Immune cells of the blood might replace dysfunctional brain cells

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Blood-circulating immune cells can take over the essential immune surveillance of the brain, this is shown by scientists of the German Center for Neurodegenerative Diseases and the Hertie Institute for Clinical Brain Research in Tübingen. Their study, now published in *PNAS*, might indicate new ways of dealing with diseases of the nervous system.

The immune system is comprised of multiple cell types each capable of specialized functions to protect the body from invading pathogens and promote tissue repair after injury. One cell type, known as monocytes, circulates throughout the organism in the blood and enters tissues to actively phagocytose (eat!) foreign cells and assist in tissue healing. While monocytes can freely enter most bodily tissues, the healthy, normal brain is different as it is sequestered from circulating blood by a tight network of cells known as the blood brain barrier. Thus, the brain must maintain a highly specialized, resident immune cell, known as microglia, to remove harmful invaders and respond to tissue damage.

In certain situations, such as during disease, monocytes can enter the brain and also contribute to tissue repair or disease progression. However, the potential for monocytes to actively replace old or injured microglia is under considerable debate. To address this, Nicholas Varvel, Stefan Grathwohl and colleagues from the German Center for Neurodegenerative Diseases (DZNE) Tübingen and the Hertie Institute for Clinical Brain Research in Tübingen used a transgenic mouse model in which almost all brain microglia cells (>95%) can be removed within

two weeks. This was done by introducing a so-called suicide gene into microglia cells and administering a pharmaceutical agent that leads to acute death of the cells. Surprisingly, after the ablation of the microglia, the brain was rapidly repopulated by blood-circulating monocytes. The monocytes appeared similar, but not identical to resident microglia. The newly populated monocytes, evenly dispersed throughout the brain, responded to acute neuronal injury and other stimuli—all activities normally assumed by microglia. Most interestingly, the monocytes were still present in the brain six months - nearly a quarter of the life of a laboratory mouse - after initial colonization.

These studies now published in *PNAS* provide evidence that blood-circulating monocytes can replace brain resident microglia and take over the essential immune surveillance of the brain. Furthermore, the findings highlight a strong homeostatic mechanism to maintain a resident immune cell within the brain. The observation that the monocytes took up long-term residence in the brain raises the possibility that these cells can be utilized to deliver therapeutic agents into the diseased brain or replace microglia when they become dysfunctional. Can monocytes be exploited to combat the consequences of Alzheimer's disease and other neurodegenerative diseases? The scientists and their colleagues in the research groups headed by Mathias Jucker are now following exactly this research avenue.

More information: "Microglial repopulation model reveals a robust homeostatic process for replacing CNS myeloid cells", Nicholas H. Varvel, Stefan A. Grathwohl, Frank Baumann, Christian Liebig, Andrea Bosch, Bianca Brawek, Dietmar R. Thald, Israel F. Charo, Frank L. Heppnerf, Adriano Aguzzi, Olga Garaschuk, Richard M. Ransohoff, and Mathias Jucker, *Proceedings of the National Academy of Sciences* (*PNAS*): www.pnas.org/cgi/doi/10.1073/pnas.1210150109