SEROUS TUMORS

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Serous Borderline Tumors (SBTs)

Somatic genetics

Clonality studies have attempted to dilucidate whether multiple, synchronous or metachronous, SBTs (found at different sites in the abdominal cavity) arise as a result of spread from a single ovarian site, or whether such deposits are polyclonal representing independent primary tumors. Evidence for a multifocal origin of bilateral and advanced SBTs has been reported in two sudies based on X-chromosome inactivation analysis. However, tumor-related changes may interfere with X-chromosome inactivation and this method is not thought to be appropriate for assessing clonality. In contrast, loss of heterozygosity (LOH) is an irreversible genetic event acquired during tumorigenesis. Its weakness, however, is that the absence of informative markers, and the failure to detect LOH underestimates the frequency of clonality. In a study for evaluating LOH on chromosome 17p13, genetic concordance was found between the noninvasive peritoneal implants and the primary ovarian SBTs in all three cases studied. More recently, clonality has been assessed by a genome-wide allelotyping in 47 synchronous and/or metachronous multifocal (bilateral ovarian SBTs and noninvasive peritoneal implants) tumors from 22 patients using 59 microsatellite markers. Concordant results

were obtained in 7 of 9 SBTs with LOH in informative markers and identical chromosomal breakpoints in 6 of 7 cases. Although the subsequent involvement of the contralateral ovary in a patient who had a previously resected unilateral SBT is usually interpreted as development of second and independent serous tumor, these molecular genetic findings lend further support to the implantation theory.

SBT: Somatic genetics

(Clonality)

- Concordant LOH 17p13 patterns in noninvasive implants and synchronous ovarian SBTs favor the metastatic nature of the former lesions
- Data on invasive implants is lacking
- Evidence for a clonal origin of bilateral SBTs is in contrast to their favorable prognosis

SBTs with and without micropapillary pattern frequently display *B-RAF/K-ras* mutations but rarely mutant *p53*. In contrast, *B-RAF/K-ras* mutations are very rare in conventional high-grade serous carcinomas, but *p53* mutations occur in approximately 60% of cases. These findings provide additional proof that SBT with micropapillary pattern and typical SBT are closely related neoplasms. The rare cases of invasive low-grade serous carcinomas with micropapillary pattern (which also have *B-RAF/K-ras* mutations) probably represent SBTs with infiltrative stromal invasion greater than microinvasion.

We have recently done RNA expression analysis of 38 ovarian serous tumors (11 SBT, 10 low-grade SCA and 15 high-grade SCA). Significance analysis of microarrays (SAM) of the expression profiles identified ERK-inhibitor Dusp 4 and uPA-inhibitor Serpina 5 as candidate key regulator genes in uncoupling the mitogenic signal and the signal leading to ECM degradation. These findings suggest that Dusp 4 and Serpina 5 are tumor suppressor genes responsible for the lack of stromal invasion in SBTs.

SBT: somatic genetics

(Gene profile)

- Frequent *B-RAF/K-ras* mutations in SBT with/without MP
- Rarely mutant *p53*

Serous carcinomas

Histogenesis and somatic genetics

Most high-grade serous carcinomas are thought to arise de novo from the surface epithelium or its inclusion cysts and spread rapidly early in their course. In contrast, low-grade serous carcinomas typically arise within borderline tumors and only occasionally de novo from the surface epithelium. Early serous carcinomas of the conventional type are already high-grade tumors which resemble morphologically their advanced stage counterparts. The histological similarities correlate with recent molecular genetic findings demonstrating *p53* mutations in small stage I serous carcinomas. Approximately 60% of advanced stage ovarian serous carcinomas have mutant *p53*. Thus,

these findings suggest that serous carcinoma in its very earliest stage of development resembles advanced stage serous carcinoma at the molecular level. As stated earlier, SBTs with and without micropapillary pattern, as well as the infrequent low-grade serous carcinomas, frequently display *B-RAF/K-ras* mutations but rarely mutant *p53*. In contrast, *B-RAF/K-ras* mutations are very rarely found in conventional high-grade serous carcinomas. Accordingly, a dualistic model for ovarian serous carcinogenesis has been recently proposed. One pathway would involve a stepwise progression from SBT to noninvasive (SBT-MP) and then invasive low-grade ('micropapillary') serous carcinoma. The other pathway would be characterized by rapid transformation of the ovarian surface epithelium into a high-grade serous carcinoma.

Serous carcinoma: histogenesis

- High-grade carcinomas arise de novo from surface epithelium or cysts
- Low-grade carcinomas stem from borderline tumors

Serous carcinoma: somatic genetics

- High-grade carcinomas have frequent *p53* mutations
- Low-grade carcinomas have frequent *B-RAF/K-ras* mutations

References

Bell DA, Scully RE. Early *de novo* ovarian carcinoma: a study of 14 cases. Cancer 1994;73: 1859-1864.

Powell DE, Puls L, van Nagell I. Current concepts in epithelial ovarian tumors: Does benign to malignant transformation occur? Hum Pathol 1992; 23:846-847.

Puls LE, Powell DE, De Priest PD, et al. Transition from benign to malignant epithelium in mucinous and serous ovarian cystadenocarcinoma. Gynecol Oncol 1992; 47:53-57.

Lu KH, Bell DA, Welch WR, et al. Evidence for the multifocal origin of bilateral and advanced human serous borderline ovarian tumors. Cancer Res 1998; 58:2328-2330.

Gu J, Roth LM, Younger C, et al. Molecular evidence for the independent origin of extra-ovarian papillary serous tumors of low malignant potential. J Natl Cancer Inst 2001; 93:1147-1152.

Zanotti KM, Hart WR, Kennedy AW, et al. Allelic imbalance on chromosome 17p13 in borderline (low malignant potential) ovarian epithelial tumors. Int J Gynecol Pathol 1999; 18:247-253.

Sieben NLG, Kolkman-Uljee SM, Flanagan AM, et al. Molecular genetic evidence for monoclonal origin of bilateral ovarian serous borderline tumors. Am J Pathol 2003; 162:1095-1101.

Caduff RF, Svoboda-Newman SM, Ferguson AW, et al. Comparison of mutations of Ki-ras and p53 immunoreactivity in borderline and malignant epithelial ovarian tumors. Am J Surg Pathol 1999; 23:323-328.

Singer G, Kurman RJ, Chang H-W, Cho SKR, Shih I-M. Diverse tumorigenic pathways in ovarian serous carcinoma. Am J Pathol 2002; 160: 1223-1228.

Pothuri B, Leitao M, Barakat R, et al. Genetic analysis of ovarian carcinoma histogenesis (Abstract). Gynecol Oncol 2001; 80: 277.

Sieben NLG, Oosting J, Flanagan AM, Prat J, Roemen GM, et al. Differential gene expression in ovarian tumors reveals Dusp 4 and Serpina 5 as key regulators for bening behavior of serous borderline tumors. In preparation.