Mouse study mirrors human findings that link chemotherapy and APOE4 to cognitive issues

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The research, led by Georgetown University Medical Center (GUMC) investigators and published in *Neurotoxicity Research*, complements findings from another GUMC-led study, published Oct. 3, that found a subset of breast cancer patients who experience long lasting cognitive deficits also have the APOE4 gene. Cancer survivors often report memory difficulties and this study, published in the *Journal of Clinical Oncology* (*JCO*), was the first large U.S. study of cognition in older breast cancer patients and the first to zero in on the cause of difficulties in memory, among other issues.

While the JCO study did not examine the specific type of chemotherapy used in the patients, who were being treated for metastatic breast cancer, the mouse study investigated a single drug, doxorubicin, which is commonly used to treat the cancer.

"These two studies took completely different approaches, yet they are telling the same story, and that is a real strength," says G. William Rebeck, Ph.D., a professor in the GUMC Department of Neuroscience and senior author of the *Neurotoxicity Research* study.

"The data in the mice is very clear—APOE4 works in concert with doxorubicin to produce significant changes in the cortex and hippocampus and to markedly impair learning," he says.

"Given how well this mouse model works, we believe we can now methodically test chemotherapy drugs, one by one, and see what effects the drugs may be producing in the brain. We could also test agents to prevent cognitive decline in cancer patients with APOE4," Rebeck says.

"These kind of direct studies can't be done in humans; our mouse models may be able to provide some valuable insight into which drugs may work best for individual patients," he says.

Rebeck, a neuroscientist, started working on this project several years ago when geriatrician Jeanne Mandelblatt, MD, MPH, came to see Rebeck. Mandelblatt, who led the JCO study, wondered, early in the study, whether APOE4 could be a culprit in the cognitive issues that some of the patients in her study were having. Rebeck is well known for his work of the link between APOE4 and Alzheimer's disease.

They talked about how chemotherapy could affect brain function in APOE4-positive patients, which led Rebeck to test a mouse model of human APOE3 (the most common variant) and APOE4. These mice lack the mouse APOE gene (which is different from the human) and instead express one of two human APOE alleles.

While both APOE3 and APOE4 chemotherapy-treated mice had brain changes, compared to a control group of knock-in mice that were not treated with doxorubicin, the difference was more severe in APOE4 treated mice. These mice also had significantly impaired functioning on learning tasks.

Rebeck cannot say why chemotherapy and APOE4 may work together to affect brain function, but "good hypotheses" are that the combination increases inflammation in the periphery of the brain that accelerates aging—and aging is linked to development of Alzheimer's disease—or that APOE4 inhibits normal growth of new brain neurons that helps replace damaged neurons.

"Our group is delighted that we can provide some insights to our colleagues who study cancer," he

says. "We hope to collaborate a great deal in the future on these issues."

Provided by Georgetown University Medical Center