Molecular Wanderings Through the DNA Damage Response and Risk for Ovarian Cancer

Michael A. Bookman

Correspondence to: Michael A Bookman, MD, University of Arizona Cancer Center, 1515 N Campbell Ave, Rm 1903, Tucson, AZ 85724-6024 (e-mail: mbookman@email.arizona.edu).

Large-scale genomic analyses and smaller targeted studies have collectively reinforced our appreciation of the DNA damage response and homologous recombination deficits as important early mutational events in the biology of high-grade serous cancer (HGSC) arising from the ovary and associated gynecologic sites, including the distal fallopian tube, peritoneal cavity, and endometrium. The near-universal loss of functional p53 occurs at the earliest stages of cancer development, including immunohistochemical and molecular identification of clonal p53 mutations or deletions in noninvasive precursor lesions. Loss of p53 contributes to a picture of “genomic instability” characterized by a large number of amplifications, mutations, and deletions present at diagnosis before initiation of chemotherapy. In addition, at least 50% of HGSCs harbor mutations or altered expression of components involved in DNA repair. Homologous recombination deficits—associated changes include loss of BRCA1, BRCA2, and RAD51, with the potential for molecular targeting through inhibition of poly-ADP-ribose polymerase, which is being explored in large randomized trials. Although the majority of HGSCs are initially sensitive to platinum-based chemotherapy, these tumors are adept in the development of resistance through multiple mechanisms, including increased damage tolerance.

In this issue of the Journal, Akbari et al. (1) provide data to extend and confirm a recent study (2) demonstrating that truncating mutations in protein phosphatase magnesium-dependent 1 δ (PPM1D) are associated with an increased risk of ovarian cancer. PPM1D appears to function as a negative regulator of p53 (3) and could generate an internal knockout of p53 function, contributing to platinum resistance in tumors that retain p53 (4). Both studies identified truncating mutations located exclusively in the last of six exons. The truncated mRNA is transcribed, and there is in vitro evidence to suggest that these modified proteins have increased biologic activity compared with wild-type full-length products. Of interest, analysis of peripheral blood mononuclear cells demonstrated simultaneous (mosaic) expression of the truncated and normal proteins, suggesting that biologic activity of the truncated protein is dominant. In addition, mutations were not found in family members, and there is no evidence of mutation inheritance.

At first review, it is surprising that molecular analysis of two ovarian tumor specimens that developed in patients with PPM1D mutations did not contain the mutation (1). However, there is frequent loss of chromosome 17q in ovarian cancer, which could contribute to loss of the mutated alleles. More important, this may offer a veiled clue regarding the role and timing of PPM1D mutations during oncogenic transformation.

Although it is hazardous to predict the biological significance of these findings in relationship to the development of HGSC, it seems clear that individuals with these uncommon and noninherited mutations have an increased risk of developing HGSC. For example, it is plausible that sustained PPM1D-mediated suppression of p53 function could make it easier for p53-deficient clones to survive, and once p53 function is permanently lost (through subsequent mutations), there would no longer be an ongoing dependency on increased PPM1D activity for tumor development.

Consistent with the lack of inheritance, it appears that family members of patients with PPM1D mutations did not have a higher risk of developing ovarian cancer compared with female first-degree relatives of noncarriers, but the analysis by Akbari et al. (1) was limited by the small number of family members at risk in their report (a total of only 54 female first-degree family members from 20 families with PPM1D mutations).

The world of molecular diagnostics is rapidly changing as the costs for wide-scale mutational screening continue to fall. It seems reasonable to anticipate that testing for uncommon mutations, such as PPM1D, will eventually become routine, facilitating the identification of women at increased risk for ovarian, breast, and other cancers and posing questions about reasonable interventions for cancer prevention. At present, we are largely limited to counseling regarding risk-reduction strategies that include oral contraceptives, pregnancy, and postchildbearing surgical removal of the distal fallopian tubes and ovaries in women with molecular confirmation of key mutations, especially BRCA1 and BRCA2, but with potential extension to RAD51, PPM1D, and other markers in the future. The mosaic biology of activated PPM1D also raises the possibility that a targeted phosphatase inhibitor could be identified to block function until definitive surgery could be performed. However, our current economic environment for drug discovery, validation, and regulatory approval would seem to make this prohibitive.

Although the majority of tumors in this report by Akbari et al. (1) were HGSC, the relationship of PPM1D mutations to uncommon histologies that are not associated with loss of p53 function, such as mucinous tumors and low-grade serous carcinoma is less clear. Other studies have suggested that PPM1D is overexpressed in clear cell carcinoma and might be a therapeutic target in that setting, but none of the patients in the Akbari et al. series had clear cell carcinoma at diagnosis (5). Mucinous ovarian tumors are almost always
stage I at diagnosis and cured with initial surgery. This is consistent with the favorable outcome observed for one patient reported by Akbari et al. with mucinous ovarian cancer, who is the only surviving patient, and this may represent an incidental surgical finding rather than direct association with PPM1D (1). Similarly, only one patient was reported with a grade 1 tumor. Although not uniformly diagnostic based on reported tumor grade, it is possible that this patient had low-grade serous carcinoma rather than HGSC. This is important because low-grade serous carcinoma is not associated with loss of p53 and is more often associated with activating mutations in B-RAF or K-RAS, with associated downstream activation of MEK and ERK. It would be interesting to specifically interrogate this tumor for evidence of p53 loss as well as RAF-RAS pathway activation because it may represent an uncommon low-grade lesion with p53 loss.

Akbari et al. have provided a thought-provoking article that confirms and extends other published findings and contributes to our evolving view of the development of ovarian cancer and associated malignancies.

References

Note
The author has no conflict of interest to disclose.

Affiliation of author: University of Arizona Cancer Center, Tucson, AZ.