Research into the Microbiome

By Sally Robertson, BSc. June 15, 2017 (From Medical Net)

Microscopic research into the human body has shown that each of us has trillions of microbes living within and on the outside of our bodies.

The roughly four million genes represented by this community of human-associated microbes are collectively referred to as the microbiome. Until recently, the microbiome has remained largely unresearched and, as a result, the influence of these microbes on human development, metabolism, physiology, nutrition, immune response and susceptibility to infection are almost completely unknown.

However, today, understanding the human microbiome is one of the most popular focuses of scientific research. In 2008, the National Institutes for Health (NIH) established the Human Microbiome Project (HMP), an initiative that encourages collaboration and contribution from researchers interested in exploring the human microbiome. The aim of the project is to enable detailed characterization of the human microbiota and to explore the roles these microbes play in both health and disease.

In one study, Janet Jansson from the Pacific Northwest National Laboratory, Washington, USA, and colleagues assessed gut microbiome composition in 100 individuals with IBD at three month intervals and compared them with the microbiomes of healthy controls. The team showed that the gut microbiome among IBD patients was much less consistent over time than among the controls.

Understanding this inconsistency in the gut microbiome could aid the design of agents aimed to restore a healthier gut microbiome, as well as helping clinicians to monitor treatment responses and health among patients with IBD. The study, called “Dynamics of the human gut microbiome in inflammatory bowel disease,” was published in Nature Microbiology in February 2017.

Gut microbiome fluctuation in inflammatory bowel disease

It is already known that the gut microbiome of individuals with inflammatory bowel disease (IBD) has a very different composition to that of healthy individuals. However, these findings have generally been based on samples taken at one single time point, while the species that make up the microbiota can change over time depending on factors such as diet, illness and antibiotic use.

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Some highlights of the activities HMP researchers have recently been engaging in are described below.

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Genome sequencing of gut bacterium that influences weight

The bacterial species Christensenella minuta has attracted significant interest from researchers keen to explore the gut microbiota. Firstly, it seems that these bacteria are only found in humans and secondly, evidence suggests it is the most inheritable of the species found in the gut microbiota.

In addition, it appears that C. minuta has a direct influence on host weight, by what until now, is an unknown mechanism. Murine studies have shown that lean people are more likely to have a microbiota that includes C. minuta. They have also shown that when these bacteria are added to the guts of mice, the mice become leaner, suggesting that C. minuta may be a candidate probiotic for weight control.

At Washington University, Missouri, USA, HMP researchers Makedonka Mitreva and colleagues have now completed and recorded the entire genome sequence of C. minuta, which is published in the article “Genome Sequence of Christensenella minuta DSM 22607,” Genome Announcements (January 2017). This will be highly valuable to any researchers interested in exploring the life cycle and metabolism of this microbe, as well as how it may influence the health of its human host.

Gut microbiome and circadian rhythms

Previously, researchers have suggested that the host circadian clock plays a role in determining the composition of the microbiome.

In 2015, HMP awardee Eugene Chang and team decided to explore whether the gut microbiome, in fact, regulates the host clock. They found that mice that were free of germs exhibited significant differences in their circadian clock genes, compared with ordinary mice and that the microbiome had a circadian rhythm of its own that was unaffected by any other cycles in the mice.

Importantly, Chang et al. found that the short chain fatty acid, butyrate, which is produced by the microbiome, had a direct influence on the host circadian clock. They also showed that the microbiome’s circadian clock could be altered by a high-fat diet. This suggests a possible link between diet, gut microbiota and obesity. The findings of this study were published in Cell Host Microbe in May 2015 (“Effects of diurnal variation of gut microbes and high fat feeding on host circadian clock function and metabolism”).

Reviewed by Afsaneh Khetrapal BSc (Hons)

Sources

Parkinson’s is partly an autoimmune disease, study finds

First direct evidence that abnormal protein in Parkinson’s disease triggers immune response.

Materials provided by Columbia University Medical Center. June 21, 2017 (From Science Daily)
Researchers have found the first direct evidence that autoimmunity -- in which the immune system attacks the body's own tissues -- plays a role in Parkinson's disease, the neurodegenerative movement disorder. The findings raise the possibility that the death of neurons in Parkinson's could be prevented by therapies that dampen the immune response.

The study, led by scientists at Columbia University Medical Center (CUMC) and the La Jolla Institute for Allergy and Immunology, was published today in Nature.

"The idea that a malfunctioning immune system contributes to Parkinson's dates back almost 100 years," said study co-leader David Sulzer, PhD, professor of neurobiology (in psychiatry, neurology and pharmacology) at CUMC. "But until now, no one has been able to connect the dots. Our findings show that two fragments of alpha-synuclein, a protein that accumulates in the brain cells of people with Parkinson's, can activate the T cells involved in autoimmune attacks.

"It remains to be seen whether the immune response to alpha-synuclein is an initial cause of Parkinson's, or if it contributes to neuronal death and worsening symptoms after the onset of the disease," said study co-leader Alessandro Sette, Dr. Biol. Sc., professor in the Center for Infectious Disease at La Jolla Institute for Allergy and Immunology in La Jolla, Calif. "These findings, however, could provide a much-needed diagnostic test for Parkinson's disease, and could help us to identify individuals at risk or in the early stages of the disease.

Scientists once thought that neurons were protected from autoimmune attacks. However, in a 2014 study, Dr. Sulzer's lab demonstrated that dopamine neurons (those affected by Parkinson's disease) are vulnerable because they have proteins on the cell surface that help the immune system recognize foreign substances. As a result, they concluded, T cells had the potential to mistake neurons damaged by Parkinson's disease for foreign invaders.

The new study found that T cells can be tricked into thinking dopamine neurons are foreign by the buildup of damaged alpha-synuclein proteins, a key feature of Parkinson's disease. "In most cases of Parkinson's, dopamine neurons become filled with structures called Lewy bodies, which are primarily composed of a misfolded form of alpha-synuclein," said Dr. Sulzer.

In the study, the researchers exposed blood samples from 67 Parkinson's disease patients and 36 age-matched healthy controls to fragments of alpha-synuclein and other proteins found in neurons. They analyzed the samples to determine which, if any, of the protein fragments triggered an immune response. Little immune cell activity was seen in blood samples from the controls. In contrast, T cells in patients' blood samples, which had been apparently primed to recognize alpha-synuclein from past exposure, showed a strong response to the protein fragments. In particular, the immune response was associated with a common form of a gene found in the immune system, which may explain why many people with Parkinson's disease carry this gene variant.

Dr. Sulzer hypothesizes that autoimmunity in Parkinson's disease arises when neurons are no longer able to get rid of abnormal alpha-synuclein. "Young, healthy cells break down and recycle old or damaged proteins," he said. "But that recycling process declines with age and with certain diseases, including Parkinson's. If abnormal alpha-synuclein begins to accumulate, and the immune system hasn't seen it before, the protein could be mistaken as a pathogen that needs to be attacked."

The Sulzer and Sette labs are now analyzing these responses in additional patients, and are working to identify the molecular steps that lead to the autoimmune response in animal and cellular models.

"Our findings raise the possibility that an immunotherapy approach could be used to increase the immune system's tolerance for alpha-synuclein, which could help to ameliorate or prevent worsening symptoms in Parkinson's disease patients," said Dr. Sette.

Reference:

New Treatment Approved for Acute Myeloid Leukemia

By Scott Roberts, August 3, 2017 From: Health-Day News

The combination chemotherapy drug Vyxeos (daunorubicin and cytarabine) has been approved by the U.S. Food and Drug Administration as the first treatment for certain high-risk types of acute myeloid leukemia (AML). AML is an aggressive blood cancer that forms in the bone marrow.

"Vyxeos combines two commonly used chemotherapies into a single formulation that may help some patients live longer than if they were to receive the two therapies separately," said Dr. Richard Pazdur, director of the FDA's Oncology Center of Excellence.

In a news release Thursday, the agency said more than 21,000 people will be diagnosed this year with AML, and more than 10,000 will die from it, according to projections from the U.S. National Cancer Institute.

The new therapy is sanctioned for high-risk forms of newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). People with either disease have a very low life expectancy, the FDA said.

Vyxeos was evaluated in clinical trials involving 309 people with either form of AML. Those given Vyxeos lived an average of 9.6 months, compared with 5.9 months among those who took an inactive placebo.

The therapy's most common side effects included bleeding, fever, low white blood cell count, rash, tissue swelling and nausea. Some users had episodes of serious allergic-like hypersensitivity reactions or dangerous bleeding, the agency said.

Women who are pregnant or breast-feeding shouldn't take Vyxeos, the FDA added. Approval of the drug was granted to the Irish firm Jazz Pharmaceuticals.