Searching for answers to the riddle of ovarian aging

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Like sequential chapters in an engaging read, during the summer holidays, our lives passage from stage to stage, each time signaling departure from one chapter and entry to the next. This metaphor may hold some measure of credibility if we liken the turning of a page approaching a thrilling and satisfying conclusion that has marked one step towards the end of your vacation—with our concept of time passing in terms of hours and days. But for our “life cycles,” measured in terms of years, approaching and passing through milestones prompts more subtle and evocative feelings of the unavoidable—aging is a given for all organisms that have opened the first page of a good book full of surprises and promises as the plot unfolds.

In the parlance of reproductive medicine pertaining to women, we use words to represent the sequence of events from puberty to menopause—and the segue from one to another brings with it the realization of the pre-reproductive, reproductive and post-reproductive stages of the life cycle. For most women, these transitions are predictable and founded upon an understanding of the endocrinological principles of dormancy, activation, and quiescence, with respect to the menstrual cycle and subject to clinical intervention, when appropriate. The heart of the problem, however—that is, the waxing and waning of the reproductive lifespan in women—resides in the ovarian follicle reserve.

Capsule A new study has identified genes regulating the immune system and DNA damage and repair as possible candidates for determining the age of menopause. What this means in terms of the riddle of ovarian aging is discussed in the context of two new papers in this month's JARG.

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Ovarian aging is, at least superficially, a reflection of how many ovarian follicles exist in the ovary. While many mysteries persist as to the causes of major follicle loss, pre- and post-natally, the ushering in of the “many are called, but few are chosen” strategy for dominant follicle selection stands firmly as the foundation for progressive follicle loss, during a women's reproductive lifespan. In like manner, it is also a major tenet of reproductive biology that the quality of oocytes diminishes with advancing maternal age—most certainly in humans—and this characteristic of aging eggs appears also in the life cycles of many other mammals (excepting those of sheep and naked mole rats—wonder what their secret is?).

Clues that would help solve the riddle of ovarian aging have been few and far between. That is, until the appearance, earlier this year, of a monumental effort to begin to define the molecular underpinnings of this fascinating problem. In an attempt to begin to understand why women experience natural menopause at varying ages, Stolk and colleagues report identification of 17 genetic loci that appear to be involved in the timing of menopause onset (Stolk L; Perry JR; Chasman DI; He C; Mangino M; Sulem P; Barbalic M; Broer L; Byrne EM; Ernst F.; Esko T; Franceschini N, et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. *Nat Genet* 2012; DOI [10.1038/ng.1051](https://doi.org/10.1038/ng.1051)). The study represents a *tour de force* by having compiled 22 genome-wide association studies from multiple centers that, in total, evaluated nearly 39,000 women. And the findings are no less extraordinary, offering both surprises and not-unexpected categories of genes that, at some level, play into the etiology of this complex process.

Take, for example, the identification of the FSH beta gene: Hardly a day goes by that our reliance on antral follicle counts, AMH and the array of hormone levels that distinguish the aging ovary, without calling into play these

factors in a given patient's assessment. No surprises here. But, along comes a cluster of genes that is implicated in immune system regulation and including candidates like interleukin-11. As more and more evidence emerges, painting the ovary as something of an immunological hotspot (immune system genes figure prominently into the vernacular of ovulation in mouse knockout studies), the interplay between ovarian signaling molecules and the immune system will provide a rich environment for future studies in this area; in fact, some may recall that one of the early roles ascribed to human chorionic gonadotropin (hCG, see cover, this month) was as a potent immune suppressor for fetal tolerance.

The main message, however, from the work of Stolk and colleagues, is one of DNA damage and repair—no less than seven genes that play a role in the pathway used by cells to sense DNA lesions and take reparative action in a reasonable period of time were identified. Except for possibly the brain, the ovary stands out as one of the few organ systems that carries with it throughout reproductive life an aging population of cells of both gametic and somatic varieties—i.e. those cells that comprise the primordial follicle. Perhaps the story line behind this provocative finding is indeed about the efforts that can and must be made to ensure the genetic integrity of the cells comprising the follicle, just in case they belong to that select group of 300 or so that is called in to deliver the oocyte of the month—speculation, but be certain to stay tuned, as the implications of this pioneering work are sorted out in the laboratory, over the next few years.

Our issue this month tends to the matter of the aging ovary, both in terms of clinical signposts and new basic science advances. Looking after the health of the genome in oocytes would seem to be a worthwhile matter, given the chances that any single oocyte could find itself the target of a self-respecting sperm lurking in the distal reaches of the female reproductive tract. But, tending to DNA damage is now appreciated to be much more than looking after the double helix. Thus, Zhu and colleagues draw attention to the appearance of abnormal patterns of DNA methylation, during aging in mice, and relate these findings to the gradual loss of reproductive fitness in this species. Of comparable relevance is the subject of mitochondria, during advancing maternal age, where alterations in number and mutation rate have been implicated in the loss of oocyte quality in humans. The group from Emory University led by Kushnir show that, again in mice, both mitochondrial number and structure become altered in oocytes taken from animals at advanced reproductive ages.

That aging is a complex process for any organism is well known. But, in a collective sense, and one that bears directly on the practice of human ARTs and treatment of infertility in older patients, taking aim at the genetic and epigenetic foundations that distinguish high quality oocytes from those compromised in their developmental potential, as a result of prolonged aging, will continue to be a subject of immediate importance for students of reproductive biology.