Gut bacteria may hold key to treating autoimmune disease

The human body is colonised by a vast number of microbes, collectively named the microbiota. The link between these microbes and our health is the focus of research for Dr Martin Kriegel at Yale School of Medicine. In an exciting new discovery, the Kriegel lab shows that bacteria found in the small intestines of mice and humans can travel to other organs where they trigger disease. Importantly, antibiotics or vaccines that specifically target the bacteria can reverse the disease, offering far-reaching public health implications.

The gut microbiota. Colonies of microorganisms are found throughout our digestive system. Shown is the small intestine in the centre that harbours an enormous number of bacteria as it reaches the large intestine (surrounding the small intestinal bowel loops). The large intestine contains around 10^{13} bacteria representing the most heavily colonised organ in the human body.

**The-Vital-Role-of-our-Microbiota-for-Health**

These microorganisms that colonise our bodies—and their genetic material, the ‘microbiome’—are essential for life. They have coevolved with us and live in an innate relationship with us that’s vital to normal health. The biggest populations of microbes reside in our gut where they aid digestion, prevent infection by pathogens, produce certain vitamins and educate our immune system on what to fight. Although it’s well recognised that the gut microbiota contributes to normal immunity, scientists are still unravelling the ways in which this can go wrong and lead to disease. Autoimmune disease in particular—one of the fastest-growing causes of disability and death in the US—has been strongly connected to the health of the human microbiota.

A CASE OF MISTAKEN IDENTITY

Keeping the immune system in balance is no mean feat; it must remain alert to spot and disarm foreign invaders but be smart enough to recognise the body’s own tissues and organs to spare them from attack. Autoimmunity can be thought of as a case of mistaken identity: the immune system reacts to its own tissues and cells as if they were pathogens. In healthy conditions, the gut microbiota does not provoke a pathologic immune response, even though our immune cells are constantly in contact with these microorganisms. In susceptible individuals, however, it is suspected that the microbiota may play a key role in kick-starting autoimmune disease.

Changing this is Dr Martin Kriegel, Adjunct Assistant Professor of Immunobiology at Yale School of Medicine, who has devoted much of his career to understanding the influence of the microbiota on our immune system and autoimmune diseases. Research in the Kriegel lab aims to better understand the triggers and sustaining factors within the microbiota of autoimmune patients which are responsible for provoking the autoimmune process which leads to disease. The researchers are also interested in the influence of genetics and diet on gut microbial communities in autoimmunity, and the role of skin commensals in cutaneous lymphoma—a type of skin cancer for which there is currently no curative treatment. The overarching aim of this work is to develop novel and effective therapies for immune-related diseases.

**SICK-FROM-YOUR-STOMACH**

Excitingly, in a recent study Dr Kriegel and his research team showed that bacteria found in the small intestines of mice and humans can travel to other organs where they trigger an autoimmune response. Importantly, the team also found that this autoimmune reaction can be suppressed with antibiotic treatment or vaccines designed to target the bacteria. Recently published in the journal Science, these findings offer a new understanding of, and exciting promise for, the treatment of autoimmune conditions such as lupus and autoimmune liver disease.

To explore the link between gut microbiota and autoimmune disease, the team looked carefully at an ordinarily harmless gut bacterium called Enterococcus gallinarum. In a series of elegant experiments using mice genetically prone to autoimmune conditions, the researchers discovered that the bacteria could spontaneously translocate; they moved from the gut to the liver, spleen, and lymph nodes. Once in these tissues, the E. gallinarum bacteria then stimulated an autoimmune response. Importantly, the team administered vaccines that specifically targeted the bacteria. Recently validated this mechanism of inflammation and autoimmune response in mice using vaccines developed for other diseases.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder that affects many organs as shown here. Clinical manifestations are due to the faulty immune system targeting these organs or tissues, which leads to inflammation and organ damage.

**Changes in death or autoimmunity of the immunised mice. Both the antibiotic and vaccine treatments suppressed the growth of the bacteria in the target organs and reduced the host’s autoimmune response, suggesting that they could reverse the effects of the bacteria on autoimmunity. This ground-breaking finding has exciting therapeutic implications, particularly for lupus and autoimmune liver disease, debilitating conditions for which there is currently no cure.

It is becoming increasingly clear that our overall health and well-being is profoundly linked to the massive population of bacteria that reside in our gut.

**Alterations of the gut barrier by a gut bacterium.** Highly magnified images of the gut lining with barrier molecules and gut wall structures stained with different colors. Shown are magnifications of the small intestine of animals colonised exclusively with the autoimmune-promoting bacterium E. gallinarum. Compared to germ-free animals without any bacteria, the pore-forming molecule Claudin-1 is upregulated (left image) and the barrier-tightening molecule Claudin-5 is downregulated (right image). Images taken from Manfredo Vieira et al., Science 2018.
MOLECULAR MIMICRY MEDIATES AUTOIMMUNITY

An ‘antigen’ is a substance which provokes an immune response and much of Kriegel’s research is directed towards exploring the vast pool of antigens presented by the microbiota. In particular, his lab at Yale has focused on the microbiota in the gut and other niches in the human body to test the concept of cross-reactivity in autoimmunity. If a microorganism within the benign gut microbiota possesses a structure that ‘mimics’ a host structure, then it is feasible that persistent exposure to this structure could lead to an immune response triggered by the bacteria, which over time may go on to cross-react with healthy tissue of a susceptible host, causing an autoimmune reaction.

In a recently published study, the team, in collaboration with the lab of Sandra Wolin, provide compelling evidence that cross-reactivity indeed occurs in lupus – a chronic, debilitating autoimmune disease which is poorly understood. Lupus patients have high levels of antibodies to a substance called Ro60. In other words, their immune cells recognise Ro60 as foreign and start to mount an immune response to it. These Ro60 antibodies are raised early on in their disease, even before the onset of symptoms. Focusing on Ro60, the research teams looked for the presence of Ro60-containing bacteria in various tissues of lupus patients, and identified them in the skin, mouth and the gut. They showed that blood from lupus patients (containing Ro60 antibodies) could bind strongly to the Ro60 from commensal microorganisms. However, blood from individuals with no Ro60 antibodies did not bind. The team also showed that immune cells from lupus patients could be activated by Ro60-containing bacteria residing in the skin or gut, functionally demonstrating that the immune cells could cross-react with host as well as bacterial Ro60. To validate their theory in vivo (in a living organism), the team used germ-free mice, that is, animals without any bacteria of their own, and colonised them with a human Ro60 gut bacterium obtained from a human commensal culture collection of the Goodman lab at the Yale Medical Sciences Institute. The mice developed an autoimmune response to human Ro60, supporting the idea that these microorganisms drive autoimmunity. They were also able to visualise Ro60-containing skin bacteria deep within skin lesions of several lupus patients. These findings open the door to potential therapies that target specific bacteria within the skin or gut microbiota, rather than the immune system, which is the current mainstay of treatment.

Gut bacteria-immune cell interaction

Gut bacteria-immune cell interactions in autoimmunity: Many factors contribute to the development of autoimmune diseases. Shown are genetics, immune cells and the gut microbiome with arrows pointing towards autoimmune diseases; many factors can be influenced by the others. Such interactions are indicated by the bidirectional arrows between the microbiome and immune cells. Emerging research supports that the gut bacteria influence various immune cells in autoimmune diseases. The precise mechanisms of these interactions and where they interact is not well understood but represents a major focus of the Kriegel laboratory.

Dr Kriegel's ground-breaking research represents a novel paradigm for how autoimmunity can arise.

FUTURE DIRECTION: FROM BENCH TO BEDSIDE

Current work in the Kriegel lab aims to further unravel the cross-reactivity theory in antiphospholipid syndrome (APS), a potentially deadly autoimmune clotting disorder often co-occurring with other rheumatic diseases such as lupus and scleroderma. The cause of APS is currently unknown. However, Kriegel and his team hypothesised that a certain bacterium in the gut may be responsible for the cross-reactivity of both immune cells and antibodies with bacterial antigens from this bacterium. APS patients have high levels of antibodies to a substance called β2-glycoprotein I, and the researchers showed in work presented at last year’s American Association of Immunologists meeting that cross-reactivity of the gut bacterial antigens with the patient’s own β2-glycoprotein I may be the underlying cause. In this project the researchers have been using sophisticated techniques and molecular biology studies to formally show cross-reactivity between the bacterial protein in the gut and the abundant self-antigen β2-glycoprotein I that circulates in the blood. They have thus unravelled a potential persistent trigger of pathogenic autoantibody production in genetically prone APS patients.

It is becoming increasingly clear that our overall health and wellbeing is profoundly linked to the massive population of bacteria that reside in our gut. Dr Kriegel’s ground-breaking research represents a novel paradigm for how autoimmunity can arise and serves as a solid foundation for development of new and effective therapeutic approaches aimed at the gut and skin microbiota.

Collaborators on work discussed here

• Andrew Goodman, PhD, Associate Professor of Microbial Pathogenesis, HHMI Faculty Scholar, Yale Microbial Sciences Institute.
• Sandra Wolin, MD, PhD, Chief, RNA Biology Laboratory, Senior Investigator and Head of Section on Nonscoring RNAs and NRPs, National Cancer Institute; Professor Emeritus of Cell Biology at Yale.

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