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Neurobiology

# Could our gut's microbes be the guardians of our brain's health?

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ABSTRACT

*Microorganisms inhabiting our gut degrade certain nutrients into molecules capable of activating brain-resident immune cells to control inflammation. This could possibly limit the progression of some neurodegenerative dis-eases such as multiple sclerosis.*

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In the same way as our genome contains the collection of all of our genes, we call microbiome the collection of microorganisms that have settled in our organism. Over the past decades, the gut microbiome in particular has been shown to affect our physical health: it helps the body to digest certain nutrients, participates to the production of some vitamins, and plays an important role in the development of an efficient immune system.

More recently, a still controversial concept has emerged: that these tiny creatures could even re-motely affect our brains. In this study the authors show that the gut's microbes produce some molecules that can reach our brain, where they activate some immune cells, and ultimately modulate the development of neurodegenerative diseases.

The brain has long been considered as an unreachable fortress for our immune system, unless something went terribly wrong. In fact, a functional brain permanently contains various immune cells, which play crucial roles in cognition, injury repair or in the progression of neurodegenera- tive diseases.

Ten years ago, the team of scientists that carried out this study were studying the progression of Experimental Autoimmune Encephalomyelitis (EAE) in mice. This disease is used as an animal model to study multiple sclerosis in humans, a disease in which an autoimmune attack (an im- mune attack

that the body directs against itself), results in the destruction of the nerves. They discovered an unexpected role for a particular protein that detected a toxin: its activation seemed to result in the reduction of symptoms of EAE. But, ten years ago no-one was even close to thinking that the gut microbiome could be involved in any way.

For this study, they kept on using the same model system, but they wanter to further study the role of this detector protein. First, they specifically removed it from the immune cells present in the mice brains, which led to much stronger symptoms of EAE. This confirmed that, indeed, this toxin detector protein somehow limits the development of the disease. Apparently, once theprotein detected a certain compound, it would bind to it, and in some yet unknown way reduce the symptoms of the disease.

But how could a protein that detects toxins be involved in the control of a neurodegenerative disease? In particular, which signals does it sense in this situation?

It turned out that it can also detect and bind to a variety of other molecules, including some food derivatives. One of these is a product of the degradation of the amino acid Tryptophan by gut bacteria. The authors then decided to test whether the ingestion of Tryptophan (a nutrient enriched in nuts, oats, chocolate or various vegetables) could affect the progression of the disease. They observed that disease symptoms worsened if the mice were deprived of Tryptophan, whereas Tryptophan enrichment had the opposite effect. By contrast, if the detector protein is first deleted, neither diets affect the development of the disease anymore.

This confirmed that this detector protein, which resides in the brain and helps to reduce the effects of a brain disease, is controlled by microorganisms living in the gut! These tiny creatures are thus real remote guardians of our brain's health!

The scientists could then reproduce key results obtained in their mouse model using tissue sam- ples from people with multiple sclerosis: they found that the same protein was activated by molecules derived from Tryptophan in human immune cells, in turn affecting the inflammatory responses. This suggests (but does not prove) that this pathway could have a role in the progression of multiple sclerosis, and might lead to new therapeutic strategies to limit unwanted inflammation in the brain, or support neuronal repair.

The fact that brain resident cells can be remotely controlled by the activity of gut microorgan- isms is intriguing, but not without precedent. More and more observations link the brain to the gut and its microbial content in what is now commonly called "the brain-gut axis". Even condi- tions including depression, anxiety or autism are now being linked to the microorganisms that in- habit our gut, even though the evidences, as fascinating as they are, still remain very prelimi- nary. But the pioneers of this field see an exciting prospect on the horizon: a whole new way of personalized medicine to influence our health and wellbeing.