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Press information

Behind a Rare Disease: A Gut Sensitive to the Cold and Intolerant of its Own Bacteria

A mechanism of tolerance towards intestinal flora is thought to be implicated in the onset of a rare familial autoinflammatory disease induced by cold temperatures. This is the finding of researchers from the Center for Infection and Immunity of Lille (Inserm/Université de Lille/CNRS/University Hospital Lille/Institut Pasteur de Lille), the Pathophysiology of Pediatric Genetic Diseases laboratory (Inserm/Sorbonne Université) and the Department of Immunology at the University of Hohenheim. Their research, published in [Nature Communications](#), reveals the implication in its onset of an exacerbated inflammatory response against the gut flora, making for a more effective immune response against certain pathogens. Findings which open up new avenues when it comes to treating patients.

Familial cold autoinflammatory syndrome (or familial cold urticaria) is characterized by episodes of fever triggered by cold temperatures, accompanied by hives and gastrointestinal and joint pain. The patients - with some twenty cases identified to date - carry an NLRP12 gene mutation that is inherited in an autosomal dominant manner (the presence of a single mutated allele is enough to bring on the disease). Until now, the pathophysiological mechanisms behind the disease were unknown.

A team led by Mathias Chamaillard, Inserm researcher at the Center for Infection and Immunity of Lille (Inserm/Université de Lille/CNRS/University Hospital Lille/Institut Pasteur de Lille) along with his coworkers at the Pathophysiology of Pediatric Genetic Diseases laboratory (Inserm/Sorbonne Université) and Department of Immunology at the University of Hohenheim, sought to elucidate the development of this syndrome through human and mouse studies.

The researchers saw that while inactivating the NLRP12 gene in mice triggered inflammation in the gut, it made it resistant to certain pathogenic bacteria, suggesting that NLRP12 could play a key role in immune tolerance towards intestinal flora.

However, they observed that another molecule, NOD2, also played a role in intestinal immunity by promoting the defense against these same bacterial pathogens. In addition, a NOD2 gene mutation predisposes to Crohn's disease, which presents disturbing similarities with the syndrome being studied here: intestinal pain and a higher prevalence in cold countries. Finally, the researchers observed the existence of a physical interaction between the proteins NOD2 and NLRP12.

Reduced tolerance of intestinal flora bacteria

In individuals with familial cold autoinflammatory syndrome, the production of protein NLRP12 is reduced. When reproduced in mice, this phenomenon modifies NOD2 activity and reduces tolerance of commensal bacteria with an intensified recruitment of inflammatory cells in the digestive tract. However, the efficacy of pathogen elimination is improved. In other words,

under normal conditions, NLRP12 suppresses NOD2 activity and improves tolerance of intestinal bacteria. These findings suggest that an inhibitor of the NOD2 pathway could attenuate these patients' symptoms.

The reduced tolerance in subjects with familial cold autoinflammatory syndrome generates chronic inflammation which could be the reason behind their intestinal pain. But why does the cold trigger additional symptoms outside the digestive tract? The researchers suspect increased intestinal permeability in the presence of low temperatures, a phenomenon which would be of no consequence in healthy subjects. However, in those with the disease, numerous pro-inflammatory molecules and bacterial debris could pass into the blood *en masse*, with secondary local inflammation thereby partially explaining the other symptoms, such as fever, headache and joint pain. A new research avenue that Mathias Chamaillard and his colleagues are now exploring, with the help of mice.

Sources

tolerance and colonization by enteropathogens

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