Cell Cycle 12:21, 3353–3354; November 1, 2013; © 2013 Landes Bioscience

Rapamycin prolongs female reproductive lifespan

Li-li Luo[1], Jin-jie Xu[2], and Yu-cai Fu[2,*]

[1]Department of Gynecology and Obstetrics of the First Affiliated Hospital; Shantou University Medical College; Shantou, PR China;
[2]Laboratory of Cell Senescence; Shantou University Medical College; Shantou, PR China

The pool of ovarian primordial follicles is established during embryonic development in humans, or after birth in rodents, and serves as the source of developing follicles and fertilizable ova for the entire length of female reproductive life.[1] Once the pool of primordial follicles has been exhausted, menopause occurs in women around 50 y old. With modern increases in longevity, more than one-third of a woman's life is now spent after menopause, which is characterized by a loss of fertility and increased risk for cardiovascular disease, osteoporosis, and cognitive dysfunction. To maintain the normal length of female reproductive life, the majority of primordial follicles must be maintained in a quiescent state for later use. Therefore, the activation of primordial follicles is a critical process for female reproductive lifespan, but the mechanism is poorly understood.

Although it has been well established that the development of primordial follicles is regulated by locally produced autocrine, endocrine, and paracrine signals, exactly how the primordial follicle integrates these signals to maintain dormant or to be activated to develop is unclear. However, recent studies have revealed that mammalian target of rapamycin (mTOR) pathway, which serves to integrate such signals, involves the control of primordial follicle activation and development.[2,3] mTOR is a ubiquitous, evolutionarily conserved serine/threonine kinase that regulates cell growth and proliferation in response to stress, nutrients, and growth factors. mTOR functions as part of 2 multiprotein complexes, mTOR complex 1 (mTORC1) and mTORC2.[4] Rapamycin inhibits mTORC1 by binding the FK506-binding protein FKBP12, which then interacts physically with the complex and decreases activity. The upstream of mTORC1, the TSC1/TSC2 protein complex, suppresses the activation of mTORC1 through a GTPase-activating protein domain located in TSC2. The major downstream effectors of mTOR known so far are S6K1 and 4E-BP1, both regulators of protein translation. Deletion of Tsc1 or Tsc2 in mouse oocytes caused premature activation of all primordial follicles around the time of puberty, and eventually led to premature ovarian failure (POF) in early adulthood. Inhibition of mTOR signaling by rapamycin effectively reversed the overactivation of primordial follicles in mutant mouse ovaries.[2,3] These findings indicate that mTOR signaling is involved in controling the activation of primordial follicles. Furthermore, rapamycin could suppress mouse granulosa cell proliferation and follicle development in vitro, and resulted in reduced numbers of ovulated eggs in vivo.[5,6]

Based on these data, we speculate that inhibition of mTOR signaling by rapamycin may suppress the activation of ovarian primordial follicles in adult mammals, and thus preserve the follicle pool reserve and prolong the female reproductive lifespan. In our current study, adult female rats fed a standard diet ad libitum were treated every other day with an intraperitoneal injection of rapamycin (5 mg/kg) for 10 weeks. Our results showed that inhibition of mTOR signaling by rapamycin resulted in a 2-fold increase in the number of primordial follicles in the rapamycin-treated rats compared with the control rats, indicating that the activation of primordial follicle was suppressed. Furthermore, the numbers of antral and atretic follicles and corpora lutea were significantly decreased, suggesting the inhibitory effects also on the development of follicles at different stages to maturation and atresia. These data indicate that rapamycin can effectively suppress the activation of ovarian primordial follicles in adult animals via inhibition of mTOR signaling, thus preserving the follicle pool reserve and prolonging the female reproductive lifespan.

However, some of the normal reproductive functions were also suppressed. The rapamycin-treated rats had irregular estrous cycles and failed to become impregnated during the mating trial. This could be explained by the fact that there were not sufficient antral follicles and corpora lutea in the rapamycin-treated rats to produce a certain amount of estrogen and progestogen to maintain these normal functions. Moreover, Yu et al. demonstrated that rapamycin inhibited ovulation in mice.[6]

In addition, it is worth noting that rapamycin induced a decrease of food intake by ~33.9%. The rapamycin-treated rats were lean and smaller than the control rats, although their calorie intake per gram of body weight was comparable to that of the control rats at the end of treatment. Meanwhile, the protein expression of SIRT1 and SIRT6 was significantly increased in the rapamycin-treated rat ovaries. Sirtuins are key regulators in the mechanism by which CR extends lifespan of various organisms from yeast to mammals.[7] The upregulated expression of SIRT1 and SIRT6 and increased follicle pool reserve were also found in CR rats in our previous study.[8] How rapamycin induces the upregulation of SIRT signaling is unclear. Since rapamycin-treated rats have a similar phenotype to CR rats, we

*Correspondence to: Yu-cai Fu; Email: ycfu@stu.edu.cn
Submitted: 08/01/2013; Accepted: 08/04/2013
http://dx.doi.org/10.4161/cc.26578
Comment on: Zhang XM, et al. Gene 2013; 523:82-7; PMID:23566837; http://dx.doi.org/10.1016/j.gene.2013.03.039

hypothesize that rapamycin may induce a CR condition, and thus upregulate SIRT signaling, or inhibition of mTOR signaling by rapamycin may lead to the activation of SIRT signaling via unknown pathways, thus mimicing CR effects. This warrants further studies.

In summary, our data indicate that rapamycin treatment has beneficial effects on the reserve of ovarian follicle pool and female reproductive lifespan in animals. We optimistically consider that rapamycin or its derivatives could be used as an effective drug for preventing POF and delaying the onset of menopause in obese or even healthy women in the future.

References

1. McGee EA, et al. Endocr Rev 2000; 21:200-14; PMID:10782364; http://dx.doi.org/10.1210/er.21.2.200
2. Adhikari D, et al. Mol Hum Reprod 2009; 15:765-70; PMID:19843635; http://dx.doi.org/10.1093/molehr/gap092
3. Adhikari D, et al. Hum Mol Genet 2010; 19:397-410; PMID:19843540; http://dx.doi.org/10.1093/hmg/ddp483
4. Johnson SC, et al. Nature 2013; 493:338-45; PMID:23325216; http://dx.doi.org/10.1038/nature11861
5. Yaba A, et al. Reprod Sci 2008; 15:128-38; PMID:18276949; http://dx.doi.org/10.1177/1933719107312037
6. Yu J, et al. PLoS One 2011; 6:e21415; PMID:21750711; http://dx.doi.org/10.1371/journal.pone.0021415
7. Qiu X, et al. Biochim Biophys Acta 2010; 1804:1576-83
8. Luo LL, et al. Aging Clin Exp Res 2012; 24:125-33; PMID:21502801