Alzheimer's disease plasma biomarker contributes to postoperative delirium-like behavior in rodents

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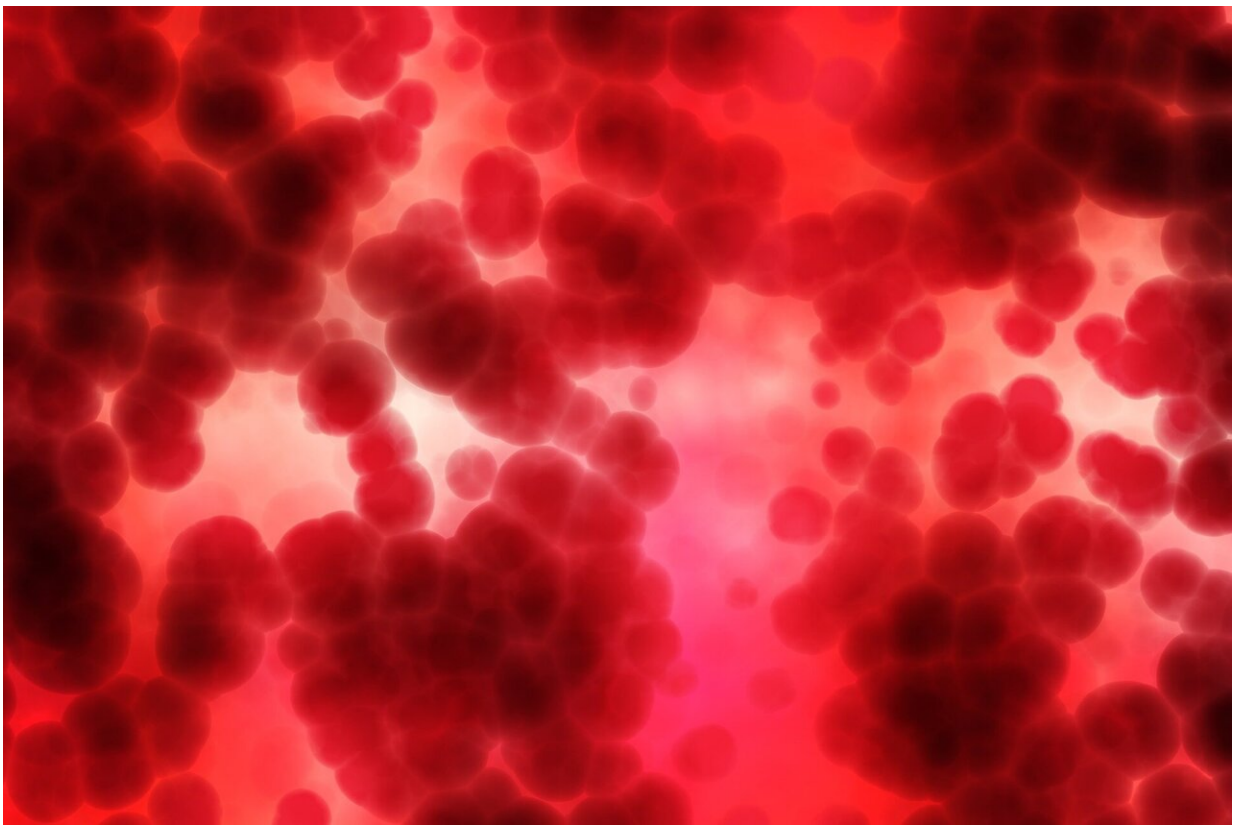

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Tauopathy is one of the hallmarks of Alzheimer's disease (AD) pathogenesis, and the phosphorylation of Tau at threonine 217 (Tau-

PT217) and 181 (Tau-PT181) represents new plasma biomarkers capable of detecting early-stages of AD.

Additionally, preoperative plasma levels of Tau-PT217 and Tau-PT181 serve as biomarkers of postoperative delirium in older patients. Moreover, plasma levels of Tau-PT217 and Tau-PT181 increase following anesthesia and surgery in patients.

Thus, understanding whether acute postoperative elevations in plasma Tau-PT217 and Tau-PT181 contribute to postoperative delirium may reveal the pathogenesis and facilitate the identification of targeted interventions for this condition.

A new study, led by researchers from Massachusetts General Hospital (MGH), Brigham & Women's Hospital, Beth Israel Deaconess Medical Center, University of Pennsylvania Health System, NanoMosaic, Inc, Columbia University Medical Center and other institutes has revealed that an acute increase in plasma Tau-PT217 levels contributes to postoperative delirium-like behavior in aged mice. These findings are published in *Alzheimer's & Dementia*.

In early studies, the same research group collaborated with NanoMosaic (Woburn, MA) to develop a novel method called nanoneedle technology, which enables the measurement of Tau-PT217 and Tau-PT181 concentrations in patients' plasma.

In the present study, the researchers initially used PET imaging to illustrate that anesthesia and surgery in aged mice could lead to elevated levels of Tau-PT217 in the lungs, blood, and brain tissues of these mice. This was further confirmed through the use of Nanoneedle and Western blot techniques.

Interestingly, the increase in Tau-PT271 was observed earlier in the

lungs compared to the brain tissues of the mice.

By employing Tau knockout mice, the investigators demonstrated that Tau-PT217 in the blood could traverse the blood brain barrier to enter the brain tissues of aged mice.

Furthermore, anesthesia/surgery was found to decrease blood B cells by impairing the mitochondrial function of B cells in aged mice. It is speculated that B cells may specifically bind to peptides containing Tau-PT217.

These data suggest that the reduction of B cells induced by anesthesia/surgery may result in the release Tau-PT217 into the blood stream from its binding to B cells.

Additionally, the administration of exogenously harvested B cell effectively mitigated the anesthesia/surgery-induced elevation of blood Tau-PT217 levels in aged mice, as well as the postoperative delirium-like behavior exhibited by the mice.

Finally, the researchers demonstrated that WS635, a novel drug known for enhancing mitochondrial function without causing immune suppression effects, was able to alleviate the anesthesia/surgery-induced impairment of B cell mitochondrial function, decrease in blood B cell levels, elevation of blood Tau-PT217 amounts, increase in brain neuronal activity, and ultimately the occurrence of postoperative delirium-like behaviors in the aged mice.

"These findings suggest that the acute rise in blood Tau-PT217 plays a crucial role in the pathogenesis of postoperative delirium-like behavior in rodents," says lead author Jing Lu, MD, Ph.D., a research fellow in the Department of Anesthesia, Critical Care and Pain Medicine at MGH.

Lu's current affiliation is the Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital in Chengdu, China.

"These results provide valuable insights into the pathogenesis of postoperative delirium; offering potential targeted interventions and shedding light on the underlying mechanisms involved in the acute elevation in blood Tau-PT217, including its generation and release," says Lu.

The data also establish a potential cause-effect relationship between blood Tau-PT217 and brain function, specifically delirium-like behavior in mice.

"Ultimately, these findings hold promise for improving postoperative outcomes in patients and ensuring patient safety." says senior author Zhongcong Xie, MD, Ph.D., from the Mass General Department of Anesthesia, Critical Care, and Pain Medicine. Dr. Xie holds the position of Professor of Anesthesia and Henry K. Beecher Chair at Harvard University.

"These data also suggest that Tau phosphorylation, known to be implicated in the AD pathogenesis, may also contribute to the pathogenesis of postoperative delirium," Xie adds.

An acute increase in the plasma concentration of Tau-PT217 has been found contribute to postoperative delirium-like behavior, while a reduction in plasma Tau-PT217 levels can lead to mitigation of the postoperative delirium-like behavior in aged mice.

"We hope that this research will encourage further studies to confirm the significance of peripheral phosphorylated Tau, which is involved in the pathogenesis of AD, in the development of postoperative delirium," says Guang Yang, Ph.D., from the Columbia University Medical Center.

"Such studies are crucial for gaining a deeper understanding of the mechanisms underlying the interplay between delirium and AD." Yang, an Associate Professor of Anesthesia, is also a corresponding author of the study.

More information: Jing Lu et al, Blood tau-PT217 contributes to the anesthesia/surgery-induced delirium-like behavior in aged mice, *Alzheimer's & Dementia* (2023). DOI: 10.1002/alz.13118

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