EphA2 Expression Is Associated with Aggressive Features in Ovarian Carcinoma

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ABSTRACT

Purpose: EphA2 (epithelial cell kinase) is a transmembrane receptor tyrosine kinase that has been implicated in oncogenesis. There are no published data regarding the role of EphA2 in ovarian carcinoma, which is the focus of the present study.

Experimental Design: Nontransformed (HIO-180) and ovarian cancer (EG, 222, SKOV3, and A2780-PAR) cell lines were evaluated for EphA2 by Western blot analysis. Five benign ovarian masses, 10 ovarian tumors of low malignant potential, and 79 invasive ovarian carcinomas were also evaluated for EphA2 expression by immunohistochemistry. All samples were scored in a blinded fashion. Univariate and multivariate analyses were used to determine significant associations between EphA2 expression and clinicopathological variables.

Results: By Western blot analysis, EG, 222, and SKOV3 cell lines overexpressed EphA2, whereas A2780-PAR and HIO-180 had low to absent EphA2 expression. All of the benign tumors had low or absent EphA2 expression. Among the invasive ovarian carcinomas examined (mean age of patients was 59.2 years), 60 (75.9%) tumors overexpressed EphA2 and the other 19 tumors had negative or minimal EphA2 expression. There was no association of EphA2 overexpression with ascites, likelihood of nodal positivity, pathological subtype, and optimum surgical cytoreduction (residual tumor <1 cm). However, EphA2 overexpression was significantly associated with higher tumor grade (P = 0.02) and advanced stage of disease (P = 0.001). The median survival for patients with tumor EphA2 overexpression was significantly shorter (median, 3.1 years; P = 0.004); the median survival for patients with low or absent EphA2 tumor expression was at least 12 years and has not yet been reached. In multivariate analysis using the Cox proportional hazards model, only volume of residual disease (P < 0.04) and EphA2 overexpression (P < 0.01) were significant and independent predictors of survival.

Conclusions: EphA2 overexpression is predictive of aggressive ovarian cancer behavior and may be an important therapeutic target.

INTRODUCTION

Ovarian carcinoma ranks as the fifth most common cancer diagnosis in females and is the leading cause of death from gynecologic cancer (1). At present, there is no effective screening tool for the general population. Unfortunately, because of a lack of early warning signs and vague symptomatology, most ovarian carcinoma patients present with widespread metastatic disease. Despite the use of primary surgical cytoreduction and systemic administration of paclitaxel- and platinum-containing chemotherapy regimens, the 5-year survival rate for patients with advanced disease has not risen above 15–20% (2, 3). There thus is a critical need for improved biological markers and therapies for ovarian carcinoma, which will come from a better understanding of the biology of the disease.

Receptor tyrosine kinases are a diverse group of transmembrane proteins involved in signal transduction pathways that control cell shape, proliferation, differentiation, and migration (4–6). Tyrosine kinase receptors therefore have important roles in normal physiology and in oncogenesis (7). The Eph receptors are the largest family of tyrosine kinases. EphA1, the first receptor of this family, was originally isolated from an erythropoietin-producing hepatoma cell line (8). At present, the Eph family comprises 14 Eph receptors and 8 ephrin ligands (9). The Eph receptor family members share functional and structural similarities and are divided into two subfamilies, EphA or EphB, depending on ephrin ligand to which they bind. Similarly, the ephrin ligands are divided into either ephrinA ligands, which are linked to the cell membrane by a glycosylphosphatidylinositol linkage, or ephrinB ligands, which encode for a transmembrane domain (10, 11). For the most part, EphA receptors bind ephrinA ligands and EphB receptors bind ephrinB ligands (4, 12–14).

Unlike the other Eph kinases, which are predominantly expressed during embryogenesis, EphA2, a 130-kDa transmembrane protein, is primarily found in adult human epithelial cells and is located on chromosome 1p36.1 (15, 16). The role of EphA2 in normal epithelia is not well understood, but it is
thought to negatively regulate cell growth and migration (9, 17). Interestingly, EphA2 is overexpressed in many cancers, including breast, prostate, melanoma, esophageal, and lung carcinomas, and functions as a powerful oncogene (17–21). In non-transformed mouse mammary epithelial cells, ectopic overexpression of EphA2 has been shown to result in a malignant phenotype in both in vitro and in vivo experiments (21). Some studies have shown that EphA2 is involved in the regulation of tumor cell growth, migration, invasion, and angiogenesis (22–27). EphA2 does not require ligand binding for its tyrosine kinase activity (17, 28). However, EphA2 needs to be phosphorylated by the ligand binding to cause inactivation of the Ras/mitogen-activated protein kinase pathway, dephosphorylation of focal adhesion kinase, suppression of integrin function, and activation of the ERK kinase signaling cascade (29–32). However, in malignant cells, EphA2 is not tyrosine phosphorylated in part because of the inability of EphA2 to bind its membrane-anchored ligand as a result of the unstable cell-cell contacts in malignant cells. Furthermore, low-molecular weight phosphatase (LMW-PTP) has been shown to negatively regulate EphA2 phosphorylation and confer transformation on nontransformed cells (33, 34). E-cadherin, which serves as a powerful suppressor of metastasis, may also regulate EphA2 ligand binding (28).

To date, there have been no published reports evaluating the role of EphA2 expression in ovarian carcinomas, particularly with respect to clinical outcome. Thus, we undertook the present study with the following aims: (a) to evaluate EphA2 expression in ovarian cell lines, and (b) to determine the clinical relevance of EphA2 expression in ovarian carcinoma.

MATERIALS AND METHODS

Cell Culture. The ovarian cancer cell lines used in this study were SKOV3, EG, 222, and A2780-PAR. The derivation and sources of the cell lines have been reported previously (35). These cells were maintained and propagated in RPMI 1640 supplemented with 15% fetal bovine serum. All of the cell lines are routinely screened for Mycoplasma (GenProbe detection kit; Fisher, Pittsfield, MA). The immortalized nontransformed human ovarian surface epithelial cell line HIO-180 was a kind gift from Dr. Andrew Godwin at the Fox Chase Cancer Center (Philadelphia, PA). All of the cell lines are routinely screened for mycoplasma species. Glioblastoma cell lines were maintained in DMEM/F12 supplemented with 10% fetal bovine serum and 0.1% gentamicin sulfate (Gemini Bioproducts, Calabasas, CA). The immortalized nontransformed human ovarian surface epithelial cell line HIO-180 was a kind gift from Dr. Andrew Godwin at the Fox Chase Cancer Center (Philadelphia, PA). All of the cell lines were routinely screened for mycoplasma species (GenProbe detection kit; Fisher, Pittsfield, MA). All of the experiments were performed with 70–80% confluent cultures.

Formalin-Fixed, Paraffin-Embedded Samples for EphA2 Immunohistochemical Staining. All of the samples were collected in compliance with requirements of the Institutional Review Board for the Protection of Human Subjects. Formalin-fixed, paraffin-embedded samples were sectioned at 5 μm and stained by hematoxylin and eosin for identification. Sections adjacent to the hematoxylin and eosin-stained sections were used for immunohistochemical staining. All of the slides were deparaffinized by use of xylene, 100% ethanol, and 95% ethanol, followed by a thorough wash with deionized water. For 5 min, the deparaffinized slides were immersed in 0.5% pepsin (Dako) for proteolytic digestion of paraffin-embedded formalin tissue sections. Slides were treated with antigen retrieval buffer [0.1 M (pH 6.0) citrate buffer] with heat (120°C) under pressure for 10 min followed by immersion in hydrogen peroxidase (Lab Vision) for 5 min to inactivate the endogenous peroxidases. Sections were blocked with 10% normal goat serum in blocking reagent for 15 min at room temperature. Monoclonal EphA2 antibody (MedImmune Inc.) was diluted with Diluent Reagent Solution (Zymed), and the slides were incubated with the primary antibody overnight at 4°C. After washing with PBS–Tween 20, the appropriate biotinylated linked antimouse/antirabbit IgG secondary antibody (Dako) was applied, and the slides were incubated with the secondary antibody for 10 min at room temperature. After washing with PBS–Tween, horseradish peroxidase-conjugated streptavidin (Dako) was added and incubated with the sections for 10 min at room temperature. After extensive washing with PBS–Tween, DAB + Substrate + Chromogen (Dako) was added to the sections to visualize the antibody staining for 2 min. Slides were counterstained with hematoxylin (Richard-Allen Scientific) for 30 s.

All of the samples were reviewed by a board-certified pathologist (M. D.), who was blinded to the clinical outcome of these patients. EphA2 expression was determined semiquantitatively by assessing the percentage of stained tumor cells and the staining intensity. The percentage of positive cells was rated as follows: 0 points, 0–5%; 2 points, 5–20%; 3 points, 20–50%; 4 points, 50–75%; 5 points, >75%. The staining intensity was rated as follows: 0 point, weak intensity; 1 point, weak/moderate intensity; 2 points, moderate intensity; 3 points, strong intensity. Points for expression and percentage of positive cells were added, and an overall score ranging between 0 and 3 was assigned. Tumors were categorized into four groups: (negative (overall score = 0), ≤5% cells stained, regardless of intensity; weak expression (overall score = 1), 1–2 points; moderate expression (overall score = 2), 3–4 points; and strong expression (overall score = 3), 5–6 points.

Western Blot and Immunoprecipitation Analysis. Cells were lysed with 1× modified RIPA buffer (50 mM Tris, 150 mM NaCl, 1% Triton X-100, and 0.5% deoxycholate) containing 25 μg/ml leupeptin (Sigma Chemical Co., St. Louis, MO), 10 μg/ml aprotinin (Sigma Chemical Co.), 1 mM sodium orthovanadate, and 2 mM EDTA. Cells were removed from the dishes by cell scraping. The samples were then subjected to three cycles of freezing–thawing and centrifuged at 12,500 rpm for 30 min. The protein concentration of the samples was determined by a bicinchoninic acid Protein Assay Reagent kit, and whole cell lysates were analyzed by 10% SDS-PAGE and stained with Coomassie BBR-250 (Sigma) to ensure equal loading (data not shown). Samples were transferred to nitrocellulose (Schleicher and Schuell, Keene, NH). Blots were blocked with 5% nonfat milk for 1 h at room temperature and then were incubated with the monoclonal EphA2 antibody (1:1,000 dilution) for 1 h at room temperature with agitation, followed by incubation with a horseradish peroxidase-conjugated antimouse secondary antibody (1:5,000; The Jackson Laboratory, Bar Harbor, ME). Blots were developed with use of an enhanced chemiluminescence detection kit (ECL; Amersham Pharmacia Biotech, Piscataway, NJ). For protein loading analyses, a monoclonal actin antibody (1:1,500; Chemicon International, Temecula, CA) was used.

For immunoprecipitation experiments, 300 μg of cell lysate were incubated with the EphA2 antibody for 1 h at 4°C. Protein–antibody complexes were incubated for 1 h at 4°C with protein A-Sepharose-conjugated beads (preincubated with rab-
Clinicopathological Variable Analysis. All of the patients underwent surgical exploration and cytoreduction as the initial treatment. The treating gynecologic oncologist determined the adjuvant therapy. Diagnosis was verified by a pathology review at the institutional gynecologic oncology tumor board. All of the patients were staged according to the International Federation of Gynecology and Obstetrics surgical staging system. A gynecologic pathologist reviewed all of the pathology results for all of the patients.

Statistical Analysis. The $\chi^2$ test was used to determine differences among variables by use of SPSS (SPSS Inc., Chicago, IL). Kaplan–Meier survival plots were generated, and comparisons between survival curves were made with the log-rank statistic. The Cox proportional hazards model was used for multivariate analysis. A $P$ value $<0.05$ was considered statistically significant.

RESULTS

EphA2 Expression in Ovarian Cell Lines. EphA2 expression in selected ovarian cell lines was assessed by Western blot analysis (Fig. 1). The cell lines HIO-180 and A2780-PAR are poorly invasive (35) and demonstrated absent to minimal EphA2 expression by Western blot analysis. Moderately (SKOV3 and EG) and highly (222) aggressive cancer cell lines overexpressed EphA2 as determined by Western blot analysis (35). To control for sample loading, the membrane was stripped and reprobed with actin-specific antibodies. To determine the EphA2 phosphorylation status, immunoprecipitation with the EphA2 antibody was performed, followed by immunoblotting with a phosphotyrosine antibody. The EphA2 protein was not phosphorylated in the SKOV3, EG, or the 222 cell lines (data not shown).

EphA2 Expression in Human Ovarian Samples. On the basis of the evidence that high levels of EphA2 predominated in aggressive cell models, EphA2 expression in clinical samples was assessed by immunohistochemical staining of sections isolated from 5 normal ovaries, 10 ovarian tumors of low malignant potential, or 79 invasive epithelial ovarian cancers. Representative examples of EphA2 staining are shown in Fig. 2. All of the normal ovaries demonstrated little or no EphA2 immunoreactivity, whereas all of the low malignant potential and invasive tumors had moderate to strong EphA2 expression. Among the patients with low malignant potential tumors, nine had stage I or II disease and 1 had stage III. A para-aortic and pelvic lymph node dissection was performed in seven patients, and all lymph nodes were negative. All patients with a low malignant potential tumor had complete removal of tumor and remain disease free with a mean follow-up of 3.96 years. Among the invasive ovarian cancers, 66 (83.5%) were positive based on the overall score of $\geq$1, and 13 (16.5%) were considered negative. Sixty (76%) of the invasive tumors overexpressed EphA2 (overall score = 3).

EphA2 Expression in Human Invasive Ovarian Cancer Samples Correlates with Clinicopathological Features. The demographic features of the patients with invasive ovarian cancers are listed in Table 1. The mean age of the patients in this cohort was 59.2 years. Eighty-three percent of all patients had advanced stage (III or IV) disease, and 85% of all patients had high-grade (III) disease. Sixty-seven percent of all patients underwent optimal surgical cytoreduction ($<1$ cm of residual disease at the end of surgery). The correlations of EphA2 overexpression with various clinical variables are listed in Table 2. There was no association of EphA2 overexpression with histological subtype (serous versus other), likelihood of nodal positivity, presence of ascites, or level of cytoreduction. In contrast, EphA2 related to disease stage and clinical outcome. For example, 83% of the high-stage ovarian cancers overexpressed EphA2 compared with 38% of the low-stage cancers ($P = 0.001$). Similarly, 81% of the high-grade tumors overexpressed EphA2 compared with 50% of the low-grade cancers ($P = 0.02$).

On the basis of the association of EphA2 with high tumor-stage and grade, we evaluated the role of EphA2 expression in predicting survival of patients with invasive ovarian cancer. Survival was adversely affected by high-stage, high-grade, and residual disease $>1$ cm (all $P$ values $<0.05$; data not shown). In univariate analysis, EphA2 overexpression was associated with significantly worse survival (median survival, 3.1 years versus at least 12 years, with the median survival not yet reached for individuals with low or absent EphA2 expression; $P = 0.004$; Fig. 3). Multivariate analysis was also performed with a Cox proportional hazards model that included stage, grade, volume of residual disease. These studies revealed that only residual disease ($P < 0.04$) and EphA2 overexpression ($P < 0.01$) were significant predictors of poor survival. Thus, EphA2 appears to represent a new independent indicator of disease progression.

DISCUSSION

The major finding of our present study is that the EphA2 receptor tyrosine kinase is overexpressed in many ovarian cancers. We also showed that EphA2 expression relates to disease grade and survival and in particular, that EphA2 may provide independent information to guide evaluations of clinical outcome.

Our work breaks new ground in linking EphA2 with ovarian cancer. These results are consistent with studies of other...
epithelial carcinomas, in which EphA2 is not phosphorylated and has been described as an oncoprotein that critically controls tumor cell growth, survival, migration, invasiveness, and angiogenesis (5, 20–24). Overexpression of EphA2 has been noted in multiple epithelial carcinomas, including breast, melanoma, prostate, non-small-cell lung, and esophageal cancers (17–21). To the best of our knowledge, our study is the first to evaluate the role of EphA2 in ovarian carcinoma, and its overexpression is predictive of aggressive ovarian cancer behavior. Interestingly, the EphA2 gene is located on chromosome 1p36.1, which is not only a genetic “hot spot” in cancer (15, 16), but also the second most common site of complex karyotypic abnormalities in ovarian cancer (36). Thus, future studies should address the potential significance of this link.

Overexpression of EphA2 was associated with a significantly worse survival (P = 0.004) and remained a predictor of poor outcome in multivariate analysis. EphA2 is therefore an independent adverse prognostic factor in ovarian carcinoma. The mortality rate for ovarian cancer remains high among

### Table 1

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* Mean (range).

### Table 2

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and EphA2 overexpression in ovarian carcinoma. We are actively evaluating the role of p53 to determine the role of EphA2 in aggressive phenotypes. Further study is necessary to understand the implications for the application of EphA2 to identify some of the more deadly forms of the disease.

EphA2 may also be a novel therapeutic target in ovarian carcinoma, and indeed we are actively developing strategies to target the EphA2 receptor. In normal cells, EphA2 is expressed at low levels and is phosphorylated (34). However, in malignant cells EphA2 is not tyrosine-phosphorylated (17, 28, 34). Because of unstable cell-cell contacts in malignant cells (37–39), EphA2 cannot bind to its membrane-anchored ligand ephrinA1 (28). Notably, the E-cadherin adhesion protein is a powerful suppressor of metastasis, and E-cadherin has been shown to regulate the ability of EphA2 to bind its ligand (40). In the context of our present findings, this link between EphA2 and E-cadherin is particularly intriguing because E-cadherin has been linked to mesenchymal-to-epithelial transitions in human ovarian surface epithelium (41). In normal ovarian surface epithelial cells, E-cadherin is rarely expressed. However, E-cadherin is expressed in metaplastic ovarian surface epithelium and primary ovarian carcinoma, but not in metastasis (41). In breast cancer cell lines, lack of proper expression and function of E-cadherin leads to EphA2 being localized in membrane ruffles of aggressive tumor cells and ultimately to its nonphosphorylation (28). We are continuing to investigate the role of E-cadherin and EphA2 in ovarian carcinoma.

In a recent study, Dohn et al. (42) showed that EphA2 transcription is regulated by p53, which is a known tumor suppressor protein and is frequently mutated in ovarian cancer (43–45). Wild-type p53 seems to regulate EphA2 through a response element in the EphA2 promoter, which appears to be involved in the regulation of cell survival (42). The positive regulation of EphA2 by p53 may seem inconsistent with the high levels of EphA2 seen in many epithelial types of cancer. However, mutations in p53 are common in cancer and contribute to aggressive phenotypes. Further study is necessary to determine the role of p53 mutations in regulating EphA2 levels (43, 44). If that is the case, then EphA2 may be a therapeutic target to treat ovarian carcinoma patients who have p53 mutations (45). We are actively evaluating the role of p53 mutations and EphA2 overexpression in ovarian carcinoma.

Tyrosine-phosphorylated EphA2 interacts with a multitude of downstream proteins and pathways, such as Shc, Grb2, SLAP, focal adhesion kinase, ERK, and phosphatidylinositol 3′-kinase (24, 29–32, 46, 47). The downstream consequences of these interactions are numerous and, in brief, include negative regulation of tumor cell proliferation, improved survival, decreased migration and invasion, and rapidly signal transduction from the cell surface to the nucleus via Grb2 (17, 27, 30, 48). In addition, Hendrix et al. (49) and Hess et al. (50) have shown that EphA2 may play a role in vasculogenic mimicry. We have previously demonstrated that aggressive ovarian cancer cells acquire the ability to engage in vasculogenic mimicry (35, 51, 52). Therefore, targeting EphA2 may have direct antitumor and antivascular effects.

Because of the prevalence of EphA2 overexpression in many cancers, including ovarian cancer as well as its many downstream effects, EphA2 is an attractive therapeutic target. To date, antiephrin monoclonal antibodies and peptide-based mimetics to ephrins produced by phage display have been used to mimic the effects of EphA2 ligand binding in vitro (47, 53), and early studies provide promising evidence that EphA2 antibodies can selectively inhibit malignant growth both in vitro and in vivo (48, 54). The potential application of these approaches for the treatment of ovarian carcinoma is not known at present and is the subject of ongoing research in our laboratory.

REFERENCES

Fig. 3 Kaplan–Meier survival of patients with invasive ovarian cancer based on EphA2 staining intensity, using the log-rank statistic.
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Clinical Cancer Research

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