UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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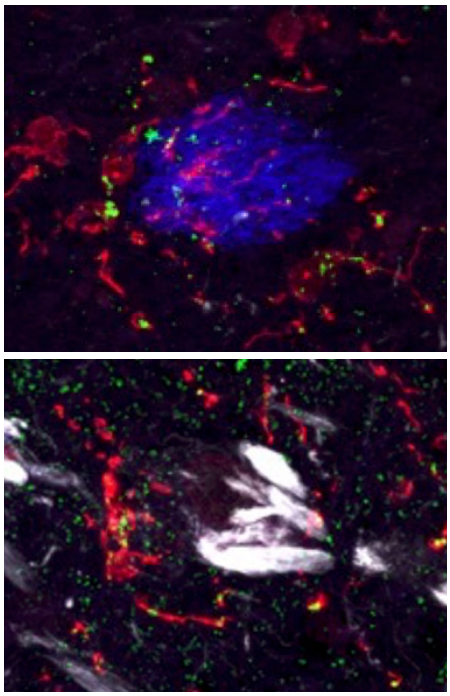
Marker for brain inflammation finally decoded

An international team co-led by UNIGE and HUG has decoded the only protein that can be used to "see" neuroinflammation. This discovery will improve the understanding of neurological and psychiatric disease mechanisms.



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TSPO protein (in green) was quantified in microglia (in red) in proximity to lesion characteristic of Alzheimer's disease, the amyloid plaques (in blue) and pTau lesions (in white), in post mortem human brain samples.

High resolution pictures

Inflammation is the sign that our body is defending itself against an aggression. But when this response escalates, for example in the brain, it can lead to serious neurological or psychiatric diseases. A team from the University of Geneva (UNIGE), the University Hospitals of Geneva (HUG), Imperial College London and Amsterdam UMC, investigated a marker protein targeted by medical imaging to visualise cerebral inflammation, but whose interpretation was still uncertain. The team reveals that a large quantity of this protein goes hand in hand with a large quantity of inflammatory cells, but that its presence is not a sign of their overactivation. These results, published in *Nature Communications*, pave the way for optimal observation of neuroinflammatory processes and a re-reading of previous studies on the subject.

Inflammation is a natural defensive reaction initiated by the immune system. It enables our cells to fight off aggression, such as injury or infection. But this response can also get out of control and lead to the onset of serious pathologies. When it occurs in the brain - in which case it is known as neuroinflammation - this overactivation can play a part in the mechanisms of neurodegenerative diseases (Alzheimer's, amyotrophic lateral sclerosis, multiple sclerosis) and psychiatric diseases (schizophrenia, bipolar disorder, depression).

In the brain, microglial cells play an important role in inflammation and in its potential overactivation. They can be "activated" when dysfunction occurs, phagocytize pathological cells or proteins and even produce protective substances. Currently, in medical imaging, only one marker can be used to locate and measure microglia non-invasively and in vivo: the TSPO protein, which is present in these cells. This protein can be observed by Positron Emission Tomography (PET), a common imaging technique.

What does TSPO protein reveal?

"Hundreds of studies have used PET scans of this protein to explore and quantify microglia. However, no study has succeeded in precisely interpreting the significance of its quantity in the context of an inflammatory reaction," explains Stergios Tsartsalis, senior clinical associate in the Department of Psychiatry at the UNIGE Faculty of Medicine. Does a large quantity of TSPO correspond to a large quantity of inflammatory cells? Is it a sign of their overactivation? Together with researchers from Imperial College London (Dr David Owen) and Amsterdam UMC (Prof. Sandra Amor), Stergios Tsartsalis and members of Prof. Philippe Millet's team from

the HUG's Laboratory of translational imaging in psychiatric neuroscience and the UNIGE's Group of molecular neuroimaging in psychiatry set out to find out.

The international research team worked on the brains of mouse models of Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis, and on post-mortem brain samples from patients affected by the same diseases. "We discovered that a high density of TSPO protein is indeed an indicator of a high density of microglia. On the other hand, the observation of TSPO does not allow us to say whether or not the inflammatory cells are overactivated," explains the UNIGE researcher, co-first author of the study.

Re-reading the past, optimising the future

This discovery highlights the value of medical imaging of TSPO: it makes it possible to identify cases where the neuroinflammatory disease is linked to a deregulation in the number of glial cells. In addition, the scientists have identified two markers of the state of microglia activation in humans - the LCP2 and TFEC proteins - which pave the way for new medical imaging approaches.

"These results represent a further step towards understanding the role of microglia in neuroinflammation. They will help to optimise the focus of future studies and also to review the conclusions of previous research," enthuses Stergios Tsartsalis. Combined with the significant development of molecular imaging at the UNIGE and the HUG, this study, supported by the Swiss National Science Foundation and the Prof Dr Max Cloëtta Foundation, set the scene for effective observation of the immune mechanisms of neurological and psychiatric diseases, within the two Geneva institutions and beyond.

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