Riquelme. ‘A large number of people remain undiagnosed for a long time but, in the meantime, have symptoms that could benefit from the right treatments.’

Tailor-made treatments

By identifying the molecular basis of non-responsiveness, 3TR hopes that more personalised and effective therapies can ultimately be created for patients regardless of their diagnosis.

Giving the right treatment from the start could reduce the severity of the disease’s effects or even prevent them.

‘The idea is that this patient has this molecular signature, so this treatment is what’s going to work,’ said Alarcón-Riquelme.

3TR has been recruiting around 3 000 patients for its investigations across the seven illnesses.

The team is collecting and analysing data from blood, other fluids and tissue throughout the treatment process and aims to find biomarkers predicting therapy response. Researchers also plan to create a centralised platform containing molecular and clinical information to aid future treatment.

In the meantime, the team has been making headway in identifying molecular signatures in the diseases.

In lupus, for example, activity in certain sets of genes was found to be related to drug response, long-term remission of symptoms and relapse.

During the project, the researchers have also made progress in identifying biomarkers for asthma and made advances in the areas of inflammatory bowel disease and rheumatoid arthritis, according to Alarcón-Riquelme.

She believes that, with further progress in the coming years, 3TR can help spur major healthcare advances.

‘We hope that the project will aid faster appropriate treatment by improving recognition of what a patient requires at a given time,’ Alarcón-Riquelme said.

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