SCIENCE CHINA
Life Sciences

SPECIAL TOPIC
• EDITORIAL •

August 2012 Vol.55 No.8: 651–652
doi: 10.1007/s11427-012-4353-4

Frontiers in reproductive aging—challenge and perspective

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Received April 28, 2012

Citation: Liu L. Frontiers in reproductive aging—challenge and perspective. Sci China Life Sci, 2012, 55: 651−652, doi: 10.1007/s11427-012-4353-4

Clinical and public health importance of reproductive aging is increasing as more women delay attempts at childbearing. Moreover, the emotional, medical and social costs of infertility and aneuploid offspring in association with reproductive aging represent a major burden to society. Reproductive aging also can lead to age-related diseases including cardiovascular disease, osteoporosis and breast cancer, which reduces living standard of females in their later life. Women exhibit reduced fertility around their mid-30th, and become infertile when menopause occurs around their 50th. By contrast, reproductivity of men can extend to later stage of life, so reproductive aging in men is not as prominent as in women. The difference is attributable to the self-renewal of germline stem cells, i.e., spermatogonia, existing in adult male gonad the testis that continuously generate new germ cells, whereas females have only fixed number of germ cells at birth, and germ cells do not replenish in the adult ovary at least *in vivo*, despite whether or not germline stem cells stay in adult females remains controversial.

Ovary is the most critical organ in female reproductive system, and thus plays a significant role in maintaining the reproductive function and endocrinal homeostasis. Ovarian aging occurs quite early, prior to the somatic aging of other organs. Ovarian aging is associated with declining reproductive capacity or even infertility, and is evidenced by loss of follicle number in ovary, decline in oocyte quality and reduction of ovarian-secreted hormone levels. In the whole female reproductive lifetime, only a scarce part of oocytes could reach maturation and be discharged from the ovary; the vast majority of the oocytes undergo apoptotic cell death with follicular atresia. Uterus also undergoes aging with women's age, as shown by atrophy, implantation failure, and loss of pregnancy. Meanwhile, the reproductive endocrine system, particularly hypothalamus-pituitary-gonad axis, changes their function and hormone levels with reproductive age. In addition to the physiological changes, the free radicals accumulated with age could form oxidative stress, in combination with environmental toxicity, resulting in DNA mutations, protein damage, telomere shortening and apoptosis, which could accelerate reproductive aging.

In this special topic on reproductive aging, we have invited several prominent experts actively involved in cutting-edge research on reproductive aging and biology to discuss the recent advance, particularly focusing on understanding of aging in the ovary and oocytes, and uterus, and evolution of reproductive aging in association with somatic aging. Also, most up-to-date analyses are provided regarding effects of reproductive aging on *in vitro* fertilization outcomes.

Deng ManQi [1] from Brigham and Women's Hospital and Harvard Medical School discusses the mechanisms of reproductive aging-associated signal transduction and compares the reproductive aging in several animal models, with conservation across all animals including humans. Shi QingHua and colleagues [2] from University of Science and Technology of China analyze the current understanding of ovarian aging, particularly focusing on follicle recruitment and attrition, accompanied by endocrine disorder, and on genetic and micro-environmental factors. Sun QingYuan and colleagues [3] at Institute of Zoology, Chinese Academy of Sciences provide a more specific view in depth on epigenetic changes and mechanisms of oocyte aging associ-

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ated with postovulatory aging as well as advanced maternal age, with particular emphasis on the changes in DNA methylation and histone acetylation and methylation. Huang HeFeng and colleagues [4] at Women's Hospital, Zhejiang University School of Medicine focus on the mechanisms of primary ovarian insufficiency or called as premature ovarian failure (POF) that affects 1% of female population under the age of 40, and provide strategies to treat this reproductive premature aging-associated disease. Wang HaiBin, Duan EnKui and colleagues [5] at Institute of Zoology, Chinese Academy of Sciences provide insights into signaling transduction that governs the process of uterine aging and also highlight the similarity and difference in reproductive aging between rodents and humans. At the end, Chen Zi-Jiang and colleagues [6] from Provincial Hospital affiliated with Shandong University carefully analyze a large number of *in vitro* fertilization and embryos transfer cycles (11830) and provide further evidence in supporting the notion that patients over 40 years old have poor IVF outcome and high miscarriage rate and suggest preimplantation genetic screening necessary for the women over 40 years old.

These selected excellent reviews and data analysis provide current understanding and mechanisms of female reproductive aging, and will likely stimulate more investment in this most exciting research area, eventually leading to strategies to combat reproductive aging and associated diseases confronted world wide.

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4 Jin M, Yu Y Q, Huang H F. An update review on primary ovarian insufficiency. Sci China Life Sci, 2012, 55: 677–686
5 Kong S B, Zhang S, Chen Y J, *et al*. Determinants of uterine aging: Lessons from rodent models. Sci China Life Sci, 2012, 55: 687–693
6 Yan J H, Wu K L, Tang R, *et al*. Effect of maternal age on the outcomes of *in vitro* fertilization and embryo transfer (IVF-ET). Sci China Life Sci, 2012, 55: 694–698