Pharmacological Inhibition of the JNK Cellular Stress Pathway Protects Ovarian Follicle Reserve from Chemotherapy-Induced DNA Damage and Apoptosis

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Advances in cancer treatment have improved patient survival, but young female cancer survivors face chemotherapy-induced primary ovarian insufficiency (POI), endocrine dysfunction, and infertility. Cryopreservation-based fertility preservation methods are invasive, delay cancer treatment, and are unsuitable for prepubertal patients. Pharmacological ovarian protectants offer a non-surgical alternative to preserve ovarian function during chemotherapy. This research investigated the c-Jun N-terminal kinase (JNK) pathway, which regulates cell survival, and is activated in oocytes in response to DNA-damaging chemotherapy. We hypothesized that pharmacological JNK inhibition would protect primordial follicles from chemotherapy-induced apoptosis, preventing POI. The objectives were to determine whether small-molecule JNK inhibitors protect ovaries from chemotherapy-induced follicle loss and elucidate how chemotherapy activates JNK and downstream apoptosis molecules, including TAp63α, PUMA, and NOXA. To investigate this, mice were treated with doxorubicin, with or without JNK inhibitor. Histological staining and follicle counting assessed ovarian morphology and follicle preservation, while qPCR quantified expression of genes involved in DNA damage response and apoptosis. Results showed that JNK inhibition protected the ovarian follicle reserve and maintained normal puberty onset, estrous cyclicity, and long-term fertility. Importantly, JNK inhibition did not compromise chemotherapy efficacy in breast cancer-bearing mice (Zhao *et al.*, 2026). Future studies will use RNA sequencing and qPCR to further characterize the JNK pathway, define mechanistic differences between oocytes and somatic cells, and evaluate surviving oocyte genetic integrity. Overall, this work advances our understanding of chemotherapy-induced POI, supporting further development of JNK inhibitors as ovarian protectants to preserve fertility and ovarian hormones in young female cancer survivors. My research was supported by NIH R25ES020721, the Society of Toxicology, and the Ernest Mario School of Pharmacy, through the Rutgers SURF and RISE programs.