Aged blood impairs hippocampal neural precursor activity and activates microglia via brain endothelial cell VCAM1

Hanadie Yousef, Cathrin J. Czupalla, Davis Lee, Michelle B. Chen, Ashley N. Burke, Kristy A. Zera1, Judith Zandstra, Elisabeth Berber, Benoit Lehallier, Vidhu Mathur, Ramesh V. Nair, Liana N. Bonanno, Andrew C. Yang, Todd Peterson, Husein Hadeiba, Taylor Merke, Jakob Körbelin, Markus Schwaninger, Marion S. Buckwalter, Stephen R. Quake, Eugene C. Butcher and Tony Wyss-Coray

Presenter: Kuang-Yu Wen Date/Time: 2020/03/05, 16:10-17:00
Commentator: Dr. Chun-Hsien Chu Location: Room 601, Med College Building

Background:

Brain structure and function deteriorate with age, steadily driving cognitive impairments and susceptibility to neurodegenerative disorders in humans. Emerging evidence carry out a surgical procedure called parabiosis to connect the circulatory systems of aged and young mice, and demonstrate the presence of a factor or factors in young blood that can restore hippocampal synaptic plasticity and improve memory and learning in aged mice. However, it is currently unclear how factors promoting youth or aging that modulate brain function.

Objective/Hypothesis:

An aged circulatory environment can activate microglia, reduce neural precursor cell activity and impair cognition in mice. The authors hypothesized that brain endothelial cells (BECs) mediate at least some of these effects.

Results:

The authors observed that BECs were activated with age, and systemic and cerebrovascular vascular cell adhesion molecule 1 (VCAM1), a protein that facilitates vascular–immune cell interactions, increased with age and heterochronic parabiosis. Considering the heterogeneity of the BBB and the low percentage of BECs that express VCAM1, the authors performed single-cell RNAseq (scRNA-seq) on $VCAM1^{+}$-enriched BECs to characterize the unique molecular and phenotypic nature of rare $VCAM1^{+}$ BECs. BECs in the aged mouse hippocampus express an inflammatory transcriptional profile with focal upregulation of VCAM1. Next the authors found plasma from aged mice increased VCAM1 expression, reduced neural progenitor cells (NPCs) activity and increased microglial reactivity. Genetic deletion of Vcam1 in BECs prevented effects of plasma from aged mice. Systemic administration of monoclonal anti-VCAM1 antibody prevented detrimental effects of plasma from aged humans and mice and reversed aging aspects, including microglial reactivity and cognitive deficits, in the brains of aged mice.

Conclusion:

Together, these findings establish brain endothelial VCAM1 at the blood–brain barrier as a possible target to treat age-related neurodegeneration.

Reference:

1. Steven M Paul & Kiran Reddy. Young blood rejuvenates old brains. *Nature Medicine*, News and Views **20,** 2014
2. Maria Teresa Rizzo & H. Anne Leaver. Brain Endothelial Cell Death: Modes, Signaling Pathways, and Relevance to Neural Development, Homeostasis, and Disease. *Mol Neurobiol* **42**, 2010