Control of the iRhom2 protein may hold the key to preventing Alzheimer's disease

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Credit: IRHOM2 in AD

It is known that the onset of Alzheimer's disease (AD) is associated with the accumulation of Amyloid beta (Aβ) peptides in small molecular clusters known as oligomers. These trigger the formation of so-called 'neurofibrillary tangles' within neurons hamper their workings, ultimately causing cell death and so significant cognitive decline. Very large Aβ oligomers which form plaques outside neurons, alongside neuroinflammation have also been found to play a key part in the progression of the disease.

The EU-funded iRhom2 in AD project took as its starting point the protein iRhom2, which has been identified as a genetic risk factor for AD due to its pro-inflammatory properties. The team were able to explore further the influence of iRhom2 on neuroinflammation in mice.

Modulating iRhom2

iRhom2 recently emerged as a protein of note in AD as it aids the maturation of an enzyme called TACE (tumor necrosis factor-α converting enzyme) guiding it towards a cell's plasma membrane where the enzyme releases a cell-signalling cytokine (TNFα), implicated in the regulation of inflammatory processes. While mice studies have shown that TNFα-dependent inflammation can lead to sepsis and rheumatoid arthritis, it is also thought that the process contributes to neuroinflammatory signalling events, which can cause harm in the brain.

The EU-funded iRhom2 in AD project worked with mice that are prone to develop the hallmarks of AD, amyloid plaques and memory deficits. The team genetically altered iRhom2 in the mice then analysed the progression of the pathology using an array of biochemical and histological methods, together with a number of behavioural tests to assess cognitive decline.

The results were somewhat surprising as project coordinator Prof. Dr. Stefan Lichtenthaler recalls, "We initially hypothesised that iRhom2 would affect one specific aspect of neuroinflammation in AD. What we discovered was even more exciting as it actually affects several different aspects of neuroinflammation simultaneously. So modulating iRhom2 appears particularly well suited to interfere with AD."

Beyond treatment to prevention

While AD is mainly a disease of the elderly, 5-10 % of all cases may have an earlier onset, especially when it comes to cases of familial AD. As Prof. Lichtenthaler elaborates, "As the first changes in an AD brain happen 25 years before the onset of AD symptoms, in order to stop the disease, we have to treat the causes and not just the symptoms, obviously

years before disease onset. We need to move beyond treatment to prevention."

Yet, until very recently, all potential cures have been tested in patients that had already developed the disease and so by definition, are applied too late in the process. Drugs are only now being tested before the onset of symptoms. But these longitudinal studies, which follow subjects from being disease-free until they develop symptoms, will not yield results until at least 2024. Another hurdle to overcome is the need for a new diagnostic that can indicate who is likely to develop the disease in the coming years.

Identifying iRhom2 as a new therapeutic target for AD sets the stage for the future development of drugs which can modulate the protein. As Prof. Lichtenthaler says, "Such drugs used for the treatment of the disease could have a terrific impact on improving the lives of many people. Crucially, this therapy could be used not only to prevent the disease, but also potentially to help patients that do already have disease symptoms."

Currently the project team are working to better understand the precise mechanism by which iRhom2 influences AD at the molecular level and apply this knowledge for drugs that can block the activity of iRhom2 in patients.

Provided by CORDIS