5-5-2022

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Background: Cancer therapies cause serious side effects, affecting the quality of life for young cancer survivors. The ovary is affected by cancer therapies, causing premature ovarian insufficiency, leading to endocrine dysfunction, infertility, and ovarian aging. Thus, maintaining ovarian function against cancer treatment is an unmet need for female cancer patients. Cyclophosphamide (CPA), a common chemotherapeutic agent, forms DNA crosslinks to induce apoptosis in rapidly proliferating tumor cells. However, the underlying mechanism of the CPA-induced oocyte death in ovarian reserve remains unclear.

Experimental design: This study aims to investigate the mechanism of oocyte death in primordial follicles by generating oocyte-specific *Abl1* and *p63* knockout and *Pik3ca** knockin mouse models using *Gdf9-iCre*+. Prepubertal day 7 female mice were utilized for further analysis.

Results: The quantification of surviving follicles validated that 90% of the primordial follicles from oocyte-specific *Abl1* knockout mice were lost following CPA treatment *in vivo* and *in vitro*. Concurrently, high expression of CHK2 was detected in the oocytes of the ovary cultured with CPA metabolite *in vitro*. Most importantly, *p63* knockout oocytes were rescued after CPA treatment and maintained functional fertility in the mating trials. To better understand the CPA-induced primordial follicle loss, *Pik3ca** mice were examined with or without CPA administration. As expected, ovarian primordial follicles with constitutive PI3K expression inside of oocytes in the *Pik3ca** mice survived against CPA. Accordingly, the apoptosis markers, BAX and cleaved PARP were highly induced with CPA injection in a time-dependent manner in the ovaries of wild-type female mice but not from the *p63* knockout. The double-strand break also occurred in the nucleus of oocytes post CPA administration as γH2AX was detected. Interestingly, OPA1, a protein required for mitochondrial fusion, was highly induced inside the oocyte cytoplasm of the *p63* knockout, while oocytes in wild-type mice time-dependently lost the OPA1 expression by CPA treatment. This indicates that oocytes without p63 in the nucleus survive and induce mitochondrial fusion to escape apoptosis by mitochondrial damage.

Conclusion: cAbl is dispensable for primordial follicle depletion caused by CPA. However, TAp63 is the key regulator in CPA-induced apoptosis in oocytes. Furthermore, CHK2 is upregulated in the oocytes of primordial follicles post CPA exposure. Activated follicles resist gonadotoxic agents, even though p63 is expressed inside their oocytes. Therefore, CPA induces depletion of oocytes in primordial follicles through the CHK2-TAp63 apoptotic pathway.