Biology of hereditary breast and ovarian cancers

In 2011, the supplement highlighting the 2009 meeting brought into focus various aspects of tumor biology that emerged from studies on cancers arising in BRCA1 or BRCA2 mutation carriers [1]. Initially, these studies were mostly descriptive but increasingly through the development of animal models and clinical observations, we have seen hypotheses being generated to explain the pathogenesis of these neoplasms. Barcellos-Hoff and Kleinberg advance the hypothesis that BRCA dysfunction early in the maturation of the breast results in stem cell expansion. These stem cells seem to be able to fix DNA damage by passing it on to daughter cells and determining a lineage of mutations. They describe the stem cell phenotype and implicate certain hormonal pathways in the mouse that have the potential to be targeted in order to restrain their replication. De Summa et al. underlined that the dysfunction of the BRCA1-ER pathway may actively lead to the development of tumours, in particular with a basal-like phenotype and double strand break DNA repair-related breast carcinogenesis.

When it comes to pathogenesis of ovarian cancer, clues have come from a risk-reducing surgery in mutation carriers that identified preneoplastic lesions in the fimbriated ends of the fallopian tubes. Drapkin and Dubeau provide the evidence for these being responsible for the eventual development of high-grade serous carcinomas that had been clinically and pathologically designated in the past as carcinomas of ovarian or primary peritoneal origin. As invasiveness and early coelomic spread become apparent, the therapeutic implications of these high-grade serous gynecologic cancers (i.e., often referred as ‘BRCAness’ phenotype) are reviewed by Pothuri. Understanding of this biology has led the way for drug-development strategies built around platinum sensitivity and defects in DNA repair by homologous recombination, whether these are the result of loss of BRCA function arising from mutations or epigenetic silencing of the BRCA genes, or from similar changes in other genes being discovered to be implicated in these repair pathways.

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disclosure
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