

CHRONOLOGY AND COMPLEXITY OF OVARIAN TUMORIGENESIS IN FORKO MICE. M Ram Sairam, Xin Lei Chen, Jayaprakash Aravindakshan, Rashmi-Tiwari Pandey; Molecular Reproduction Research Laboratory, Clinical Research Institute of Montreal, Quebec, Canada

Ovarian cancer (OC), with highest mortality rate of all gynecologic cancers is currently the 4th leading cause of cancer deaths among women in North America. Most often ovarian cancers escape notice until the tumors have advanced and the prognosis is poor. Currently early detection for OC is non-existent. Molecular studies on ovarian carcinogenesis and metastasis can be enhanced by applying model systems reflecting different aspects of the biology of this disease. As chronological studies required to define basic mechanisms are not possible in women, studies need to be conducted in animal models (of defined genetic background) mimicking the disease. This could provide a rational basis for capturing changes that precede pathology and developing early detection tests and assess other risk factors for OC.

Several theories have implicated cumulative effects of ovulation/repair injuries and high levels of gonadotropins found in menopause as contributing to OC. Our work in the FORKO (**F**ollitropin **R**eceptor **K**nock**O**ut) mouse has demonstrated that when the FSH-R gene required for normal sexual function in the female is deleted, ovarian function ceases and the mutants that never ovulate but experience sustained hormonal imbalances develop tumors as they age. This bears some similarity to older women because most OC also occurs in post-menopause when FSH-R expression is terminated and ovaries cease ovulation. Heterozygous females also develop similar phenotypes but at much later ages. Women with endocrine disorders and obesity also have higher rates of OC. In the FORKO mouse obesity occurs early and ovarian tumors develop in nearly 90% of the animals by about 1 year of age. Tumor types arise from different structures including those of the ovarian surface epithelium (OSE) that also metastasize in women. Tumor cell types are also strain dependent. Microarray analysis of whole ovaries before and after tumors arise provided clues to the chronology of changes and alterations of gene families implicated in OC. Using selected examples we have followed the chronology of the expression of cytokeratins, tight junction and adhesion proteins as well as members of the PDGF ligands and receptor proteins in the normal and mutant ovaries. High expression of cytokeratin, E-cadherin and claudin 11 and PDGFR are localized to epithelial cells that later give rise to tumors suggesting cause-effect relationships. We postulate that altered tight junctions in the mutants change cell polarity allowing access to growth factors and high androgens produced by the stromal cells. Changes in the balance of the expression of claudin family members and differential processing of adhesion proteins such as Cadherins suggest a basis for exploring molecular events. We are in the process of characterizing additional novel genes and isolating OSE from the pre-tumorigenic state of mutant ovaries for comparisons with normal OSE. Strategies to correct hormonal imbalances in FORKO mice appear to prevent the advent of pathological transformations (Supported by Canadian Cancer Research Society).