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Loss of *ARID1A*-associated Protein Expression Is a Frequent Event in Clear Cell and Endometrioid Ovarian Cancers

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Abstract

Background—Inactivating somatic mutations in the *ARID1A* gene are described in a significant fraction of clear cell and endometrioid ovarian cancers leading to loss of the corresponding protein (BAF250a). Expression of BAF250a was examined in clear cell and endometrioid cancers accrued as part of the North Carolina Ovarian Cancer Study, a population-based case-control study, to determine whether loss of expression is associated with clinical and epidemiological features.

Methods—Immunostaining for BAF250a was performed using 212 clear cell and endometrioid ovarian cancers. Associations between loss of BAF250a and clinical and epidemiological features were examined. Variables were analyzed by logistic regression.

Results—Loss of BAF250a expression was noted in 96 (45%) of 212 cancers: 34(41%) of 82 clear cell cases and 62 (48%) of 130 endometrioid cases. There was no relationship between the loss of BAF250a and stage, grade, survival, or epidemiological variables.

Conclusions—These data confirm that loss of the *ARID1A*-encoded protein BAF250a is a frequent event in the genesis of clear cell and endometrioid ovarian cancers. Loss of BAF250a was not associated with clinical or epidemiologic characteristics. One explanation for these findings is that inactivation of the chromatin remodeling pathway may be a requisite event in the development of these cancers.

Keywords

ARID1A; BAF250A; Clear cell ovarian cancer; endometrioid ovarian cancer; endometriosis associated ovarian cancer

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Serous tumors are the most common type of invasive epithelial ovarian cancer, accounting for approximately 70% of cases. Endometrioid and clear cell subtypes are less common, accounting for approximately 15% and 5% of cases, respectively.^{1,2} Researchers have traditionally studied epithelial ovarian cancers as a single disease entity; however, it has become increasingly clear that the origin of various histological types likely differs. Whereas most serous tumors probably arise from fallopian tube epithelium, endometrioid and clear cell cancers are thought to develop from endometriotic implants.^{3,4} Serous cancers usually present at an advanced stage, whereas endometrioid and clear cell cancers are usually confined to the pelvis. In addition, there are significant differences in the subtypes with respect to reproductive and hormonal exposures.⁵ Kobel et al⁶ found that whereas low-grade and high-grade serous subtypes share similar expression patterns, endometrioid and clear cell carcinomas infrequently express WT1 and p53, both commonly expressed in serous tumors.

Population-based studies have consistently identified endometriosis as a significant risk factor for the development of clear cell and endometrioid cancers,^{7,8} yet the specific steps involved in the molecular pathogenesis of these cancers have not been identified to date. Molecular studies have shown that endometrioid and clear cell carcinomas have a low frequency of mutations in the *KRAS*, *BRAF*, *PTEN*, and *beta-catenin* genes.^{9–11} Mutations in transforming growth factor- β receptor type 2 have been found in clear cell cancers, and microsatellite instability is seen in both clear cell and endometrioid ovarian cancers.¹² Multiple theories exist as to the causative factors involved in the transition to malignancy. Ness¹³ recently proposed that this involves complex biologic interactions between inflammatory mediators, an aberrant hormonal milieu, and intrinsic immunologic variations.

Wiegand et al¹⁴ and Jones et al¹⁵ recently described *ARID1A* as a candidate tumor suppressor gene that is mutated in a significant portion of clear cell and endometrioid ovarian cancers but unaffected in serous ovarian tumors. The *ARID1A* gene encodes a member of the SWI/SNF family that is thought to regulate transcription of certain other genes by altering their chromatin structure. BAF250a, the encoded protein, is part of this chromatin-remodeling complex and plays an important role in the regulation of tumor suppression and other important cellular functions.¹⁶ There is a strong correlation between mutation of the *ARID1A* gene and loss of immunohistochemically detectable BAF250a protein. The finding of loss of BAF250a in atypical endometriosis adjacent to some of these cancers suggests that this is an early event in the development of many of these cancers.

The first aim of this study was to validate the observation that loss of BAF250a is a frequent event in clear cell and endometrioid ovarian cancers. In addition, we sought to determine whether this somatic event was associated with clinical features or epidemiological risk factors.

MATERIALS AND METHODS

Study Subjects

Cases and controls were identified from the North Carolina Ovarian Cancer Study (NCOCS), a population-based case-control study of newly diagnosed epithelial ovarian cancer. Identification and recruitment of EOC and controls has been described in detail in other reports.¹⁷ Briefly, newly diagnosed cases of epithelial ovarian cancer were identified through the North Carolina Central Cancer Registry using a rapid case ascertainment system. Eligible EOC were aged 20 to 74 years at diagnosis, had no history of ovarian cancer, resided in the study area, and were able to give consent and complete an interview in English. Paraffin blocks of ovarian cancer tissue were obtained from the Pathology departments in participating hospitals where the patients had surgery. One slide from each

case was reviewed by the study pathologist to confirm the diagnosis of epithelial ovarian cancer. An extensive review of all the pathological material was not performed. Controls were matched by age and race.

Variables examined in the case-case analysis and the case-control analysis included age at diagnosis (0-49, 40-59, 60-69, and 70+), race (white or not white), histologic diagnosis (clear cell or endometrioid), grade (well differentiated, moderately differentiated, and poorly undifferentiated), stage (I/II and III/IV),¹⁸ history of doctor-diagnosed endometriosis (yes or no), number of pregnancies (0, 1-2, 3-4, and 5+), tubal ligation (yes or no), history of doctor-diagnosed infertility (yes or no), and oral contraceptive use (never, 0-1 year, 1-5 years, 5+ years). There are 234 clear cell and endometrioid cancer cases in the NCOCS, and tissue sections from paraffin blocks were available for 218 cases.

Immunohistochemistry

Immunohistochemical staining was performed to identify cases lacking BAF250a expression as a surrogate marker for *ARID1A* gene mutation. Immunohistochemistry for BAF250a was performed using formalin-fixed, paraffin-embedded tissues. Sections 4- to 5- μ m thick were deparaffinized in 3 changes of xylene and then rehydrated in graded alcohols. The slides were placed in 0.01-mol/L citrate buffer, pH 6.0, for 15-minute heat-induced antigen retrieval in the Decloaking Chamber (Biocare Medical, Concord, CA). The slides were quenched for endogenous peroxidase with an aqueous solution of 3% hydrogen peroxide for 10 minutes. The slides were then incubated in background terminator (Biocare Medical) for 20 minutes. The slides were incubated in a humidity chamber with mouse monoclonal antibodies to BAF250a (Abgent, San Diego, CA) at a dilution of 1:50 for 1 hour at room temperature followed by antibody detection using the 2-step Universal 4plusHRP horseradish peroxidase kit (Biocare Medical). Slides were developed using chromogen diaminobenzidine and then counterstained with hematoxylin. Mouse monoclonal IgG antibodies were used as a control for each tumor specimen. The level of BAF250a immunostaining was evaluated based on the percentage of nuclear staining in the tumor specimen as well as the adjacent stroma. Loss of BAF250a was defined as staining of 5% or less of the cancer nuclei in the presence of retention of nuclear staining in the adjacent nonmalignant stromal elements. Specimens with no tumor or stromal nuclear staining were considered technical failures.

Statistical Analysis

Of the 218 cases, 6 were considered technical failures and were excluded from analysis. A total of 212 cases were included in the final evaluation. Continuous variables were analyzed by the general linear model, and categorical variables were analyzed using χ^2 analysis. Two-tailed *P* values were used, and statistical significance was set at *P* = 0.05. All statistical analyses were performed using SAS version 4.3 (Cary, NC).

RESULTS

Clinical and demographic characteristics of the 212 patients are reported in Table 1. The mean age of the patient population was 54.3 years. The cases included 130 endometrioid cancers (61%) and 82 clear cell (39%) cancers. There were 35 patients (16.5%) with a self-reported history of endometriosis. Early-stage (I/II) disease was noted in 61% of the cases, and 91.5% of the patients were white. Clear cell cancers were poorly differentiated in 99% of the cases. Endometrioid cancers were well differentiated in 35%, moderately differentiated in 32%, and poorly differentiated in 33% of the cases.

Of the 212 cases, 116 (55%) expressed BAF250a in greater than 5% of cancer cells and were considered positive, whereas 96 cases (45%) were considered negative with 5% or less of cancer cells staining. Of the cases with greater than 5% staining, 53% demonstrated 50% or greater cancer nuclei staining, and all had some degree of staining in surrounding stromal cells. Loss of BAF250a expression was seen in 62 (48%) of the 130 endometrioid cases and 34 (41%) of the 82 clear cell cases. The relationship between BAF250a expression and clinicopathologic features is shown in Table 2. After adjusting for the patients' ages, there was no relationship between the loss of BAF250a staining and histologic diagnosis, grade, stage, or survival. Overall survival for endometrioid cases was 70% with a mean follow up of 68 months: 65% in cancers that retained BAF250a expression and 75% in cases with loss of expression. Overall survival for clear cell cases was 64% with a mean follow-up of 73 months: 66% in cancers that retained BAF250a expression and 61% in cases with loss of expression. Because endometriosis is a precursor of many clear cell and endometrioid ovarian cancers, we examined the relationship between endometriosis and BAF250a expression. Endometriosis was reported in 19 (20%) of 96 cases with loss of BAF250a compared to 16 (14%) of 116 that retained BAF250a ($P = 0.251$). In addition, there was no relationship with age at diagnosis, history of tubal ligation, oral contraceptive use, or family history of breast and ovarian cancer.

The clear cell and endometrioid ovarian cancer cases were compared to 1085 control subjects from the NCOCS who did not have ovarian cancer. Similar relationships were seen between cases with or without loss of BAF250a and epidemiological risk factors and are shown in Tables 3 and 4. After adjusting for age, the cases with loss of BAF250a staining were significantly more likely to have a history of endometriosis and to have a history of infertility than controls. They were less likely to have had a tubal ligation. The cases that retained BAF250a expression also were more likely to have a history of endometriosis and to have a family history of breast and ovarian cancer than controls. They were also less likely to have had a tubal ligation.

DISCUSSION

Despite advances in our understanding of the molecular and epidemiological etiology of ovarian cancer, survival remains poor. Effective early detection strategies have not yet been identified, and most cases present at an advanced stage. One area where there has been a significant improvement in outcome is identification of *BRCA1/2* mutation carriers, in who risk reducing surgery has been shown to improve survival.¹⁹ Most *BRCA1/2*-associated cancers are high-grade serous lesions. Discovery of etiologic factors that place women at risk for other histological types of ovarian cancer could be useful and has the potential to further improve outcomes in this disease.

Endometriosis is recognized as a significant risk factor for endometrioid and clear cell ovarian carcinomas.^{7,8,20} Whereas endometriosis is a relatively common disease, affecting approximately 10% of reproductive-age women, only a small percentage subsequently develops ovarian cancer.^{21,22} A recent pathological study of epithelial ovarian cancer by Kumar et al using strict criteria for the diagnosis of endometriosis found evidence that 19% of cases of epithelial ovarian cancer were associated with endometriosis.²³ Melin et al showed that women diagnosed with endometriosis at a younger age had an increased risk of developing endometriosis-associated ovarian cancer.²⁴ Women who were hospitalized with a diagnosis of endometriosis for the first time between the ages of 20 to 30 years had higher risk than those hospitalized for the first time between the ages of 30 and 40 years. Endometriosis-associated ovarian cancers may be less susceptible to standard platin/taxane-based chemotherapeutic regimens,²⁵ making identification of those patients who are at

highest risk of malignant transformation and in whom early intervention may provide the most benefit even more important.

Although the exact mechanisms by which transformation from endometriosis to atypical endometriosis, to ovarian cancer occurs has not been fully elucidated, mutations in several oncogenes and tumor suppressor genes have been identified that presumably represent critical molecular targets. Dinulesca et al¹⁰ have shown that oncogenic *K-ras* mutations can lead to the development of endometriosis in a mouse model. Furthermore, they were able to induce endometrioid ovarian carcinoma in the mouse model by introducing both mutant *K-ras* and *PTEN* genes.

Recently, Wiegand et al¹⁴ have shown that mutation of the *ARID1A* gene, with loss of the BAF250a protein it encodes, is the most frequent molecular event in the development of clear cell and endometrioid ovarian cancers. Whereas there is a high correlation between the *ARID1A* gene mutation and BAF250a protein expression, this relationship is not absolute. In their validation cohort, Weigand found approximately 70% of tumors with a gene mutation showed loss of protein expression. This could be explained by the presence of a truncated but nonfunctional protein or detection of protein products encoded by mutant *ARID1A* genes from the other nonmutated allele.

We examined the frequency of BAF250a loss in the context of the NCOCS. This provided the opportunity to confirm the findings of Wiegand et al and to determine whether loss of BAF250a was associated with recognized clinical features or epidemiological risk factors. Similar to Wiegand et al who found loss of protein expression in 42% of the clear cell and 31% of the endometrioid cancers,¹⁴ we found that 48% of endometrioid cancers and 41% of clear cell ovarian cancers had lost BAF250a expression and that there was no association between BAF250a expression and any clinicopathologic risk factors or survival. The availability of detailed information on all major ovarian cancer risk factors allowed us to examine the relationship between etiologic factors such as endometriosis and BAF250a expression. Both BAF250a-positive and BAF250a-negative cases had a higher frequency of self-reported endometriosis compared to unaffected controls in the NCOCS. No convincing associations were seen between BAF250a expression and epidemiological risk factors.

One weakness of the present study is that self-reported history of endometriosis is not always accurate and may be affected by recall bias. In many cases, endometriosis may be asymptomatic, and this likely leads to underreporting of the disease. Pathological confirmation of the presence of endometriosis would be more accurate, but only one slide from each case underwent review by the study pathologist. That said, pathology review probably only identifies endometriosis in a fraction of the clear cell and endometrioid cancer cases in which it served as the site of origin. It is possible that endometriosis may be missed in some cases owing to sampling or the presence of only minimal residual endometriosis.

The goal of molecular epidemiological studies is to resolve disease heterogeneity by defining disease subsets that are characterized by different risk factors and genetic mutations. The use of such a classification would be in the development of different treatment or prevention strategies for various subsets of a disease based on this knowledge. In this study, we tested the hypothesis that clear cell and endometrioid ovarian cancers that have lost BAF250a expression are etiologically different from those that retain expression. This was not found to be the case. BAF250a plays a role in the SWI/SNF chromatin remodeling complex that regulates transcription of other genes. It is possible that inactivation of this pathway is a requisite event in the development of all clear cell and endometrioid ovarian cancers. This theory would be supported by the identification of alterations in other genes in this pathway in cases that have not lost BAF250a expression.

Further understanding of the molecular pathogenesis of these cancers may provide opportunities for prevention or earlier detection, leading to improved outcomes.

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Table 1

Clinicopathologic features of patients from the NCOCS included in the study

Variable	Number (%)
Age (years)	
Mean	54.3
Range	26-74
0-49	71 (33.5%)
50-59	74 (34.9%)
60-69	54 (25.5%)
70+	13 (6.1%)
Race	
White	194 (91.5%)
Black	18 (8.5%)
Histology	
Endometrioid	130 (61.3%)
Clear cell	82 (38.7%)
Grade	
Well differentiated	45 (21.2%)
Moderately differentiated	40 (18.9%)
Poorly/Undifferentiated	123 (58.0%)
Missing	4 (1.9%)
Stage	
I/II	128 (60.4%)
III/IV	82 (38.7%)
Unknown	2 (0.9%)
Endometriosis	35 (16.5%)
History of Tubal ligation	43 (20.3%)
History of Infertility	33 (15.6%)
Oral Contraceptive use	
Never	62 (29.2%)
0-1 year	33 (15.6%)
1-5 years	54 (25.5%)
5+ years	57 (26.9%)
Missing	6 (2.8%)
Family history of breast or ovarian cancer	44 (20.8%)

Table 2

Comparison of clinicopathologic features between tumors with and without BAF250a staining

	Staining absent(n=96)	Staining persent (n=116)	OR	CI
Age (years)				
0-49	37(38.5%)	34(29.3%)	1(ref)	-
50-59	27(28.1%)	47(40.5%)	0.53	0.27-1.03
60-69	26(27.1%)	28(24.1%)	0.85	0.42-1.73
70+	6(6.3%)	7(6.0%)	0.79	0.24-2.58
Histology				
Endometrioid	62(64.6%)	68(58.6%)	1(ref)	-
Clear cell	34(35.4%)	48(41.4%)	0.78	0.45-1.37
Stage				
I/II	61(64.2%)	67(58.3%)	1(ref)	-
III/IV	34(35.8%)	48(41.4%)	0.78	0.44-1.37
Missing	1(1.0%)	1(0.9%)		
Grade				
Well differentiated	25(26.6%)	20(17.5%)	1(ref)	-
Moderately differentiated	19(20.2%)	21(18.4%)	0.72	0.31-1.70
Poorly differentiated	50(53.2%)	73(64.0%)	0.55	0.27-1.10
Missing	2(2.1%)	2(1.7%)		
Endometriosis	19(20.0%)	16(13.9%)	1.49	0.69-3.23
History of infertility	17(17.7%)	16(13.8%)	1.42	0.65-3.07
Tubal ligation	16(16.7%)	27(23.3%)	0.66	0.33-1.31
Family history of breast or ovarian cancer	16(16.7%)	28(24.1%)	0.62	0.30-1.25
Number of pregnancies				
0	23(24.0%)	20(17.2%)	1(ref)	-
1-2	39(40.6%)	55(47.4%)	0.61	0.28-1.33
3-4	25(26.0%)	16(13.8%)	1.32	0.51-3.40
5+	9(9.4%)	25(21.6%)	0.32	0.11-0.89
Oral contraceptive use				
Never	28(30.1%)	34(30.1%)	1(ref)	-
0-1 years	12(12.9%)	21(18.6%)	0.73	0.30-1.78
1-5 years	27(29.0%)	27(23.9%)	1.24	0.56-2.74
5+ years	26(28.0%)	31(27.4%)	1.02	0.46-2.25
Missing	3(3.1%)	3(2.6%)		

Table 3

Comparison of clinicopathologic features between tumors without BAF250a staining and controls without cancer

	Staining absent (n=96)	Controls (n=1085)	OR	CI
Age (years)				
0-49	37(38.5%)	325(30.0%)	1(ref)	-
50-59	27(28.1%)	339(31.2%)	0.70	0.42-1.18
60-69	26(27.1%)	287(26.5%)	0.80	0.47-1.35
70+	6(6.3%)	134(12.4%)	0.39	0.16-.95
Endometriosis	19(20.0%)	69(6.4%)	3.58	2.04-6.27
History of infertility	17(17.7%)	101(9.3%)	2.06	1.17-3.62
Tubal ligation	16(16.7%)	398(36.7%)	0.34	0.20-0.60
Family history of breast or ovarian cancer	16(16.7%)	180(16.6%)	1.05	0.56-1.85
Oral contraceptive use				
Never	28(30.1%)	308(28.4%)	1(ref)	-
0-1 years	12(12.9%)	108(10.0%)	1.13	0.55-2.32
1-5 years	27(29.0%)	291(26.8%)	0.88	0.49-1.58
5+ years	26(28.0%)	343(31.6%)	0.70	0.38-1.27
Missing	3(3.1%)	33(3.0%)		

Table 4

Comparison of clinicopathologic features between tumors with BAF250a staining and controls without cancer

	Staining present (n=116)	Controls (n=1085)	OR	CI
Age (years)				
0-49	34(29.3%)	325(30.0%)	1(ref)	-
50-59	47(40.5%)	339(31.2%)	1.33	0.83-2.11
60-69	28(24.1%)	287(26.5%)	0.93	0.55-1.58
70+	7(6.0%)	134(12.4%)	0.50	0.22-1.15
Endometriosis	16(13.8%)	69(6.4%)	2.33	1.30-4.17
History of infertility	16(13.8%)	101(9.3%)	1.54	0.87-2.72
Tubal ligation	27(23.3%)	398(36.7%)	0.53	0.34-0.82
Family history of breast or ovarian cancer	28(24.1%)	180(16.6%)	1.67	1.05-2.65
Oral contraceptive use				
Never	34(29.3%)	308(28.4%)	1(ref)	-
0-1 years	21(18.1%)	108(10.0%)	1.67	0.92-3.02
1-5 years	27(23.3%)	291(26.8%)	0.75	0.43-1.31
5+ years	31(26.7%)	343(31.6%)	0.72	0.41-1.24
Missing	3(2.6%)	33(3.0%)		