Immune cell defect stimulates Alzheimer's

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Defects in the gene TREM2 are linked to increased risk of Alzheimer's disease. The gene is required to activate immune cells called microglia in the brain, which help to eliminate the neurotoxic deposits that are typical of the disease.

The hallmark of Alzheimer's disease is the appearance of insoluble and toxic protein deposits called amyloid plaques in the brain. Immune cells called microglia, which are found specifically in the brain, play a vital role in the removal of these pathological plaques. The TREM2 gene codes for the TREM2 protein, which is responsible for the activation of microglia and, as such, it is an important target for the development of novel approaches to the effective treatment of Alzheimer's. To gain a more detailed understanding of the role of TREM2, a team of Munich neurobiologists led by Christian Haass (Professor of Metabolic Biochemistry at LMU Munich, Coordinator of the Munich Branch of the German Center for Neurodegenerative Diseases (DZNE) and a leading Alzheimer's researcher) have now characterized the progression of the disease in mice in which the TREM2 gene had been deleted, and compared its course with that in normal mice.

During the early phase of Alzheimer's in mice in which the TREM2 gene is functional, microglia were observed to cluster around small plaques and effectively prevent their growth and dissemination. "We were able to show that microglia are specifically attracted to new born amyloid plaques. The cells surround individual plaques and progressively degrade them," Haass explains. In mice that lacked the TREM2 gene, on the other hand, the microglia were unable to disintegrate such plaques. This finding suggests that pharmacological activation of the TREM2 gene at an early stage in the development of the Alzheimer's could help to prevent the build-up of toxic deposits.

However, the study also revealed another aspect of TREM2's function. While the protein inhibits the formation of plaques during the early phase of the disease, it appears to have the opposite effect at later times – as indicated by the observation that, in mice bearing the intact TREM2 gene, rates of plaque growth were higher than in the strain in which the gene was absent. Further investigation of this phenomenon revealed that TREM2 in the microglia also stimulates production of the protein ApoE, which promotes the aggregation of plaques. "Our study thus underlines the fact that great care must be taken to characterize the effects of every new therapeutic strategy in detail in animal models before they can be tested in humans," says Haass. "In light of our results, overactivation of microglia could accelerate rather than ameliorate the progression of the disease, with disastrous consequences."

"Our findings indicate that future therapies will need to be applied in a stage-specific manner," says Haass. "Based on the outcome of our study, activation of microglia by TREM2 would be a useful strategy to apply during the early phase of the condition." Indeed, Haass and his colleagues are already engaged in developing antibodies that are capable of stabilizing the TREM2 protein, thus

increasing its ability to activate microglia. Using several animal models and various experimental approaches, they are now testing a range of possible therapeutic strategies, including combination therapies with other agents.

"All of the genetic alterations that are associated with increased risk of developing Alzheimer's affect the process of plaque formation," Haass points out. This strongly supports the idea that the aggregates are the proximate cause of Alzheimer's disease. The new study now demonstrates that it is in principle possible to inhibit plaque formation by activating TREM2. In addition, it points to the risks attendant on such a strategy, which scientists will have to take into account in following up the findings detailed in the new publication from the Haass group.

More information: Samira Parhizkar et al. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE, *Nature Neuroscience* (2018). DOI: 10.1038/s41593-018-0296-9

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