A Mouse Model of APOE Genotype in Chemotherapy Related Cognitive Impairment
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OBJECTIVES/SPECIFIC AIMS: Chemotherapy-related cognitive impairment (CRCI) affects 15-35% of breast cancer survivors and constitutes a significant challenge for survivor quality of life. Among older breast cancer survivors who received chemotherapy treatment, carriers of at least one e4 allele of the APOE gene, which encodes apolipoprotein E, are at higher risk for developing CRCI than non-carriers. APOE4 is well characterized as the strongest genetic risk factor for Alzheimer’s disease, but how it contributes to CRCI is not yet understood, and no animal models of APOE genotype and CRCI have yet been established. To better understand how APOE4 acts as a risk factor for CRCI, we used APOE targeted replacement (TR) mice to develop a model of its effects on cognition following treatment with doxorubicin, a chemotherapy drug commonly used in breast cancer treatment. METHODS/STUDY POPULATION: Twelve-to-thirteen month old APOE3 and APOE4 targeted replacement mice expressing human APOE3 or human APOE4 under control of the endogenous murine promoter were treated with 10 mg/kg doxorubicin or equivolume saline given via two IP injections spaced one week apart. One week post-treatment, mice were tested using Open Field and Elevated Zero apparatuses to assess baseline locomotive activity and anxiety and exploratory behaviors. Five weeks post-treatment, mice were assessed using the Barnes Maze over four days of training trials and one 72 hour memory probe. RESULTS/ANTICIPATED RESULTS: We found no differences in Open Field and Elevated Zero behavior, indicating limited influence of doxorubicin treatment on locomotive and anxiety behaviors in both genotypes. During Barnes Maze training, APOE4 mice treated with doxorubicin showed increased latency compared to untreated APOE4 mice as well as treated and untreated APOE3 mice, indicating deficiencies in spatial learning. In APOE3 mice, no differences in performance were seen between doxorubicin-treated and untreated mice (n = 15-16/group, p <.0001). DISCUSSION/SIGNIFICANCE OF IMPACT: These results indicate that APOE4 targeted replacement mice have specific cognitive vulnerabilities to doxorubicin treatment that can be reliably detected using the Barnes Maze assessment. Future directions include experiments to determine how other chemotherapy drugs or drug combinations impact cognition of APOE4 mice. Ultimately this model may be used to assess preventive measures or therapies for CRCI in the vulnerable APOE4 carrier population with the ability to validate cognitive impacts of these interventions.