Boosting the brain's waste disposal system

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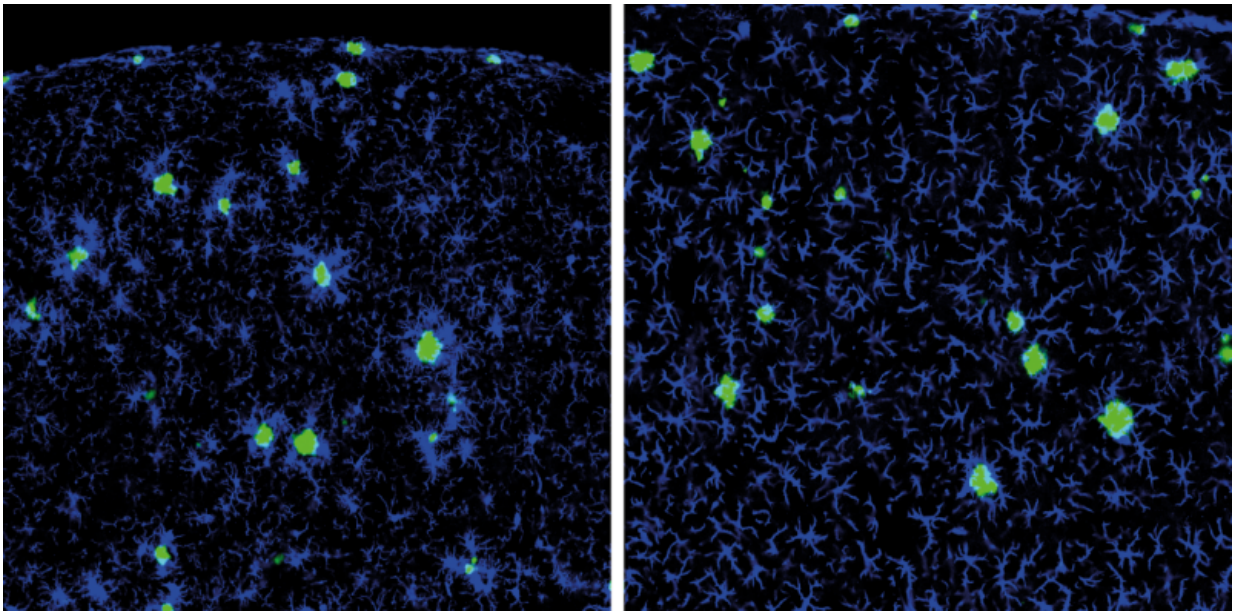

Left: Aβ plaques (green) surrounded by resident microglia (blue) in AD mouse brains. Right: "new" peripheral macrophages (blue) that migrated into the brain of AD mice upon ablation of resident microglia, but ignore Aβ plaques. Credit: JEM

Universitätsmedizin Berlin have been investigating the extent to which macrophages, a type of phagocytic immune cell, might be used to eliminate the abnormal protein deposits typically found in the brains of patients with Alzheimer's disease. Results from this study were published in the current volume of the *Journal of Experimental Medicine*.

Worldwide, more than 20% of persons over the age of 85 suffer from Alzheimer's disease (AD). Deposits of beta-amyloid (Aβ) peptide represent an important target for research into AD. These peptide fragments, which accumulate in the brains of AD patients, play an important role in the pathogenesis of AD. A research team headed by Prof. Dr. Frank Heppner, Director of Charité's Department of Neuropathology, had previously demonstrated that the brain's immune cells, known as microglia, are impaired in the course of AD., Thus, microglia in AD are unable to fulfill their primary purpose, which is the elimination of foreign substances or abnormal structures such as pathological beta-amyloid peptides.

In this current study, the same team of researchers set out to investigate whether it might be possible to prompt macrophages, the peripheral counterparts of microglia that reside outside the brain and in the blood, to migrate to the brain, in order to take over role of the dysfunctional microglia. The researchers started by developing a mouse model of AD, in which they ablated microglia. This created an emergency situation, which prompted the brain to initiate an infiltration response, and resulted in blood-borne macrophages migrating from peripheral sites to repopulate the brain. These peripheral derived cells subsequently underwent further development in the brain that rendered them similar to microglia, however, without impacting AD pathology and, rather than clustering around Aβ deposits , they completely ignored their presence. These findings are mirrored by another study, which was conducted by a group of researchers from the University of Tübingen, and also published in the current volume of the *Journal of Experimental Medicine*.

Prof. Dr. Frank Heppner explains that "in order to make these peripheral macrophages interested in Aβ peptides, AD mice harboring blood-borne macrophages instead of resident microglia in the brain were given an Aβ vaccine - an approach that is currently being investigated in several clinical trials, and remains the subject of intense discussion."However,

even this additional stimulation did not render these peripheral macrophages any more effective than the brain's resident microglia. "Obviously, motivating resident microglia or peripheral macrophages to realize their full potential will require a different, or additional, stimulus," says Prof. Heppner. "However, our data is of relevance, insofar as many recent studies have identified microglia as a crucial player in both the development and progression of Alzheimer's disease. It is therefore of fundamental importance, not least in relation to the development of new treatment options, that we should gain a detailed insight into both the role and function of microglia and macrophages in AD."

The researchers are now planning to conduct further studies aimed at identifying the missing stimulus. By doing so, they hope to ensure that the phagocytic cells in question can return to fulfilling their original function.

More information: *Impact of peripheral myeloid cells on amyloid-ß pathology in Alzheimer's disease–like mice. Stefan Prokop, Kelly R. Miller, Natalia Drost, Susann Handrick, Vidhu Mathur, Jian Luo, Anja Wegner, Tony Wyss-Coray and Frank L. Heppner. *J. Exp. Med*. 12. Oct 2015. DOI: 10.1084/jem.20150479

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