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EDITOR'S COMMENTARY

NOBOX does right for the follicle reserve: insights into premature ovarian failure

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Investing in the future takes on much more than a financial undertone when one is dealing with the currency of reproduction, our gametes. Whether the perspective is that of the male with its constitutive assembly line turning out many millions of new sperm on an hourly basis or that of the female, with a cautious and methodical rate of consumption at each ovulation, gamete supply and demand principles are at the core of our reproductive capacity.

Finding replacements for these specialized cells has yet to be realized despite claims to the contrary regarding the ability of embryonic stem cells to generate sperm or oocyte-like cells. This challenge in part reduces to our ignorance as to the key genes that dictate the process of gametogenesis in the ovary or testis and the complete failure to fully appreciate that like real estate-location, location, location nurses the potential of germ cells to take on the character of their mature products and players in the choreography of fertilization and embryogenesis.

Over and above the wonderment of gametogenesis that has attracted the attention of scientists since the advent of microscopy, the clinical reality for those treating infertility disorders of many kinds is that in too many circumstances, the number or quality of gametes produced is compromised. Not insignificant among these disorders is the case of premature ovarian failure (POF).

POF in its various forms displays the common attributes of complete follicle loss after birth and the replacement of follicles by fibrotic tissue in the ovary. Some years ago, led by the studies of Rajkovic and colleagues, a gene was discovered and accorded the name NOBOX to represent the fact that it was of the homeobox gene family and expressed in the newborn ovary, specifically in oocytes. It has since become appreciated that NOBOX is a master regulator of key oocyte genes in mice and when "knocked out" results in POF. Moreover, there is now evidence that misregulation of the NOBOX homeodomain occurs in women with POF, implicating this gene among others in the etiology of POF. What is not clear is when this gene imparts the signal for follicular demise and how is it that lesions in NOBOX lead to the gradual elimination of the follicle reserve? The paper by Kloc and colleagues in this issue of JARG takes a major step in improving our understanding of the pathogenesis of POF in humans.

Recognizing the expression pattern for NOBOX was confined to the earliest stages of follicle assembly in the newborn mouse ovary, this work took advantage of electron microscopy to analyze the nature of somatic cell and germ cell interactions. The results demonstrate a defect in the ability of somatic granulosa cell progenitors to encase individual oocytes as the process of germ cell cyst breakdown proceeds. Instead, without NOBOX clusters of oocytes are only partially enclosed resulting in the formation of polyovular follicles. In addition, signs of abnormal cell cell interactions are in evidence suggesting that the cell specific recognition and adhesion properties required during follicle assembly have been abrogated in a fashion that spells demise of these abnormal follicles early in postnatal life.

This work emphasizes the importance of initiating and maintaining a dialogue between somatic cells and the oocyte from the very inception of the primordial follicle pool. We have long come to appreciate the essential role that supporting granulosa cells play in the support of oogenesis through both the growth and maturative phases.

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But relatively little has been known about the primal forms of cell communication that set aside what will be the life long reservoir of follicles required to support fertility in adult life. While studies of this kind will continue to rely upon genetically tractable models such as the mouse, gaining insights into the genetic basis of such fundamental processes shapes approaches that could be brought to bear on human investigations.

It should come as no surprise that carrying out the dialogue between gonadal somatic cells and germ cells over the duration of gametogenesis is a trademark of successful reproduction in both the testis and the ovary. Perhaps recognizing this essential feature of gametogenesis will guide future studies into the area of stem cell derived germ cells since afterall, it has worked well for Mother Nature.