Epithelial Membrane Protein-2 Is a Novel Therapeutic Target in Ovarian Cancer

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Abstract

Purpose: The tetraspan protein epithelial membrane protein-2 (EMP2) has been shown to regulate the surface display and signaling from select integrin pairs, and it was recently identified as a prognostic biomarker in human endometrial cancer. In this study, we assessed the role of EMP2 in human ovarian cancer.

Experimental Design: We examined the expression of EMP2 within a population of women with ovarian cancer using tissue microarray assay technology. We evaluated the efficacy of EMP2-directed antibody therapy using a fully human recombinant bivalent antibody fragment (diabody) in vitro and ovarian cancer xenograft models in vivo.

Results: EMP2 was found to be highly expressed in >70% of serous and endometrioid ovarian tumors compared with nonmalignant ovarian epithelium using a human ovarian cancer tissue microarray. Using anti-EMP2 diabody, we evaluated the in vitro response of nine human ovarian cancer cell lines with detectable EMP2 expression. Treatment of human ovarian cancer cell lines with anti-EMP2 diabodies induced cell death and retarded cell growth, and these response rates correlated with cellular EMP2 expression. We next assessed the effects of anti-EMP2 diabodies in mice bearing xenografts from the ovarian endometrioid carcinoma cell line OVCAR5. Anti-EMP2 diabodies significantly suppressed tumor growth and induced cell death in OVCAR5 xenografts.

Conclusions: These findings indicate that EMP2 is expressed in the majority of ovarian tumors and may be a feasible target in vivo. Clin Cancer Res; 16(15); 3954–63. ©2010 AACR.

Ovarian cancer is the foremost cause of death from gynecologic malignancy in the United States, with an estimated 21,550 new cases and 14,660 deaths in 2009 (1). Ovarian cancer is classified based on the histology of the tumor, clinical behavior, and epidemiology. Epithelial ovarian cancer is the most common type in origin, and it includes both serous and endometrioid tumors. The incidence of ovarian cancer generally increases with age, with the majority of cases occurring in postmenopausal women (2).

Screening for ovarian cancer has met with limited success (3–6). This is largely due to a lack of early detection markers, and efficient screening tools for surveillance typically lack sensitivity and specificity. In fact, almost 70% of patients with ovarian cancer are not diagnosed until they have reached the high stage of the disease (7). The primary treatment for ovarian cancer is surgical resection and adjuvant chemotherapy, but recurrence is common (8, 9). Therefore, there is a need to develop and validate molecular markers sensitive to disease onset and progression to improve patient management as well as to point to new targets for drug design.

An emerging molecule in female reproductive cancers is the tetraspan protein epithelial membrane protein-2 (EMP2). In normal tissue, EMP2 has a discrete tissue distribution, with high expression in secretory endometrium (10, 11), lung alveolar epithelium (12), and in retinal pigmented epithelium within the eye (13). Dysregulation of EMP2 has been implicated in endometrial cancer, in which EMP2 expression correlates with poor prognosis and survival (14), and EMP2 is the only known early diagnostic marker to predict endometrial hyperplasia progression to endometrial cancer (15). As recombinant antibodies have been successful in treating a variety of carcinomas and lymphomas (16–19), we recently developed an engineered anti-EMP2 diabody that binds to its second extracellular domain with high specificity and avidity (15). Treatment of endometrial adenocarcinoma...
cells with anti-EMP2 diabody resulted in a significant increase in apoptotic cell death in vitro and a reduction in tumor volume in vivo (15).

The basic biology of EMP2 provides insights into its potential role in reproductive epithelial carcinogenesis. EMP2 is a member of the growth arrest-specific gene 3/peripheral myelin protein 22 four-transmembrane protein family (20–22). It associates with integrin αvβ3 and focal adhesion kinase (FAK), and it can regulate αvβ3 integrin expression and localization, functions critical for its physiologic role in blastocyst implantation (10, 23, 24).

An assessment of public databases indicated that EMP2 mRNA may be upregulated in serous and endometrioid ovarian tumors, including poorly differentiated and high-grade cancers (25), and it may be selectively upregulated in carboplatin-resistant ovarian tumors (26). Thus, in the present study, we tested the association of EMP2 expression using a human ovarian cancer tissue microarray (TMA). Next, we evaluated the ability of anti-EMP2 diabodies to alter cell growth and induce cytotoxicity in human ovarian cancer cell lines in vitro and in vivo. Our findings indicate that EMP2 protein is expressed in the majority of human ovarian carcinomas, and that anti-EMP2 diabody is effective in targeting human ovarian cancer cell lines and xenograft tumors. These results suggest that EMP2 has merit for further assessment as a potential target for imaging and therapy in ovarian cancer.

Materials and Methods

Cell lines and cell culture

OVCA432 and OVCA433 (27) were generously provided by Dr. Robert Bast (M.D. Anderson Cancer Center, TX). A1847 (28) was a gift from Dr. Stuart Aaronson (Mount Sinai Medical Center, NY), and the CAOV-3, ES-2, OV90, PA-1, OVCAR-5, IGROV-1, and SKOV-3 cell lines were purchased from the American Type Culture Collection. Cells were cultivated in appropriate medium supplemented with 10% FCS (Hyclone Laboratories), 2 mmol/L L-glutamine, 1 mmol/L sodium pyruvate, 100 U/mL penicillin, and 100 U/mL streptomycin (all from Invitrogen Life Technologies), incubated at 37°C in a humidified 5% CO2 and passed every 7 days.

Anti-EMP2 reagents

Rabbit polyclonal anti-human EMP2 antibody has been described previously (13, 29). Human bivalent anti-EMP2 antibody fragments (diabody) KS49 and KS83 were generated with specificity and avidity to both human and mouse EMP2 peptides and native cell-surface EMP2 protein. A10, a human diabody without known specificity, was used as a negative control. These diabodies have been described previously (15).

Tissue microarray analysis

Ovarian cancer patients who were surgically treated at Memorial Sloan-Kettering Cancer Center from 1980 to 2004 had their tumor specimens banked according to Institutional Review Board (IRB) guidelines after they had provided informed consent. A TMA was constructed as described previously (14). Initially, samples from 161 patients were present on the TMA, consisting of 34 borderline tumor patients, 53 low-stage carcinoma patients [Federation of International Gynecologists and Obstetricians (FIGO) stages I and II], and 74 high-stage carcinoma patients (FIGO stages III and IV). Patients were excluded from our analyses if no clinical information could be obtained or if the targeted histology contained no relevant cells (i.e., benign or malignant cells). Ultimately, data from 129 patients were utilized in our analyses: 21 borderline tumor patients, 34 low-stage carcinoma patients, and 74 high-stage carcinoma patients. Tumor stage was classified according to FIGO classification. Table 1 summarizes clinical variables and patient groups.

An independent validation sample, including 10 normal ovaries with no significant pathologic changes and 10 ovary tumor samples, was obtained from the University of California at Los Angeles (UCLA) Translational Pathology Core Laboratory with IRB approval. Samples were analyzed for the presence or absence of EMP2 expression by immunohistochemistry or Western blot analysis as described below.

Immunohistochemistry

The immunohistochemical staining for EMP2 has been described previously (14). Briefly, formalin-fixed, paraffin-embedded tissue sections were heated at 95°C for 20 minutes in 0.1 mol/L citrate buffer (pH 6.0) for antigen retrieval. The sections were incubated with rabbit anti-human EMP2 polyclonal antibody (I:400) in a humidified chamber overnight at 4°C. The corresponding preimmune serum was used as a negative control and was processed at the same condition. A biotinylated antirabbit secondary
antibody was used from the Vectastain Elite ABC kit (Vector Laboratories) following the manufacturer’s protocol. Antibody signal was detected using the Vector Laboratories DAB substrate kit (Vector Laboratories) according to the manufacturer’s instructions.

**Immunohistochemical scoring**

We conducted a semiquantitative analysis of the EMP2-stained ovarian cancer TMA, ovarian tumors, and normal ovary samples by two independent pathologists (RAS and MA). These pathologists were both blind to clinical information. We quantified EMP2 staining per TMA spot or whole tissue by considering the staining intensity (0, below the level of detection; 1, weak; 2, moderate; and 3, strong) and the percentage of cells staining at each intensity level (0-100%). For each spot, we then calculated an integrated value of intensity combined with frequency that was derived using the formula: \((3x + 2y + 1z)/100\) where x, y, and z are % staining at intensity 3, 2, and 1, respectively. These values were used for comparing spot-level expression of EMP2 across different histopathologies.

**Western blot analysis**

Frozen normal and ovarian cancer tissue were obtained from the Tissue Procurement Laboratory Core at UCLA. Five normal ovaries and five ovarian tumor samples were homogenized and lysed in ice-cold radioimmunoprecipitation assay buffer containing a cocktail of EDTA-free protease inhibitors (Roche). After centrifugation at 14,000 \(\times\) g for 10 minutes at 4°C, supernatants were collected and protein concentrations were measured using BCA protein assay kit (Pierce).

For experiments involving ovarian cancer cell lines, cells were washed in PBS, counted, and then lysed in Laemmli buffer. Samples were treated with peptide \(N\)-glycosidase F (PNGase; New England Biolabs) to deglycosylate the proteins as previously described (21). Equivalent cell lysates were separated on 18% SDS-PAGE gel, and proteins were transferred to nitrocellulose membrane.

EMP2 was detected using primary antihuman EMP2 (1:2,000) antisera, and secondary horseradish peroxidase–conjugated goat anti-rabbit IgG (Transduction Laboratories). Actin was detected as a loading control using primary monoclonal antihuman \(\beta\) actin (Sigma) and secondary horseradish peroxidase–conjugated sheep antimouse IgG (Amersham). The secondary antibodies were detected using ECL detection reagents (Amersham). Specific bands were quantified by scanning and densitometric analyses using Scion Image software (Scion Corp.).

**Cell growth and cell death analysis**

Cells (5 \(\times\) 10^5) were placed in duplicate in a 12-well plate (Becton Dickinson) and incubated with 20 \(\mu\)g/ml.
diabody A10 (control), KS49, or KS83 for 48 hours. After incubation, cells at 60% to 70% confluence were washed in PBS and trypsinized. Cell viability was determined by trypan blue exclusion. Cell growth was determined by comparing the ratio of final viable cells to initial cells using a hemocytometer.

To quantitate diabody-induced apoptosis, cells were harvested and stained using an Annexin V–FITC apoptosis detection kit I according to the instructions of the manufacturer (BD Biosciences). Flow cytometry was done in the UCLA Jonsson Comprehensive Cancer Center (JCCC) and Center for AIDS Research Flow Cytometry Core Facility.

**Tumor xenografts and treatment**

Four- to six-week-old female BALB/c nude mice were purchased from Charles River Laboratories for xenograft research. Following the National Academy of Science Guide for the Care and Use of Laboratory Animals, the mice were fed with a controlled light schedule (14L:10D) and controlled temperature range at the vivarium of UCLA. To obtain the solid tumors, $2 \times 10^6$ ovarian cancer cells suspended with 5% matrigel (BD Biosciences) were injected s.c. into the right or left shoulder flank of each mouse. On day 8, with the tumor diameter ~1 mm, therapy was started by injection twice a week with 1 mg/kg anti-EMP2 diabody KS83, KS49, control diabody A10, or a vehicle control (sterile saline). Four mice were utilized per group. Tumors were measured with Vernier calipers and tumor volumes were calculated by the formula $(\pi/6 \times \text{larger diameter} \times \text{smaller diameter})$. The mice were maintained until the tumor diameter reached 1.5 cm or the mice were moribund. Following treatment, all tumors were excised, formalin fixed, and paraffin embedded. Tumor sections were stained with H&E, EMP2, or $397^{\text{p-FAK}}$ expression as described above.

**Statistical analysis**

Significant differences in EMP2 expression levels among various subgroups in the TMA were determined by the Mann-Whitney or Kruskal-Wallis rank sum test. For outcome analyses, spot expression levels were pooled using criteria described in a number of our publications (30–36). The Cox proportional hazards model (univariate and multivariate) was used to determine the significance of various factors related to recurrence or survival. The proportional hazards assumption was verified using Schoenfeld, martingale, and df$b$ residuals. LogRank and Fisher's exact $P$ values were two-sided. A $P < 0.05$ was considered significant.

In addition to exploring the population as a continuous variable, we also dichotomized the population into relatively high- versus relatively low-EMP2-expressing patients. To find significant dichotomizing cut points, we used either recursive partitioning or regression trees (available in the rpart software package), and/or plotted log-rank $P$ values versus hazard ratios (31, 37). Survival curves were calculated using the Kaplan-Meier method and comparisons were made using the log-rank test. The Cox proportional hazards model (univariate and multivariate) was used to determine the significance of various factors related to survival. The proportional hazards assumption was verified using Schoenfeld, martingale, and df$b$ residuals. Log rank and Fisher exact $P$ values were two-sided and $P < 0.05$ was considered significant.

Differences in the in vitro cell growth and cell death with diabodies and various in vivo experimental groups were evaluated using one-tailed Student's unpaired $t$ test at a

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**Fig. 1.** EMP2 expression stratified by histologic type and stage. The mean integrated intensity of EMP2 protein expression for each category is shown using bar plots. Error bars, SE; $n$, number of sample. A, EMP2 expression was significantly increased in borderline (BL, $P = 0.0088$), clear cell (CC, $P = 0.0233$), endometrioid (Endo, $P = 0.0025$), mixed ($P = 0.0121$), and serous ($P = 0.0003$) compared with nonmalignant normal (NL) ovarian epithelium. B, EMP2 expression was significantly higher in borderline ($P = 0.0088$), early-stage ($P = 0.0021$), and advance-stage tumors ($P = 0.0003$) compared with nonmalignant normal ovarian epithelium. There was a trend towards higher EMP2 expression from borderline to early- to advance-stage tumors, but these differences were not statistically significant.
95% confidence level (GraphPad Prism version 3.0; GraphPad Software).

**Results**

**EMP2 expression is associated with serous and endometrioid ovarian tumors**

The expression of EMP2 in ovarian cancer was initially evaluated in a TMA containing samples from 129 ovarian cancer patients (Table 1). When we considered EMP2 expression level as a function of histology, in general, non-neoplastic ovarian epithelium expressed significantly lower levels of EMP2 than all malignant variants (Fig. 1A). EMP2 was somewhat elevated in early- and advanced-stage cancer compared with borderline tumors (Fig. 1B; \( P = 0.210 \) and \( P = 0.021 \), respectively) with a trend towards slightly elevated levels in advanced-compared with early-stage ovarian malignancies (Fig. 1B).

To validate the expression of EMP2 in ovarian cancer, we analyzed the expression of EMP2 in independent samples from the UCLA tissue procurement core facility within the Department of Pathology and Laboratory Medicine by both immunohistochemistry and Western blot analysis. By immunohistochemistry, strong EMP2 expression was observed in 10 ovarian tumors (1 borderline tumor, 1 clear cell carcinoma, 5 endometrioid carcinoma, 1 mixed carcinoma, and 3 serous carcinoma), whereas 10 normal ovaries showed a low to negligible staining pattern in both epithelial cells and follicle somatic cells (Fig. 2A). The EMP2 staining pattern of the patients showed the same trends as TMA data (Fig. 2B). To further verify these results, a Western blot analysis was done on an additional five normal ovary and five ovarian cancer specimens. EMP2 expression was significantly higher in the tumor specimens compared with the normal ovaries (Fig. 2C and D).

We next considered whether EMP2 expression levels were predictive of patient survival. However, whether as a continuous or as a dichotomized variable, EMP2 levels had no significant predictive value (\( P = 0.5507 \); data not shown).

**EMP2 is expressed in most ovarian cancer cell lines**

Similarly, in ovarian cancer cell lines, EMP2 was expressed in a number of serous derived primary ovarian tumors (OVCA432, OVCA433, A1847) as well as in ovarian endometrioid carcinoma cell lines (OVCAR-5, CAOV-3, ES-2, SKOV-3, IGROV-1). Positive control cell lines included the endometrial carcinoma cell line RL95-2 (10) and cervical cancer HELA cells. Overall, EMP2 expression...
was detected in all cells except the serous carcinoma cell line OV90. Curiously, the one clear cell tumor (PA-1) was also EMP2 positive (Fig. 3A). These findings indicate that, as in native ovarian tumors, the majority of ovarian cancer cell lines are EMP2 positive.

In a number of cell types, EMP2 has been shown to reside within cytoplasmic compartments or on the plasma membrane. To assess the targetability of EMP2, we analyzed the surface expression of EMP2 in ovarian cancer cells using flow cytometry. In a number of cell lines, including OVCAR5, CaOV3, and SKOV3, high levels of EMP2 were observed on the plasma membrane using anti-EMP2 antibody fragments. A representative cell line (OVCAR5) is depicted in Fig. 3B. In addition, some cell lines that expressed moderate/low levels of EMP2 by Western blot analysis still had detectable expression on the surface. These include OVCA433 (Fig. 3B) and A1847 cells (data not shown). Finally, no surface expression of EMP2 was observed on OV90 cells (Fig. 3B). These results show that EMP2 may serve as an accessible therapeutic target for ovarian cancer.

**Diabodies to EMP2 inhibit cell growth and promote cell death**

We had previously shown that our anti-EMP2 recombinant antibody fragments (diabodies) selectively bind EMP2 and induce apoptosis in a number of endometrial cancer cells (15). To determine if selective targeting of EMP2 may be an effective therapy in ovarian cancer, cell lines with high EMP2 expression (OVCAR5, CAOV-3, OVCA432) and an EMP2-low cell line (OVCA433) were utilized. Cells were treated with 20 μg/mL KS83, KS49, or control diabody A10 for 48 hours. Significant cytostasis was observed in all three EMP2-high ovarian cancer-bearing cell lines treated with anti-EMP2 diabodies KS83 or KS49 but not with control diabody A10 (Fig. 4A). In contrast, negligible changes in cytostasis were observed in OVCA433 cells.

To correlate the decrease in cell number with an increase in cell death, dead cells were counted by trypan blue under the same experimental conditions. Consistent with the cell growth inhibition data above, diabody KS83 induced significant cell death in three of the four cell lines tested: OVCAR5, CAOV-3, and OVCA432 cells. KS49 induced a similar response in OVCAR5 and OVCA432 cells, although the response was not as robust in CAOV-3 cells (Fig. 4B). Finally, OVCA433 cells with low EMP2 expression on the plasma membrane did not significantly respond to anti-EMP2 therapy, suggesting that there is a threshold EMP2 level necessary for eliciting an efficient therapeutic response (Fig. 4B).
To confirm that anti-EMP2 diabodies induced cell death via an apoptotic pathway, OVCAR5 cells were stained with propidium iodide and Annexin V. Of the cells, 14% and 18% were Annexin and/or propidium iodide positive when treated with diabodies KS49 and KS83, respectively, for only 24 hours. In contrast, <3% of cells were Annexin and/or propidium iodide positive when treated with the control diabody A10 (Fig. 4C).

**In vivo tumor targeting**

To test the efficacy of EMP2 immunotherapy in vivo, a mouse xenograft model was created using the ovarian cancer cell line OVCAR5. Female BALB/c nude mice were injected s.c. with OVCAR5 cells. On day 8, when tumors were approximately 1 mm in diameter, anti-EMP2 diabody KS83, KS49, and control A10 were injected intratumorally twice a week, and progression of tumor size was measured using calipers. Saline (0.9%) was used as an additional negative control. By day 29, KS83 and KS49 significantly retarded OVCAR5 tumor growth (Fig. 5A).

All tumors were excised on day 29. Significantly, KS83 and KS49 both exhibited >2-fold difference in tumor size compared with A10 or sterile saline treatment (Fig. 5B, insets). Moreover, large areas of necrosis were observed in tumors treated with KS83 or KS49 but not with A10 or saline control (Fig. 5B). These results suggest that anti-EMP2 immunotherapy reduces ovarian tumor load.

We next analyzed all treated tumors for EMP2 expression on day 30. As shown in Fig. 5C, all tumors retained similar expression of EMP2, regardless of treatment. To confirm that EMP2-specific diabody treatment did not alter the distribution of EMP2, immunohistochemistry was done on excised tumors. Detailed immunohistochemical analysis revealed that following diabody KS83 and KS49 treatments, the surface expression of EMP2 within the tumor was largely unaffected as compared with tumors treated with controls diabody A10 or sterile saline (Fig. 5D). This suggests that increasing the dosage or length of treatment time with anti-EMP2 diabodies may be more effective at reducing the residual tumor.

**Discussion**

In this study, we described the utilization of EMP2 as a therapeutic target in ovarian cancer. Previous studies have shown the importance of EMP2 in human endometrial cancer (14, 15). To date, however, limited data exist on the role of EMP2 in ovarian cancer. In this study, we assessed the expression of EMP2 in an ovarian cancer TMA, and determined its suitability as a therapeutic target using anti-EMP2 recombinant antibody fragments.

Analysis of 129 ovarian carcinoma patients revealed that EMP2 expression was prevalent among serous and
endometrioid tumors, although its expression was not predictive of overall survival probability. As these subtypes represent the majority (90-95%) of ovarian cancers diagnosed in North America, we further evaluated the potential of EMP2 to serve as a therapeutic target. Preliminary experiments in a panel of ovarian cancer cell lines showed that EMP2 is highly expressed in the majority of cell lines. Moreover, incubation with recombinant EMP2 diabodies significantly inhibited cell growth and induced cell death both in vitro and in vivo.

EMP2 is a member of the tetraspan superfamily of proteins. The tetraspan family has been implicated in a multitude of processes including malignancy, regulation of the immune system, fertilization, and infectious disease processes (15, 38–40). Moreover, targeting of specific tetraspan proteins has been shown to induce the subsequent activation of an intracellular signal transduction cascade resulting in cell death, cell growth inhibition, antibody-dependent cellular cytotoxicity, complement-mediated cytotoxicity, or activation of antitumor immune response (38, 41). Similarly, EMP2 in several cell types plays a role in growth control, invasion, metastasis, and protein trafficking (20–22, 29). Biochemically, EMP2 can directly associate with integrin αvβ3 and FAK, and promote integrin-mediated FAK-Src activation (23, 24). Although the exact mechanism of EMP2 diabodies on ovarian cancer has yet to be elucidated, we predict that the diabodies dysregulate the integrin-FAK nexus, leading to apoptosis. Accordingly, it is possible that EMP2 contributes to malignant progression in part by augmenting integrin-mediated functions essential to tumor cell biology.

Human ovarian cancer cell xenografts in immunodeficient mice are useful research models for analyzing cell tumorigenicity and evaluation of therapeutics in ovarian cancer (42, 43). In the present study, treatment of OVCAR5 human ovarian cancer xenografts with anti-EMP2 diabody blocked tumor growth and induced tumor necrosis. These findings are similar to the effect of anti-EMP2 diabody on EMP2-positive human endometrial cancer xenografts (15). Anti-EMP2 diabodies lack detectable toxicity to normal tissues, including the lung, which physiologically express high levels of EMP2 (15). These findings suggest that in contrast to tumor cells, physiologic expression of EMP2 is either inaccessible to anti-EMP2 antibody, perhaps due to tight junction sequestration (44), or its ligation does not interfere with critical functions required by these normal cell types. Additional studies will be required to further delineate the in vivo biodistribution and Fig. 5. Anti-EMP2 diabodies retarded tumor formation in vivo. A, OVCAR5 cells were inoculated s.c. in nude mice, and tumor formation was monitored. At day 8 (arrow), mice were injected twice a week with 1 mg/kg of anti-EMP2 diabody KS83, KS49, and control diabody A10 or a vehicle control. Comparison by Student’s t test, *, P < 0.05. B, at day 29, xenograft tumors were excised. Tumor histology was assessed by H&E staining (magnification, ×400). Insets, size of excised tumors (scale bar, mm). EMP2 expression was detected by Western blotting (C) or immunohistochemistry (D; magnification, ×200).
safety of anti-EMP2 therapy, and the efficacy of anti-EMP2 diabody (or other native or antibody fragments) for in vivo cytotoxicity of ovarian cancer cell lines.

In conclusion, EMP2 expression is a common feature of major subtypes of human ovarian carcinoma, and treatment of human ovarian cancer cell lines with human bivalent anti-EMP2 diabodies directly induced cell death and retarded cell growth both in vitro and in tumor c. These results suggest that EMP2 may be a potential target for ovarian cancer antibody therapy. Finally, reengineering of anti-EMP2 diabody fragments into a native antibody format may offer improved therapeutic benefits relative to pharmacokinetics, biodistribution, and effector functions (16, 45).

Disclosure of Potential Conflicts of Interest


Acknowledgments

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