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TAp63 is instrumental for oocyte fate against DNA damage

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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), an alkylating chemotherapeutic agent, forms DNA crosslinks to induce apoptosis in rapidly proliferating tumor cells. However, the underlying mechanism of CPA-induced oocyte death in ovarian reserve remains unclear. Advanced cancer therapies induce long-term consequences including the loss of fertility. However, the underlying mechanism of oocyte death by chemotherapeutic agents has not been well understood. This study improves our knowledge of the mechanisms of cancer therapies-induced primordial follicle loss and proposes the potential targets in fertility preservation during chemotherapies. ABL inhibitor has been proposed to prevent primordial follicle loss by CPA, while later studies validated the TAp63 phosphorylation by other chemotherapeutic agents in the oocytes. Here, we hypothesize that CPA induces ovarian follicle depletion through TAp63-related signaling pathways. This study utilized oocyte-specific *Abl1* and *Trp63* knockout mouse models using *Gdf9-iCre* to delineate the mechanism of primordial follicle loss induced by CPA. checkpoint kinase 2 (CHK2) inhibitor was tested in postnatal day 7 mice for fertility preservation against chemotherapy. ABL allosteric inhibitor, GNF2, did not impede the loss of primordial follicles induced by CPA, and the number of primordial follicles from oocyte-specific *Abl1* knockout mice declined after CPA treatment. Instead, CHK2 was time-dependently expressed in the oocytes exposed to CPA metabolite, and p63 was hyperphosphorylated by CPA administration. *Trp63* deletion in oocytes prevented primordial follicle depletion caused by CPA. CPA-treated *Trp63* knockout mice delivered a comparable number of litters and pups to solvent-treated control females. Consistently, oocytes from CPA-treated *Trp63* knockout mice had undetectable levels of BAX and cleaved PARP, as well as increased OPA1 expression. The administration of CHK2 inhibitor preserved the ovarian reserve from CPA. This study clarified the underlying mechanism of CPA in oocyte death and provided a path to preserve ovarian follicles in cancer patients. TAp63 is fundamental in determining the signaling of oocyte death against DNA damage. CHK2-TAp63 pathway rather than ABL is the main pathway in oocyte death of primordial follicles against CPA. Therefore, TAp63 is potentially an effective target to prevent cancer treatment-induced primordial follicle loss without compromising the efficacy of chemotherapy in female cancer patients.