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Premature ovarian failure, menopause and ovarian cancer, three nodes on the same string: *Pten* and other potential genes on the go

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SUMMARY

Background: Why do women have menopause? The evolution of menopause has long been the puzzle and interest of sociologists regarding Darwinian fitness. However, in a biological/medical perspective, the underling drive force of menopause has never been provided in a satisfactory form.

Hypothesis and rationale: It has been well established that the overall reproductive lifespan is reflected in the speed of ovarian primordial follicles depletion. And, every ovarian cycle involves disruption and regeneration of the ovarian epithelium, which is potentially mutagenic. In this regard, menopause could be evolved to protect reproductive organs from over-disruption–reconstruction cycling, as to preclude mutagenic tissue changes.

Recent discoveries by tissue/cell specific deletion of one single gene (*Pten*) within different compartment of ovary have revealed strikingly distinct ovarian phenotypes, ranging from advanced primordial follicle depletion to neoplastic ovarian lesions. To explain the onset of menopause, here we propose a model that the relative amount/activity of *Pten* between different ovarian compartments (follicular, granulosa and epithelial cells) is spatiotemporally programmed, creating a "menopause tone" fine tuning the speed of follicle depletion and therefore the normal timing of menopause. While imbalanced expression of *Pten* within the ovary cause either pre-arrived menopause (premature ovarian failure) or over-menstrual cycles which are well recognized as a risk factor for ovarian (and other reproductive) cancer. This hypothesis, if validated, could help us understand ovarian aging and related diseases in a more integrated manner; they are just different nodes on the same string. And *Pten* could just be the tip of the iceberg involved in the regulation of "menopause tone".

Background

The evolution of human menopause remains to be a puzzle for both sociologist and biologist. Because in regards to reproductive aging, menopause performed as a complete "shut down" of reproductive lifespan at middle age of women (around 50), rather than a gradual degenerating process observed in most other species or man. Different theories about menopause have been raised by sociologists to maximally explain Darwinian fitness [1]. However, what is the biological/medical significance of menopause for each individual within her lifespan? Does it linked with important health concerns of an individual? And what is the underling drive force of menopause in the perspective of physiology and cellular/molecular biology? To date, it is known that the depletion of primordial follicle reservoir is the key step towards menopause [2], but how the timing of menopause is predetermined regarding follicular recruitment and exhaustion is not well defined.

Hypothesis and rationale

In our belief, menopause is evolved to protect reproductive organs from over-disruption–reconstruction cycling, as to preclude mutagenic tissue changes such as ovarian cancer and other reproductive cancers. This viewpoint could be support by two lines of evidences. First, it is well established that every ovarian cycle involves disruption of ovarian epithelium (follicular rupture at ovulation) and subsequent repair by proliferation of epithelial cells from the adjacent of rupture sites [3]. This process, if repeated overtime, could be potentially mutagenic. Second, regarding overall lifespan, human being is longer-lived than any other mammalian species. In this regard, if the female ovarian cycles continue with the ages increase, there will be increasing risk for the ovaries undergo mutagenic changes. Indeed, there have been evidences supporting more reproductive cycles is associated with increased reproductive cancer [4].

Considering the hypothesis that menopause is evolved to protect reproductive organs from over-disruption–reconstruction cycling, a deeper question remains: how the timing of menopause

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was predetermined? Or in a more confined discussion, how the recruitment and depletion of primordial follicle pool is timely regulated to reach the on time exhaustion (menopause)? Recent discoveries by tissue/cell specific deletion of a single gene in mouse model have given us valuable clues regarding the timing of menopause. It is reported that *Pten*, when specifically deleted in the oocyte, cause premature activation of the primordial follicle pool and early onset of follicle depletion at early adulthood, a phenotype very familiar with premature ovarian failure (POF) in human [5]. While *Pten* is specifically deleted in granulosa cells, it resulted in increased follicle growth and ovulation [6], and when the deletion is confined in ovarian epithelium, it caused neoplastic ovarian lesions [7]. These strikingly distinct ovarian phenotypes by deletion of *Pten* at different compartment of ovary have strongly indicated that *Pten* governs a wide range of ovarian pathophysiological events in a cell specific manner. Moreover, given the well established existence of "oocyte–granulosa cell interaction" during mouse follicular development [8], here we propose a model trying to explain the onset of menopause at the cellular/molecular level. We propose that the expression/activity of *Pten* within different compartments of ovarian tissue (follicular, granulosa and epithelial cells) is spatiotemporally programmed, creating a "menopause tone" fine tuning the speed of follicle development/depletion and therefore the timing of menopause. In this regard, *Pten* could be acting as an enzymatic gatekeeper, regulating on-site activity of its downstream signaling within the ovary. At normal situation, the well programmed expression of *Pten* within the ovary resulted in on time menopause; however, imblanced/ectopic expression cause either advanced menopause (Premature ovarian failure) or delayed menopause (over-menstrual cycles) which is associated with increased ovarian (and other reproductive) cancer.

Further evaluation of the hypothesis

This hypothesis could be further tested by well designed experiments. Primarily, quantitive analysis of *Pten* expression/activity within different compartments of ovarian tissues at different reproductive stages would be sound. Further experiments could be done to compare the relative ovarian distribution of *Pten* between patients with premature ovarian failure and those with prolonged reproductive lifespan, as well as those with ovarian cancer. Our hypothesis, if validated, could help understand ovarian aging, menopause and related reproductive diseases in a more integrated manner: they are just different nodes on the same string. And *Pten* could just be the tip of the iceberg involved in the underling mechanisms. Future genome-wide screening and tissue/cell specific gene deletion would possibly find more candidates involving the regulation of "menopause tone" in the scenario we discuss *Pten*.

Conflict of interest statement

Here I state that there are no conflict of interest of our paper.

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