Nature Reviews Cancer | AOP, published online 19 May 2011; doi:10.1038/nrc3073

OVARIAN CANCER

Model building

> evidence that FTSECs may be a cell of origin for HGSOC

Although the prevailing hypothesis has been that high-grade serous ovarian carcinoma (HGSOC) arises from ovarian surface epithelial cells, recent evidence suggests that around 50% of these tumours arise from fallopian tube secretory epithelial cells (FTSECs). Therefore, Ronny Drapkin and colleagues set out to create a new HGSOC model based on the transformation of primary human FTSECs.

The authors immortalized primary FTSECs from women with benign gynecological conditions by expressing TERT, the catalytic subunit of telomerase, and SV40 large and small T antigens. These immortalized FTSECs were susceptible to oncogenic transformation by constitutively active HRAS ($HRAS^{V12}$) or MYC; the expression of either oncogene enhanced *in vitro* proliferation and anchorage-independent growth. That MYC induced transformation is particularly relevant, as the *MYC* locus is frequently amplified in HGSOC.

To determine whether the transformed FTSECs were tumorigenic *in vivo*, $HRAS^{V12}$-expressing cells were intraperitoneally injected into five nude mice; all developed tumours. Furthermore, the authors demonstrated that immortalized and $HRAS^{V12}$-transformed FTSECs derived from a different patient were also tumorigenic, indicating that unique features of the parental FTSECs were unlikely to be the cause of tumour formation. MYC-expressing immortalized FTSECs were also tumorigenic in two of five NOD SCID gamma (NSG) mice, although these tumours had a longer latency than those arising from $HRAS^{V12}$-transformed FTSECs. Despite differences in growth, tumours derived from $HRAS^{V12}$ or MYC expression exhibited the same histology — high-grade epithelial neoplasms that were similar to those observed in poorly differentiated HGSOC.

Given the physiological irrelevance of SV40 T antigens to human ovarian cancer, and the possible additional effects of these viral oncogenes, the authors improved their model by replacing SV40 large T antigen (which inactivates p53 and RB) with short hairpin RNA (shRNA) against p53 and expression of cyclin-dependent kinase 4 (CDK4) with the R24C mutation, which phenocopies loss of RB. They also replaced SV40 small T antigen with shRNA against the B56γ subunit of protein phosphatase 2A (PP2A), as SV40 small T interacts with B56γ to deregulate PP2A. Expression of MYC in these non-virally immortalized FTSECs also increased proliferation and anchorage-independent growth *in vitro*, and intraperitoneal injection of the cells led to the formation of tumours that were histologically similar to human HGSOC in two of four NSG mice. Furthermore, the tumours metastasized to the peritoneal cavity and liver and exhibited severe genomic instability, as assessed by array comparative genomic hybridization (aCGH), both of which are common in HGSOC.

Drapkin and colleagues have provided evidence that FTSECs may be a cell of origin for HGSOC, and their model should serve as a platform for investigating the contributions of other genetic events to the development of human HGSOC.

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ORIGINAL RESEARCH PAPER Karst, A. M., Levanon, K. & Drapkin, R. Modeling high-grade serous ovarian carcinogenesis from the fallopian tube. *Proc. Natl Acad. Sci. USA* 18 Apr 2011 (doi:10.1073/pnas.1017300108)

FURTHER READING Bowtell, D. D. L. The genesis and evolution of high-grade serous ovarian cancer. *Nature Rev. Cancer* **10**, 803–808 (2010)