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Review

Molecular profiles of hereditary epithelial ovarian cancers and their implications for the biology of this disease

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ABSTRACT

BRCA1 and BRCA2 germline mutations account for the majority of hereditary ovarian cancers and comprise 10% of total cases. Ovarian cancers arising from these mutations exhibit both overlapping and distinct clinical and molecular features. The expression profiles of sporadic ovarian cancers show similarities to those of BRCA1 and BRCA2-related tumors suggesting that BRCA-related pathways may be involved in their development as well. The purpose of this review is to consider the available data on ovarian cancers in the context of other investigations of BRCA-related transcriptional alterations, and highlight areas for future research.

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1. Introduction

Approximately 10% of ovarian cancers arise in the setting of known genetic predisposition (Pavelka et al., 2007). The vast majority of these cases are associated with germline mutations in the BRCA1 and BRCA2 genes. As such these cancers are frequently grouped together as hereditary or BRCA-related cancers in contradistinction to non-hereditary cases referred to as sporadic cancers. While BRCA1 and BRCA2 mutations are firmly established as important etiologies for hereditary breast and ovarian cancers, important questions remain unanswered regarding the involvement of BRCA-related pathways in the development of sporadic cancers. The purpose of

this review is to consider the available data on the molecular features of BRCA-related and sporadic ovarian cancers and identify areas for future research. While studies on BRCA-related and sporadic breast cancers will not be specifically reviewed, they will be used as comparisons when applicable.

2. Clinical features of BRCA-related and sporadic ovarian cancers

The ultimate purpose of investigating the molecular features of hereditary and sporadic ovarian cancers is to gain insight into their clinical behavior and mechanisms of carcinogenesis.

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Hence, before considering the molecular phenotype of BRCA-related and sporadic ovarian cancers, it is instructive to consider their clinical features. Not infrequently BRCA1 and BRCA2-related ovarian cancers are grouped together, however, this overlooks important clinical (and molecular) differences between these tumors. The most obvious clinical difference between BRCA1 and BRCA2 germ line mutations is the risk of subsequent ovarian cancer. The cumulative risk (defined in most studies as risk by age 70 or 80) of developing ovarian cancer due to BRCA1 and BRCA2 mutations are approximately 40–50% and 20–25%, respectively (King et al., 2003; Evans et al., 2008; Antoniou et al., 2005; Chen et al., 2006; Risch et al., 2001). In contrast to this consistently observed 2-fold higher risk of ovarian cancer associated with BRCA1 mutations, most larger studies show equal rates of breast cancer penetrance in women with BRCA1 and BRCA2 mutations (King et al., 2003; Evans et al., 2008; Milne et al., 2008).

A second notable clinical difference between BRCA1 and BRCA2-related ovarian cancers is the age of presentation. In most studies BRCA1-related ovarian cancers are diagnosed about a decade earlier than the BRCA2 and sporadic cancers (median age of 50 versus 60) (Rubin et al., 1996; Boyd et al., 2000; Jazaeri et al., 2002; Sekine et al., 2001; Modugno et al., 2003). Finally, several independent groups of investigators have reported improved outcomes in patients with BRCA1 and BRCA2 mutations compared to sporadic cases or historical controls (Rubin et al., 1996; Boyd et al., 2000; Ramus et al., 2001; Pal et al., 2007; Thrall et al., 2006; Cass et al., 2003; Quinn et al., 2007; Tan et al., 2008). Although refuting studies exist (Buller et al., 2002; Pharoah et al., 1999), after taking into consideration some of the methodological limitations, the bulk of the data supports a favorable outcome associated with BRCA-related ovarian cancers possibly secondary to enhanced platinum sensitivity of these tumors.

3. Transcriptional phenotypes of BRCA1 and BRCA2-related ovarian cancers

Our group investigated the expression profiles of BRCA-related and sporadic ovarian cancers using cDNA microarrays (Jazaeri et al., 2002). We discovered that the greatest contrast in expression profiles was observed between BRCA1 and BRCA2-related ovarian tumors. Even more intriguing, when combined into a single group, the BRCA1 and BRCA2-related ovarian cancers were indistinguishable from the sporadic tumors (Figure 1). These observations suggested that the sporadic ovarian cancers possessed a dichotomous gene expression profile with approximately half exhibiting a BRCA1-like profile and the other half resembling BRCA2-linked tumors. Confirming this hypothesis we found that the genes whose expression best discriminated BRCA1 and BRCA2-related tumors, also segregated the sporadic ovarian cancers into BRCA1 and BRCA2-like clusters (Figure 2). Our findings were consistent with those reported by Hedenfalk and colleagues on the expression profile of BRCA-related and sporadic breast cancers (Hedenfalk et al., 2001). They also found the greatest expression differences between BRCA1 and BRCA2-related breast cancers, however their study had too few sporadic samples to allow any conclusions regarding BRCA-like profiles

Figure 1 – Overall expression differences between BRCA1-linked, BRCA2-linked, and sporadic ovarian epithelial cancers. (A) Unsupervised multidimensional scaling model based on the overall gene expression in BRCA1-linked, BRCA2-linked, and sporadic tumors. **(B)** The magnitude of differences in gene expression between various tumor groups as determined by the number of genes differentially expressed among the tumor groups when the uniform statistical cutoff $P < 0.0001$ is applied. Figure reproduced with permission from Jazaeri et al. (2002).

in this group. Furthermore, one of the sporadic samples that clustered with the BRCA1 samples was found to have silencing of BRCA1 via promoter hypermethylation. In a follow-up study the same group of investigators evaluated the gene expression profile of sixteen familial but non-BRCA1/BRCA2 breast cancers (Hedenfalk et al., 2003). However, the design of this investigation was one of class discovery and they did not address whether the BRCA1 and BRCA2 discriminating gene set would also divide these non-BRCA tumors into two groups as well.

The above observations raise the question: why do sporadic ovarian cancers exhibit transcriptional phenotypes like that of BRCA1 and BRCA2-related cancers? One potential mechanism would be the loss of BRCA1 and BRCA2 expression through epigenetic and somatic alterations. A number of studies have demonstrated a reduction in BRCA1 expression and/or function through promoter hypermethylation, loss of heterozygosity, and haploinsufficiency (for an excellent recent review of this subject see reference by Weberpals et al., 2008). Mechanisms of BRCA1 silencing may be histological subtype specific. A recent study reported that 47% of the 38 consecutive high-grade serous or undifferentiated carcinomas had loss of BRCA1 via genetic or epigenetic mechanisms (Press et al., 2008). The same study found that none of the 11 endometrioid, clear cell, and low grade serous cancers exhibited loss of BRCA1.

Figure 2 – BRCA1 and BRCA2-discriminating genes also segregate sporadic ovarian cancers into two groups. (A) Hierarchical clustering of 110 non-redundant genes with statistically significant differential expression between BRCA1-linked (B1) and BRCA2-linked (B2) tumors (modified *F* test, $P < 0.0001$). The red and green intensities represent standard normal deviation (Z score) values from each gene's mean expression level (represented as black) across all 61 tumor samples. (B) Hierarchical clustering of sporadic and BRCA-linked tumor samples based on the expression pattern of the 110 BRCA-discriminating genes. The two major clusters correspond to BRCA1-like (blue) and BRCA2-like (orange) patterns of gene expression. B = BRCA1-linked tumor; B2 = BRCA2-linked tumor; C = sporadic tumors. Tumor histology for each sample is indicated below the sample label as follows: S = serous; A = adenocarcinoma not otherwise specified; E = endometrioid; C = clear cell; M = mixed features. (C) Hierarchical clustering of sporadic samples in the absence of BRCA-linked tumors. Note the maintenance of cluster integrity. Each sporadic sample is colored according to its cluster identity in B. The median age in years is shown for each major cluster. Figure reproduced with permission from Jazaeri et al. (2002).

Genetic and epigenetic mechanisms for BRCA2 deficiency appear to be much less prevalent than those for BRCA1 (Chan et al., 2002; Hilton et al., 2002). It is likely that alternative pathways resulting in net loss of BRCA2 and BRCA1 function play a role in a subset of sporadic ovarian cancers. Both BRCA1 and BRCA2 interact with multiple protein partners, especially as a part of DNA damage response, and it is conceivable that deficiency of key interactors may mimic BRCA dysfunction. One such class of interactors is the Fanconi anemia complex proteins that form a multi-protein ubiquitin ligase and DNA helicase whose role in DNA damage response and maintenance of chromosomal integrity is becoming increasingly defined (Levitus et al., 2006; Gurtan and D'Andrea, 2006). In the past few years increasing crosstalk between the BRCA and Fanconi anemia pathways has been discovered (Kennedy and D'Andrea, 2005). BRCA2 (also known as FANCD1), is itself a part of the Fanconi anemia complex. In addition, two important BRCA partners, BRCA1 interacting protein 1 (BRIP1/FANCF) and partner and localizer of BRCA2 (PALB2/FANCL) are also part of the Fanconi complex (Levran et al., 2005; Levitus et al., 2005; Rahman et al., 2007; Xia et al., 2006). While mutations in BRIP1 and PALB2 each account

for only about 1% of hereditary non-BRCA1, non-BRCA2 (so called BRCAx) cancers (Rahman et al., 2007; Tischkowitz et al., 2007), recent investigations suggest higher rates of promoter hypermethylation of Fanconi anemia genes in ovarian tumors ranging between 8 and 28% (Taniguchi et al., 2003; Wang et al., 2006; Lim et al., 2008; Potapova et al., 2008). It is important to point out that while epigenetic changes in BRCA1 and BRCA2 and their protein partners may result in a molecular phenotype resembling that associated with BRCA dysfunction direct evidence in support of this hypothesis is lacking at this time.

Another potential mechanism for the development of BRCA2-like tumors involves EMSY (also known as FLJ90741 and C11orf30), a gene mapped to the 11q13.5 amplicon and amplified almost exclusively in 13% of breast and 17% of ovarian cancers (Hughes-Davies et al., 2003; Brown et al., 2006). The EMSY protein interacts with the N terminus of BRCA2, has endogenous transcriptional repressor activity, and participates in DNA damage focus formation (Hughes-Davies et al., 2003). It is tempting to speculate that a portion of BRCA2-like ovarian cancers may be related to abnormal EMSY amplification or expression, however, at this time there is insufficient

information available to draw any firm conclusions about the biological role of EMSY in ovarian carcinogenesis.

4. Insights from other expression profiling studies

Numerous studies have examined transcriptional changes following alterations of BRCA1 or BRCA2 in established cell lines. However, there is considerably less data available on the role of BRCA proteins on transcription in human tissues or primary cell cultures. In this regard, a recent study by Walker and colleagues is worthy of mention (Walker et al., 2008). In this investigation lymphoblastoid cells from BRCA1 ($n = 17$) and BRCA2 ($n = 19$) germline mutation carriers as well and healthy controls ($n = 17$) were exposed to 10 Gy of radiation and induced gene expression changes were compared between the BRCA groups and controls (Walker et al., 2008). In comparing the radiation induced gene sets using a uniform statistical cutoff, 875 genes differentiated the cells from BRCA2 mutation carriers from normal controls. The corresponding number for BRCA1-mutated cells was 578, and the overlap between these two gene sets was only 346 genes. In other words, 30 min after radiation there were 529 unique BRCA2-regulated, and 232 unique BRCA1-regulated genes with altered expression compared to BRCA wildtype cells. These findings were consistent with those of an earlier smaller study that also showed normal cells from heterozygous BRCA1 mutation carriers display a different gene expression profile from controls in response to DNA damage (Kote-Jarai et al., 2004). These observations highlight the fact that even non-malignant cells heterozygous for BRCA1 and BRCA2 exhibit discrete gene expression alterations with only partial overlap following a genetic insult. Further support for the concept of “haploinsufficiency,” was recently provided in a mouse model (Jeng et al., 2007). BRCA1 heterozygous female mice had a 3–5-fold higher incidence of ovarian tumors compared to wildtype animals following exposure to ionizing radiation. Of note, cancer cells from the heterozygous mice retained the wildtype allele and expressed BRCA1 protein, supporting the notion that partial loss of BRCA1 was sufficient for tumorigenesis in this model (Jeng et al., 2007).

5. Summary and future research

The advent of high throughput technologies has revolutionized global assessment of tumors, and in many ways, all biological investigations. These methods have helped reveal overlapping but also largely unique biological phenotypes associated with BRCA1 and BRCA2 dysfunction in ovarian cancer as well as other malignant and normal tissues. The clinical significance of these differences is just now beginning to emerge as illustrated by the preferential response of BRCA-related cancers to poly ADP ribosylase (PARP1) inhibitors and other chemotherapeutic agents (Taniguchi et al., 2003; Bryant et al., 2005; Sakai et al., 2008). Over the past two decades significant progress has been made in elucidating the functions of BRCA1 and BRCA2. However, future research must address not only common, but also unique functional properties of these important tumor suppressors. Important unanswered questions include: why do BRCA1 mutations result in higher

incidence and earlier age of presentation of ovarian cancer? What are unique and common contributions of BRCA proteins to chemotherapy drug resistance and how can they be overcome?

Finally, while this review has focused on the downstream transcriptional phenotypes of BRCA protein dysfunction, it is important to keep in mind that both BRCA1 and BRCA2 are components of multimeric ubiquitin ligases and participate in numerous other protein modification interactions. As such, it is likely that continuing advances in high throughput proteomics will serve as important tools in gaining a better understanding of BRCA1 and BRCA2 function in normal and pathological states.

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