Scientists identify protein related to neurodegeneration processes

The study may collaborate to understand and treat diseases such as Parkinson's and Alzheimer's

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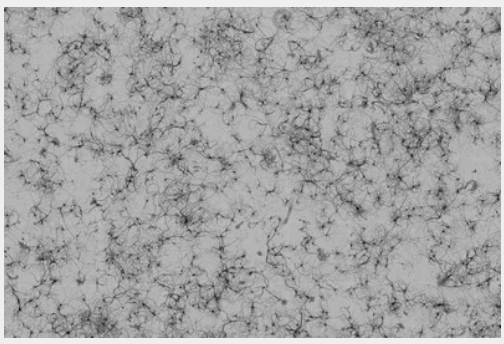
A group of researchers has found a protein responsible for initiating neurodegeneration processes after the body experiences acute inflammation. This discovery can contribute to an understanding of the origin of degenerative conditions such as Alzheimer's and Parkinson's. This protein, the Receptor for Advanced Glycation Endproducts (RAGE), is in our immune system, but it can also be found in different cells when we have inflammation. In experiments on mice, scientists could suppress the protein's activity in the animals' brains and preserve them from neurodegeneration. They published the results of the study in 2017, in the Journal of Biological Chemistry, and this year, the same journal chose the article to be in a unique issue: a collection of the most representative research findings on the progress of scientific research in biochemistry carried out in South America in the last four years.



Inhibition of Rage protein in the brain of rats halted the development of Parkinson's disease, protecting them from loss of neurons – photo: Zeiss Microscopy/CC by NCD ND 2.0

To explore the relationship between the progress of inflammation and neurodegeneration and what the role of Rage in this process is, scientists induced sepsis in animals. The sepsis occurs when, to defend the body from an infectious agent, the immune system provokes a generalized inflammation, which extends through the body and results in affecting other organs and may even endanger their functioning.

The motivation for the work began from the observation of septic patients that, even after their recovery, had a high frequency of sequelae, with many neurological issues, explains Daniel Pens Gelain, professor at the Department of Biochemistry at UFRGS and co-author of the research. "And then, we wondered if one inflammation event, or several inflammation events, could not be related to the onset of neurodegenerative diseases, because most of the time, these diseases are silent. When a patient is diagnosed with Parkinson's or Alzheimer's, a process of advanced neurodegeneration in the brain is already in course," the professor explains.

The scientists have confirmed the hypothesis that, after the recovery from sepsis, the animals presented a set of modifications in biochemical markers, showing neurodegeneration and signs of Alzheimer's condition, such as the beta-amyloid peptide and the phosphorylated tau protein, elements identified in the brain of patients with the disease. On the other hand, animals that had Rage inhibited after sepsis, recovered from these biochemical markers, and performed better in cognitive tests. "In this work, the observation that I consider most relevant is that we suppress the protein, Rage, way after the sepsis and at a stage when the first symptoms of neurodegeneration in the brain occur. This is something that is much welcomed in the clinical practice today: early treatments that we can apply when we previously have the diagnostic of the disease," says Gelain.

The inhibition of Rage was made directly in the animals' brains, by a process called immune neutralization. An antibody "programmed" to recognize this specific protein was injected into the affected part: the hippocampus - a fundamental structure for keeping memories. "The inhibition we made is experimental. This is a relatively recent protein; it was detected in the 1990s and is identified by a few groups. And there is no medication developed to operate on it. This is partly true, to be honest. There is a drug that was developed to act on it and that was tested for Alzheimer's disease, but in clinical tests, the results were not considered significant," explains the professor.

Parkinson's disease

In another article, published in the Scientific Reports' magazine, the researchers showed that the inhibition of Rage blocked the development of Parkinson's disease in rats. This is a progressive neurodegenerative disease, defined by the loss of dopaminergic neurons, and whose major symptoms are related to the motor system. What they observed in the study was that the rats in which they stopped Rage had lost fewer neurons and had a better performance in tests of motor coordination; they had approximately the same performance as the group of animals without Parkinson's disease.

"It was a very positive result, and we are now focusing on Parkinson's disease for our next works," observes Gelain. Now, the group remains studying laboratory animals, but with a closer-to-the-disease model. In the previous work, neuronal loss developed in a period of about a month. In the alternative model, the researchers induce inflammation in the animals, and the neurodegeneration process has been developing gradually, over a year and a half – a long time, considering the life expectancy of these rats ranges from two to three years. "It is a model much closer to reality, and we have already seen results in its application. We blocked Rage right in that same region of the brain long after neurodegeneration had started. And we had a promising response. We are only with a few other groups of animals away to conclude this work, to solve a little more the biochemical mechanism of the signaling pathway; but the result of conservation against the evolution of neurodegeneration is clear, and even surprising," the researcher says.

For him, the works can contribute to an understanding of the processes that involve neurodegeneration and for the search for alternative forms of treatment. "We are forming and establishing some hypotheses linked to the origin of Parkinson's disease. We think an inflammatory event, of unknown origin, or that a sequence of inflammatory events during people's lives, provokes an inflammatory process in the brain. When this is in the region that is affected by Parkinson's, it ends up becoming Parkinson's. When this is in the region affected by Alzheimer's, it becomes Alzheimer's. And when the brain cannot stop this inflammation process, Rage stands there because the inflammatory response is something that the body does to get rid of a problem, only that sometimes we cannot end it. The reason for not being able to end it sometimes is not clear, but it happens a lot". And Gelain adds: "What we knew before is that, in chronic inflammation, Rage was always increased. And the chronic inflammation ceased when we inhibited Rage. So, we believe that we are somehow breaking this maintenance cycle of the neuroinflammation component of these diseases".

Human testing

Parallel to these works, the researchers have been developing studies with human brains, analyzing samples from healthy people and patients with Parkinson's, in a partnership with the Brain Bank of the Universidade de São Paulo (USP). They also carry out clinical studies with patients with the disease, in collaboration with the Santa Casa de Misericórdia and the Hospital de Clínicas de Porto Alegre. In the hospitals, the coordination is by Professors Arlete Hilbig and Carlos Rieder, respectively. For about three years, researchers have been monitoring patients, collecting, and analyzing blood samples, and checking symptoms and their changes over time. They seek to verify Rage and molecules that modulate this receptor in the blood of patients and to correlate the results of biochemical tests with changes in symptoms. The study's goal is that its findings may contribute to bring a more precise diagnosis of Parkinson's disease, which today is done by the analysis of symptoms, which usually occur when the disease has considerably advanced. There is still no examination capable of identifying it accurately.

"Developing a blood test that reveals any alteration related to the disease before its manifestation would be excellent for treatment. The problem with neurodegeneration is that after we recognize it, there is already a huge neuronal loss happening. The treatments are all meant to ease symptoms; there is no treatment to end neurodegeneration," professor Gelain explains. Therefore, the identification of clinical markers that indicate the existence of the disease before it becomes worse would be a major advance for treatment and the quality of life of patients. "So, we are very excited about these clinical data and this study. The doctors are providing us with a lot of samples and are also very optimistic," highlights the professor.

Scientific articles

GASPAROTTO, Juciano et al. Receptor for advanced glycation end products mediates sepsis-triggered amyloid-β accumulation, Tau phosphorylation, and cognitive impairment. *Journal of Biological Chemistry*, v. 293, n. 1, 10 nov. 2017.

GASPAROTTO, Juciano et al. Targeted inhibition of RAGE in substantia nigra of rats blocks 6-OHDA–induced dopaminergic denervation. *Scientific Reports*, v. 7, n. 1, 18 ago. 2017.

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