2020 IMPACT CIRCLE

Title: Battle with 0.05% -- reset the biological clock of female reproductive aging

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Unmet Need: Ovarian aging starts in a woman's mid-30s and progresses rapidly for the next 15 years. Because of the early onset of ovarian aging, women spend ~40% of their lifetime battling with symptoms and health issues associated with menopause. Currently, the only solution for relieving negative health issues in postmenopausal women is hormone-replacement therapy (HRT), which was first introduced in the 1940s. However, HRT needs to be carefully evaluated and recommended by physicians due to its health risks, including heart disease, stroke, blood clots and breast cancer. New medical solutions that delay ovarian aging safely and effectively are urgently needed.

Background: A long-standing mystery of ovarian aging is that a woman is only able to use 0.05% - just 500 - of the million egg cells to support ovarian function throughout her reproductive lifespan. Over 99% of these egg cells, known as oocytes, are dormant, never grow and die rapidly after age mid-30s, which leads directly to the loss of ovarian function. One question our groups continue asking is 'Can we use more than 0.05% of dormant oocytes to let ovaries function longer?'. Our studies have started to shed light on the answer. By using mice as a research model, we found that the Balbiani body (B-body), an aggregate of Golgi complexes, is the key for keeping oocytes dormant. When we dispersed the B-body pharmacologically, dormant oocytes were activated to become growing oocytes successfully.

Novel Hypothesis: Modifying oocyte dormancy to delay ovarian aging.

Proposal: We propose to identify 1) the drugs that can maintain the B-body structure in young dormant oocytes and thus protect oocytes from death due to aging and other unknown factors, and 2) the drugs that can disperse the B-body and activate dormant oocytes in mid-age and older females to support adult ovarian function. We will achieve this goal by conducting a two-step high throughput drug screen.
Step 1: Large-scale drug screening by monitoring B-body integrity. We will use a transgenic mouse line, in which Golgi complexes in oocytes are tagged with green fluorescent protein (GFP). We will image green fluorescence-tagged B-body in drug-treated ovarian tissues by automated cell imaging system.

Step 2: Small-scale drug effect validation. For the drugs that show an effect on B-body integrity, we will confirm their effect on oocyte activation by observing oocyte growth using automated cell imaging system. A transgenic mouse line, in which oocytes are tagged with green fluorescent protein will be used.

Impact: The drugs identified by our study will allow us to reset the biological clock of ovarian aging by changing the dynamics of oocyte dormancy. The ovaries with prolonged function are able to produce hormones in a physiological manner. Prolonged ovarian function and self-regulated hormonal production and usage will reduce menopausal symptoms and the risk of health issues, and thus improve overall quality of life in females.

Specialized Equipment Needs: Incucyte live-cell imaging