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Debate

Strong science challenges conventional wisdom: new perspectives on ovarian biology

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Conventional wisdom, sometimes defined as "truth", is said to be based on evidence that may or may not be so. The same definition may apply to dogma. A wonderful aspect of the scientific community is that it is not afraid to challenge dogma. Johnson et al., in their 11 March 2004 paper in Nature [1], have provided compelling evidence for the existence of proliferative germ cells that give rise to oocytes and follicle production in the postnatal period of development of mice. Debates for or against ovarian germ cells for replenishment of the pool of oocytes were raised in the 1920 s, but additional studies led to "provisional dogma" of a fixed oocyte supply from the fetal period of life that came to be generally accepted for mammals by reproductive biologists and others in the 1950 s – reviewed in Ref. [2]. Johnson et al. [1] provide results from a systematically executed set of experiments that strongly indicate that:

Ovaries of juvenile and young adult mice contain large ovoid cells, resembling germ cells of fetal mouse ovaries, in the surface epithelial cell layer. Immunohistochemical staining for mouse Vasa homologue (MVH), a gene expressed exclusively in germ cells, confirmed that these large ovoid cells were of a germline lineage. Additional experiments confirmed the presence of 5-bromdeoxyuridine-MVH double-positive cells limited to the ovarian surface epithelium. These results, with their histomorphometric findings, provide a strong case for germ-cell proliferation and follicle renewal in the postnatal mouse ovary [1].

Johnson et al. [1] also found that the meiotic entry gene is expressed in cells located in or proximal to the surface epithelium of juvenile and young adult mouse ovaries, and expression of synaptonemal complex protein 3 in juvenile and adult ovaries. The wild-type ovaries grafted into transgenic mice expressing green fluorescent protein (GFP) showed appearance of preantral follicles with GFP negative granulosa cells and GFP positive oocytes. Finally, the germ cell toxicant busulphan eliminated primordial follicle reserves by early adulthood without inducing follicular atresia, indicating the presence of proliferative germ cells between postnatal days 25 and 40.

Johnson et al. [1] conclude that "in addition to providing new directions to explore with respect to elucidating the biology of mammalian female germ stem cells, this work has significant clinical implications related to the therapeutic expansion of the follicular reserve as a means to postpone normal and premature ovarian failure."

The findings of Johnson et al. [1] on follicular renewal from germline stem cells in the postnatal mammalian ovary raise many interesting and important questions. It has been suggested that determining the exact number and location of these functional germline stem cells will require tagging germ cells [3]. The question of whether germline stem cell descendants form follicles and, ultimately, mature oocytes also remains unanswered [2,3]. Allan C. Spradling in his commentary in Nature [3] (11 March 2004) indicates that identification of germline stem cells in female mice [1] points to similarities with germline stem cells in gonads of male mammals. However, Roger G. Gosden [4] notes that large ovoid cells in mouse ovaries described by Johnson et al. [1] were reported in immature mice and human fetuses in the past, and were considered to be supernumerary germ cells exhibiting a suicidal migration out of the ovary [5].

Nevertheless, results of the studies of Johnson et al. in ovaries of postnatal mice [1] resulted in the conclusion that "the question on everyone's lips will be whether there are germline stem cells in the human ovary" [3].

Bukovsky et al. [6] (28 April 2004) further challenged conventional wisdom regarding primary follicles in adult human ovaries. They expanded former studies [7] and reported a dynamic population of differentiating and regressing ovarian follicles in adult women [6]. This study was based on the hypothesis that mesenchymal cells in the tunica albuginea are bipotent progenitors for both granulosa cells and germ cells. The authors demonstrate that cytokeratin positive mesenchymal cells of tunica albuginea differentiate into surface epithelium, by a mesenchymal to epithelial cell transition. The surface epithelial cells associated with the ovarian cortex are overgrown by tunica albuginea and form solid epithelial cords that fragment into epithelial nests in the deeper ovarian cortex and associate with zona pellucida positive oocytes [6]. The authors report that germ cells derive from surface epithelial cells that cover the tunica albuginea, enter and are transported by a vascular network and incorporated into the epithelial nests associated with the blood vessels. No germline type stem cells resembling those found in mice were detected, but occasional vessels in the ovarian medulla showed accumulation of naked oocytes or their remnants, suggesting that some intravascular oocytes degenerate. The authors conclude that differentiation of primitive granulosa and germ cells from bipotent mesenchymal cell precursors of tunica albuginea represents a novel mechanism that developed during the evolution of the ovary [6]. Such a system allows for dynamic turnover in oocytes due to their aging, and elimination of spontaneous and/or environmentally-induced genetic alterations in quality of oocytes that would not be in the best interests of the female who bears the primary burden and responsibility for propagation of each mammalian species.

The reports of Johnson et al. [1] and Bukovsky et al. [6] represent challenges to established dogma and portend what should be a series of very exciting studies that will either solidify their challenges to dogma or challenge their own findings. In either case, strong science is challenging conventional wisdom so that what we define as "truth" is based on the strongest possible evidence.

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