

Glitch in neural garbage removal enhances degenerative risk

July 3 2014

An international team of researchers identified a pathogenic mechanism that is common to several neurodegenerative diseases. The findings suggest that it may be possible to slow the progression of dementia even after the onset of symptoms.

The relentless increase in the incidence of dementia in aging societies poses an enormous challenge to health-care systems. An international team of researchers led by Professor Christian Haass and Gernot Kleinberger at the LMU's Adolf-Butenandt-Institute and the German Center for Neurodegenerative Diseases (DZNE), has now elucidated the mode of action of a genetic defect that contributes to the development of several different dementia syndromes.

Neurodegenerative disorders such as Alzheimer's and Parkinson's diseases or <u>frontotemporal dementia</u> display a number of common features. They are all characterized by the appearance in the brains of affected patients of abnormally high levels of insoluble protein deposits, which are associated with massive loss of <u>nerve cells</u>. In order to minimize further damage to nerve cells in the vicinity of such deposits, <u>dead cells</u> and the proteinaceous aggregates released from them must be efficiently degraded and disposed of. This task is performed by specialized phagocytic cells – the so-called microglia – which act as "sanitary inspectors" in the brain to ensure the prompt removal of debris that presents a danger to the health of nearby cells. Microglia are found only in the central nervous system, but functionally they represent a division of the body's innate immune system.



As Haass and his colleagues now report in the latest issue of the journal *Science Translational Medicine*, specific mutations in the gene for a protein called TREM2, which regulates the uptake of waste products by microglia, lead to its absence from the cell surface. TREM2 is normally inserted into the plasma membrane of microglial cells such that part of it extends through the membrane as an extracellular domain. This exposed portion of TREM2 is responsible for the recognition of waste products left behind by dead cells. "We believe that the genetic defect disrupts the folding of the protein chain soon during its synthesis in the cell, so that it is degraded before it can reach the surface of the microglia," says Kleinberger. As a result, the amount of debris that the microglia can cope with is significantly reduced. Consequently, the toxic protein deposits, as well as whole dead cells, cannot be efficiently removed and continue to accumulate in the brain. This is expected to trigger inflammatory reactions that may promote further nerve-cell loss.

The new study thus pinpoints a mechanism that influences the course of several different brain diseases. "In addition, our findings may perhaps point to ways of slowing the rate of progression of these illnesses even after the manifestation of overt signs of dementia, which has not been possible so far," says Haass. "That this may indeed be feasible is suggested by the initial results of an experiment in which we were able to stimulate the phagocytic activity of microglia by pharmacological means."

More information: "TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis", Gernot Kleinberger, Yoshinori Yamanishi, Marc Suárez-Calvet, Eva Czirr, Ebba Lohmann, Elise Cuyvers, Hanne Struyfs, Nadine Pettkus, Andrea Wenninger-Weinzierl, Fargol Mazaheri, Sabina Tahirovic, Alberto Lleó, Daniel Alcolea, Juan Fortea, Michael Willem, Sven Lammich, José L. Molinuevo, Raquel Sánchez-Valle, Anna Antonell, Alfredo Ramirez, Michael T. Heneka, Kristel Sleegers, Julie van der



Zee, Jean-Jacques Martin, Sebastiaan Engelborghs, Asli Demirtas-Tatlidede, Henrik Zetterberg, Christine Van Broeckhoven, Hakan Gurvit, Tony Wyss-Coray, John Hardy, Marco Colonna and Christian Haass, Sci Transl Med 2 July 2014: Vol. 6, Issue 243, p. 243ra86. *Sci. Transl. Med.* DOI: 10.1126/scitranslmed.3009093

Provided by Ludwig Maximilian University of Munich

Citation: Glitch in neural garbage removal enhances degenerative risk (2014, July 3) retrieved 6 May 2024 from <u>https://medicalxpress.com/news/2014-07-glitch-neural-garbage-</u> <u>degenerative.html</u>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.