Review

UHN Microarray Centre

Gene expression profiles of luteal phase fallopian tube epithelium from *BRCA* mutation carriers resemble high-grade serous carcinoma

Review of: Tone AA, Begley H, Sharma M, Murphy J, Rosen B, Brown TJ, Shaw PA. Gene Expression Profiles of Luteal Phase Fallopian Tube Epithelium from *BRCA* Mutation Carriers Resemble High-Grade Serous Carcinoma. Clin Cancer Res 2008, 14(13):4067

High-grade serous carcinoma (SerCa) is the most common type of ovarian and fallopian tube carcinoma and has a high mortality rate (1). The lifetime risk of ovarian cancer in women with *BRCA1* or *BRCA2* mutations is estimated to be as high as 56% and 27%, respectively, depending on family history (2). Recent studies have found that the distal fallopian tube epithelial (FTE) may be a source for SerCa (3,4).

The goal of this study was to identify molecular alterations that may be involved in predisposition to SerCa in the nonmalignant FTE of *BRCA1/2* mutation carriers (1). To identify these alterations, the gene expression profiles of epithelial cells from nonmalignant distal fallopian tube of *BRCA1/2* mutation carriers was compared with control samples, as well as high-grade ovarian and tubal SerCa specimens. This is the only study to date of gene expression profiles in the histologically normal FTE of *BRCA1/2* mutation carriers and control patients (1).

Gene profiling experiments were carried out at the UHN Microarray Centre using the Affymetrix platform. An initial comparison found that the gene expression profile of high-grade ovarian SerCa is indistinguishable from fallopian tube SerCa (1). The gene expression profiles of SerCa samples were then compared with the profiles of FTE samples from *BRCA1/2* mutation carriers and control samples. Despite the fact that the FTE samples from *BRCA1/2* mutation carriers were histologically indistinguishable from the control samples, a subset of the FTE *BRCA1/2* mutation carrier samples clustered with the SerCa samples. The subset of FTE samples that clustered with the SerCa samples were obtained during the luteal phase of the ovarian cycle. This unexpected finding prompted Tone *et al*. to further explore the association of ovarian cycle with FTE gene expression. Subsequent analysis revealed that the number of differentially expressed probe sets between luteal and follicular phases was far greater in mutation carriers than in normal controls (1). The main hormonal difference between the luteal and follicular phase is the elevation of circulating progesterone during luteal phase. Studies have found progesterone to be protective factor in ovarian cancer development (5). It is possible that other hormonal changes associated with the luteal phase may affect gene expression in the FTE (1).

To identify proteins that were potentially involved in the initiation of SerCa, the Interologous Interaction Database (I2D), an on-line database of known and predicted protein-protein interactions (6), was queried. Two proteins, Disabled-2 (DAB2) and Ski-like protein (SKIL), were identified as potentially being involved in the initiation of SerCa. DAB2, which had decreased expression in *BRCA1/2* (luteal phase) and SerCa samples, has a tumour suppressive function and is an essential component of the transforming growth factor β (TGF-β) signaling pathway (7). SKIL, which acts to inhibit Smad2 and Smad3 (targets that are enhanced by DAB2) (8), was upregulated in *BRCA1/2* (luteal phase) samples.

Other studies have observed similar loss of DAB2 in ovarian carcinomas compared with normal ovarian surface epithelium (9,10), although this has not previously been found in histologically normal ovarian surface epithelium from *BRCA1/2* mutation carriers. SKIL has not previously been implicated in ovarian cancer development although the gene lies within a chromosomal region (3q26) previously found to be amplified in serous fallopian tube and ovarian carcinomas by CGH (11). It is likely that a combined effect of decreased DAB2 and increased SKIL in *BRCA1/2* mutation carriers would promote malignant transformation (1).

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Gene expression changes potentially involved in the earliest events of tubal and ovarian SerCa have been identified in histologically normal FTE from *BRCA1/2* mutation carriers. These expression changes seem to be influenced by reproductive hormones, with components of the luteal phase inducing changes similar to those observed in SerCa specimens. Increased expression of SKIL, combined with decreased expression of DAB2 in mutation carriers during this phase, could represent some of the earliest initiating or predisposing events of SerCa (1).

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