

Targeting mTOR signaling to preserve reproductive longevity

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Activation and loss of the ovarian primordial follicle pool is responsible for the irreversible decline in reproductive function culminating in menopause. The mammalian/mechanistic target of rapamycin (mTOR) pathway is critical to primordial follicle activation and is implicated in both physiologic ovarian aging and accelerated loss during genotoxic chemotherapy. We previously demonstrated that co-treatment with mTOR inhibitors during alkylating chemotherapy preserved primordial follicles, maintained baseline anti-mullerian hormone (AMH) levels, and preserved fertility in mice exposed to gonadotoxic chemotherapy.

Understanding the significant impact of mTOR inhibitors on the preservation of the primordial follicle pool, we subsequently investigated the impact mTOR inhibitor treatment on reproductive longevity in a murine model of physiologic ovarian aging. Female reproductive-aged C57BL/6 mice were treated with either an mTOR1 inhibitor (RAD001, Everolimus) or dual mTORC1/2 inhibitor (INK128), or no treatment, and were subsequently harem-bred with reproductively-proven male mice until surpassing the average age of reproductive senescence. Reproductive potential was assessed by total number of litters and reproductive longevity. Mice that received dual mTORC1/2 inhibitors had twice as many litters and pups throughout the breeding period compared to control. RAD001 and INK128-treated mice were reproductively active for an average of 1.5 months longer than untreated mice. Given the critical relationship between mTOR inhibition and aging, our data suggest a possible pharmacologic target to delay physiologic age-related fertility decline.

This talk will address the critical role of mTOR signaling in ovarian biology and the potential use of a targeted pharmacologic approach to preserve ovarian function in physiologic ovarian aging.