

The Immediate Effects of Gonadotoxic Agents on the Viability of the Mammalian Ovary—Are Multidrug Resistant Transporters Protective?

Niesha Voigt, BA; Nathalie Oulhen, PhD; Gary M. Wessel, PhD; Lynae M. Brayboy, MD

Alpert Medical School of Brown University (Author 1)

Women & Infants Hospital (Author 4)

Department of Molecular Biology, Cell Biology and Biochemistry, Brown University (Author 2 and 3)

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Background

Chemotherapy-induced ovarian toxicity is collateral damage that is becoming a leading cause of ovarian insufficiency, which prejudices the patient to premature onset of menopause-associated risks such as osteoporosis, increased cardiovascular risk, and sexual dysfunction in addition to infertility. The purpose of this research study is to determine the immediate gonadotoxic defense mechanisms imparted by multidrug resistant transporters (MDRs) in the two major cell types of the follicle, the granulosa cells and the oocytes by assessing the ovary in situ.

Methods

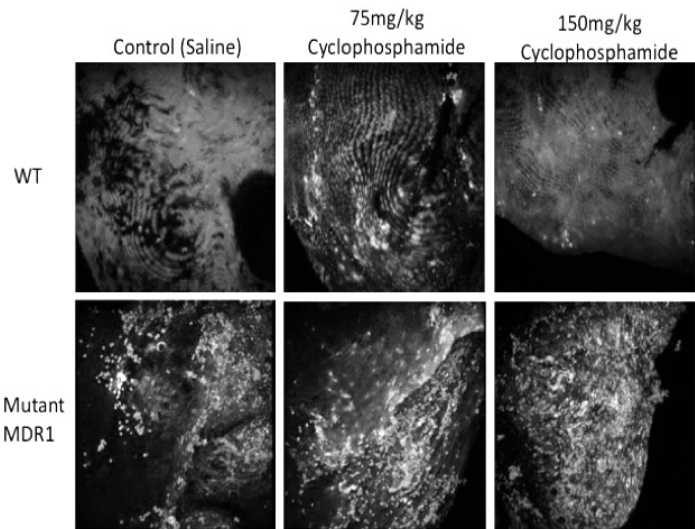
Laboratory experiment using FVBN, CF-1 wild type, MDR1a (-/-) CF-1 spontaneous mutant, and C57Bl6 aged mouse ovaries. Western blot and immunofluorescence protocols were performed on isolated mouse granulosa cells and oocytes were incubated with anti-MDR1a antibodies. Wild type and mutant CF-1 mice were injected with cyclophosphamide and their ovaries were imaged for granulosa cell death after Live/Dead assay (Life Technologies Carlsbad, CA) incubation.

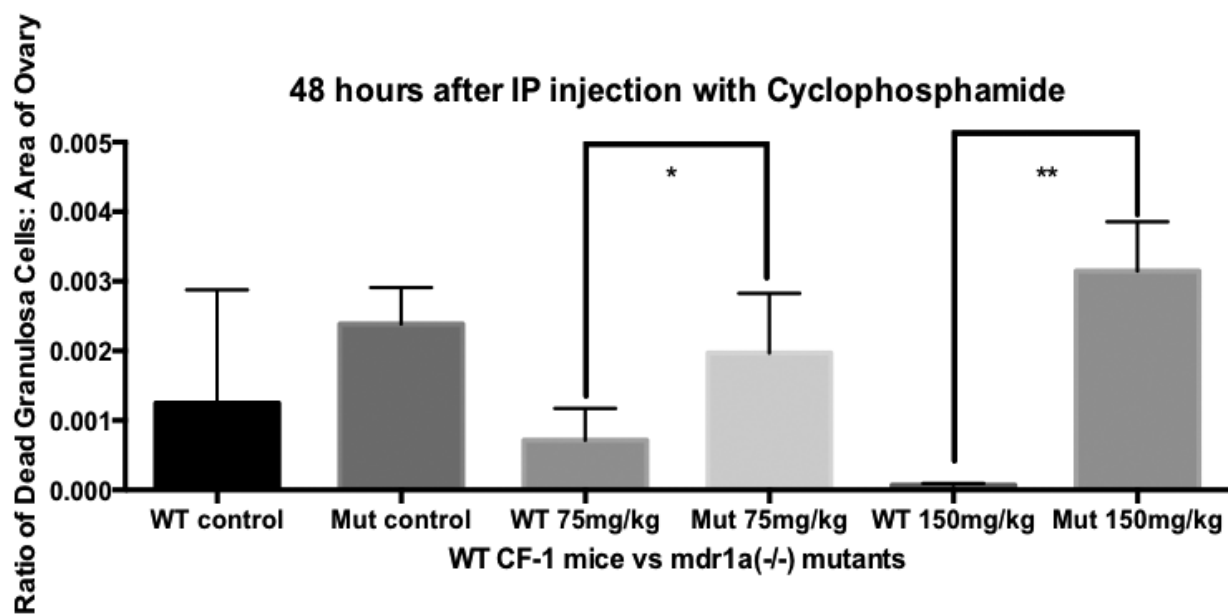
Results

Mouse granulosa cells expressed MDR-1 with less efflux capability than oocytes. Whole ovaries of MDR-1a mutants showed more cell death in comparison to wild type ovaries.

Conclusion

While oocyte have MDRs that are protective, granulosa cells express MDR-1 that has ineffective efflux capability of toxins compared to oocytes. This implies that granulosa cells are more vulnerable than oocytes and the death of granulosa cells may consequently impair the oocyte viability leading to primary ovarian insufficiency.





*p=.0257

**p=.0001