Gut microbiota influences blood-brain barrier permeability

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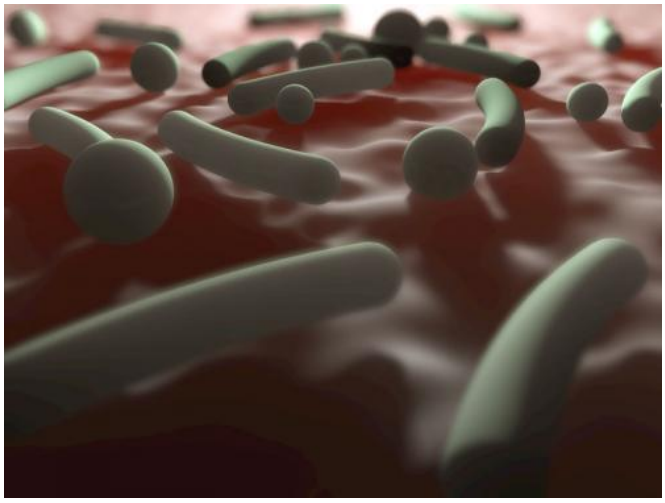

Healthy gut microbiota may influence the early development of the blood-brain barrier. Credit: V. Altounian/Science Translational Medicine

A new study in mice, conducted by researchers at Sweden's Karolinska Institutet together with colleagues in Singapore and the United States, shows that our natural gut-residing microbes can influence the integrity of the blood-brain barrier, which protects the brain from harmful substances in the blood. According to the authors, the findings provide experimental evidence that our indigenous microbes contribute to the mechanism that closes the blood-brain barrier before birth. The results also support previous observations that gut microbiota can impact brain development and function.

The blood-brain barrier is a highly selective barrier that prevents unwanted molecules and cells from entering the brain from the bloodstream. In the current study, being published in the journal *Science Translational Medicine*, the international interdisciplinary research team demonstrates that the transport of molecules across the blood-brain barrier can be modulated by gut microbes - which therefore play an important role in the protection of the brain.

The investigators reached this conclusion by comparing the integrity and development of the blood-brain barrier between two groups of mice: the first group was raised in an environment where they were exposed to normal bacteria, and the second (called germ-free mice) was kept in a sterile environment without any bacteria.

"We showed that the presence of the maternal gut microbiota during late pregnancy blocked the passage of labeled antibodies from the circulation into the brain parenchyma of the growing fetus", says first author Dr. Viorica Braniste at the Department of Microbiology, Tumor and Cell Biology at Karolinska Institutet. "In contrast, in age-matched fetuses from germ-free mothers, these labeled antibodies easily crossed the blood-brain barrier and was detected within the brain parenchyma".

The team also showed that the increased 'leakiness' of the blood-brain barrier, observed in germ-free mice from early life, was maintained into adulthood. Interestingly, this 'leakiness' could be abrogated if the mice were exposed to fecal transplantation of normal gut microbes. The precise molecular mechanisms remain to be identified. However, the team was able to show that so-called tight junction proteins, which are known to be important for the blood-brain barrier permeability, did undergo structural changes and had altered levels of expression in the absence of bacteria.

According to the researchers, the findings provide experimental evidence that alterations of our indigenous microbiota may have far-reaching consequences for the blood-brain barrier function throughout life.

"These findings further underscore the importance

of the maternal microbes during early life and that our bacteria are an integrated component of our body physiology", says Professor Sven Pettersson, the principal investigator at the Department of Microbiology, Tumor and Cell Biology. "Given that the microbiome composition and diversity change over time, it is tempting to speculate that the blood-brain barrier integrity also may fluctuate depending on the microbiome. This knowledge may be used to develop new ways for opening the blood-brain-barrier to increase the efficacy of the brain cancer drugs and for the design of treatment regimes that strengthens the integrity of the blood-brain barrier".

More information: 'The gut microbiota influences the blood brain barrier permeability in mice', Viorica Braniste, Maha Al-Asmakh, Czeslawa Kowa, Farhana Anuar, Afrouz Abbaspour, Miklos Toth, Agata Korecka, Nadja Bakocevic, Ng Lai Guan, Parag Kundu, Balazs Gulyas, Christer Halldin, Kjell Hultenby, Harriet Nilsson, Hans Hebert, Bruce T. Volpe, Betty Diamond, Sven Pettersson, *Science Translational Medicine*, online 19th November 2014. stm.sciencemag.org/lookup/doi/ … scitranslmed.3009759

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