Pharmacological control of follicle recruitment

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The ovarian follicle reserve is maintained in a delicate state of homeostasis aimed at preserving the majority of follicles in a dormant state. Key regulatory factors in follicle activation and quiescence include the PI3K/PTEN/Akt signaling pathway in the oocyte, as well as external paracrine inhibitory factors such as anti- Mullerian hormone (AMH). Mice with oocyte-specific deletion of one or more elements in the PI3K/PTEN/Akt pathway, or AMH-knockout mice, exhibit premature activation and rapid depletion of ovarian follicle reserve. Disturbance of ovarian homeostasis has been shown to be a mechanism of follicle loss in the case of iatrogenic ovotoxicity.

The most recent theory of chemotherapy-induced destruction of dormant follicles suggests that *in-vivo,* chemotherapy agents such as Cy and cisplatin trigger an initiation of dormant follicle growth, occurring simultaneously with large follicle apoptosis. The activation of dormant follicles was shown to be mediated by an upregulation in the PI3K/PTEN/Akt signaling pathway. The route by which chemotherapy terminates follicle dormancy and induces activation of the PI3K/PTEN/Akt pathway may be via direct influence on the oocytes and pregranulosa cells of primordial follicles, or indirectly via chemotherapy-induced destruction of larger follicles. Destruction of large follicles results in a reduction of Anti Mullerian Hormone (AMH) suppression on the primordial follicle pool, thereby resulting in activation of primordial follicles in an attempt to replace the dying cohort of growing follicles.

Ovarian tissue cryopreservation and transplantation (OTCP-TP) induce activation and loss (‘burn out’) of the dormant follicle pool. Extensive increase in PMF activation was observed in grafted tissue compared to frozen-thawed untransplanted controls. Recovered grafts showed dormant follicle activation and ‘burn out’ after transplantation. Freezing-thawing-transplantation protocols result in the loss of the majority of growing follicle populations leading to a drop in AMH levels. This understanding of the mechanisms behind the follicle loss that limits the lifespan of ovarian tissue grafts, and potential use of AMH as protective agent for treatment women undergoing ovarian tissue cryopreservation- transplantation procedure will provide new targets for optimization and improvement of this fertility preservation technique.