Genetic control of ovarian reserves

Abstract:

The numbers of ovarian follicles at birth, and the rate of follicular atresia, are important biological determinants of reproductive life span. A long-term consequence of premature ovarian insufficiency and diminished ovarian reserves is 50% higher overall mortality as compared to women with average menopause, and an increased risk for premature osteoporosis, ischemic heart disease, and infertility. The size of the initial primordial follicle pool and the rate of primordial follicle activation depend on several known molecular factors and processes. The early steps in the formation of primordial follicles are critical, since primordial follicles constitute the fundamental reproductive units of the ovary and give rise to all dominant follicles. Primordial follicle activation is a process by which primordial follicles are selected into the growing follicle pool. Primordial follicle activation is independent of gonadotropins, occurs prior to puberty and is spontaneously observed when ovary is transplanted or cultured in vitro. Recent studies showed the importance of the PI3K-Akt-mTORC1 signaling pathway within oocytes in regulating primordial follicle activation. Conditional ablation of Foxo3a, Pten, Tsc1, and Pdk1 in oocytes, trigger massive primordial follicle activation. In addition to ubiquitous pathways, critical transcriptional regulators, preferentially expressed in the soma or oocytes, have been identified in the ovary. Foxl2 is expressed in the granulosa cells that surround the oocyte, and Foxl2 deficiency causes infertility and aborts the transition of flat granulosa cells that surround primordial oocytes, to cuboidal granulosa cells that surround primary oocytes. Figla was one of the first germ cell specific basic helix-loop-helix transcription factors shown to be important in primordial follicle formation. Transcriptional regulators Sohlh1, Sohlh2, Lhx8, and Nobox repress follicle activation and promote oocyte survival. Much remains to be understood about pathways that are regulated by these oocyte-specific molecules. Genes involved in double stranded DNA break repair, such as MCM8 and MCM9, also accelerate oocyte loss, can have systemic effects on endocrine function, and the age of menopause. Genomewide association studies and whole genome sequencing in humans are identifying novel loci involved in oocyte aging, which are then modeled in animals to better understand their mechanisms of action. It is clear that ovarian reserve is dependent upon many genes and only individualized approaches will help our patients.