

Long-Term Effects of Chemotherapy in Mouse Survivorship Model

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Introduction: Survivors of adolescent and young adult (AYA; age 15-39 years at diagnosis) cancers are a growing population with the potential to live for many decades after treatment completion. However, they often face long-term treatment-related toxicities that can affect the immune system and reproductive and cognitive health for decades after therapy. Although cisplatin, cyclophosphamide, and doxorubicin remain the first line of cancer treatments, the cellular mechanisms driving these late survivorship effects are not well defined. The goal of this study is to characterize chemotherapy-induced late effects across hematopoietic/immune, reproductive, and nervous-system tissues through longitudinal phenotyping and multi-organ single-cell transcriptomic profiling in a mouse survivorship model.

Methods: Male C57BL/6J wild-type mice (2 months old) were treated with two weekly doses of PBS, cisplatin (4 mg/kg), cyclophosphamide (50 mg/kg), or doxorubicin (2 mg/kg) and monitored periodically after chemotherapy administration. Peripheral blood was analyzed by flow cytometry at baseline and at serial post-treatment time points. Behavioral assessments were conducted during late survivorship.

Results: Post-chemotherapy analyses showed durable remodeling of peripheral T-cell populations, particularly in doxorubicin-treated mice. Compared with controls, chemotherapy-treated mice had reduced CD44⁺CD62L⁺ naïve T cells and increased CD44⁺CD62L⁺ central-memory-like T cells, indicating persistent adaptive immune reprogramming beyond acute cytotoxic depletion and without acute pathology. This trend persisted after several months post treatments, suggesting that, after chemotherapy, persistent T-cell dysregulation may promote chronic inflammation, and potentially contribute to reproductive dysfunction.

Conclusion: This work provides new insights on chemotherapy-related late effects and might shed new light on potential strategies to restore immune, reproductive, and cognitive health in cancer survivors. This preliminary work could help on finding treatments and interventions aimed at improving long-term quality of life for AYA cancer survivors.

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