Molecular Sleuthing: Tracking Ovarian Cancer Progression

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The simple explanation for their findings is that a small proportion of benign ovarian cysts or tumors of low malignant potential (fewer than one in 37) harbor p53 mutations. These mutations then mark the affected tissues as predestined to become ovarian carcinomas through several possible pathways (progression models I and II; Fig. 1). Such a progression model of p53 action can be clinically applied, since a patient carrying a cyst with malignant potential (i.e., carrying a p53 mutation) may need to, at least, undergo more vigorous postoperative surveillance. To prove this point, however, many more benign ovarian cysts will need to be screened for aberrations of the p53 gene so that the prevalence of p53 mutations may be estimated. In other disease systems in which p53 or ras mutations are common in the malignant cells, genetic mutations at these loci have been readily detected in the premalignant counterparts. In breast cancer, p53 mutations are present in approximately 25%-50% of invasive cancers (4,5), in 20%-30% of in situ carcinomas (6), and in 5% of biopsy specimens of tissues taken from patients with benign breast disease (7). The ras mutations are found in 50% of colon carcinomas (8) and in 10%-15% of polyps (8) and are detectable in the earliest precancerous lesions, the aberrant crypt foci (9,10). In ovarian cancers, however, there has not been the same level of molecular scrutiny to ascertain the frequency of genetic alterations in purely benign ovarian tissues. Thus, if the true prevalence of p53 mutations in ovarian cysts is small (e.g., one in 200), then proving the clinical utility of a p53 assay in this situation would require large trials and long follow-up. Moreover, at this frequency, the molecular screening of benign ovarian masses for p53 alterations would not be cost-effective.

The more intriguing possibility is that the benign cysts are differentiated cells derived from the adjacent carcinoma. Given the data presented by Zheng et al. (3), this differentiation model may be the likely scenario. In building models of tumor progression, the probability of finding identical pairs and triplets of
mutant genes appearing in both the benign and malignant components of a tumor would be higher in a differentiation model than in a progression model. (Compare progression model I and differentiation model in Fig. 1.) Thus, evidence for differentiation appears more compelling. If true, then up to six of 24 or 25% of p53-positive adenocarcinomas studied by Zheng et al. may have demonstrated the capacity to differentiate into morphologically benign ovarian tissues. This tumor cell differentiation has been documented in early studies of acute promyelocytic leukemia (11), leading to the suggestion that induction of differentiation may be a viable treatment alternative to cytotoxic therapy for this disorder. This hope was partially realized when all-trans-retinoic acid was found to be an effective single agent in obtaining complete remissions in acute promyelocytic leukemia (12). Using molecular approaches that tagged the PML/RARA (i.e., retinoic acid receptor alpha gene) translocation, the mode of action of the all-trans-retinoic acid was confirmed to be the induction of differentiation (13). The potential finding of spontaneous differentiation in ovarian carcinomas ascertained by molecular methods raises the possibility that a distinct differentiation agent could be found for ovarian cancer cells. Although this concept is far from being actualized, the impact of a new therapeutic agent for this deadly disease targeting differentiation may ultimately be as important as all-trans-retinoic acid in the management of acute promyelocytic leukemia (14).

Regardless of which model is correct, the observation that one half of ovarian adenocarcinomas have discernible mutations in p53 immediately suggests that these mutations can be used as a target for the detection of residual disease or for molecular staging. Thus, detection of the p53 mutation in morphologically normal cells of the peritoneal wash is a sign either of tumor spillage or of metastatic disease. After chemotherapy, the disease in those patients with pathologic complete remissions can be mo-
molecularly restaged, using the p53 mutations of the original tumor as the target. We assume that the absence of p53-positive cells in the peritoneum will signal a better prognosis for the patient than the presence of such tagged tumor cells. A similar molecular approach in assessing tumor involvement of surgical margins using p53 mutations as a tag has proven predictive for relapse in head and neck cancers (15,16). Since PCR techniques can detect cancer-associated molecular mutations in stool (17), saliva (18), and urine (19), there has been great hope that these methods can be used for prospective cancer screening. Unfortunately, the strenuous nature of the molecular analyses precludes the use of these tests as general screening tools. But, then, progress was similarly stalled in molecular oncology before the advent of PCR. Given the pace of scientific development, it would not be surprising that another technologic advance would bring this research concept into diagnostic reality.

References