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In Vivo Inhibition of CD44 Limits Intra-Abdominal Spread of a Human Ovarian Cancer Xenograft in Nude Mice: A Novel Role for CD44 in the Process of Peritoneal Implantation

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Abstract

Ovarian cancer cells frequently metastasize by implanting onto the peritoneal mesothelial lining of the abdominal cavity. Data obtained from in vitro adhesion studies have suggested a possible role for the CD44 molecule in this process. The purpose of the present study was to determine the in vivo role of CD44 in ovarian cancer metastasis by using a nude mouse xenograft model of peritoneal implantation. Three groups of 10 athymic female nude mice each received an i.p. inoculum of 10 x 10^6 cells from a CD44-positive human ovarian cancer cell line (36M2) in the presence of either anti-D144 antibody (Ab; nonreactive IgG1), anti-DF3 Ab (reactive IgG1 Ab that does not inhibit in vitro binding), or neutralizing anti-CD44 Ab (IgG1). The number of peritoneal and diaphragmatic implants at 5 weeks for anti-D144 and anti-DF3-treated groups was 103 ± 17 and 120 ± 20, respectively (mean ± SE; P > 0.2). In contrast, animals treated with anti-CD44 Ab experienced a significant reduction in the number of tumor implants (35 ± 4; P < 0.002). Anti-CD44 Ab was not inhibitory to the growth of 36M2 cells in vitro and did not inhibit s.c. tumor growth in vivo, suggesting that the observed effect was related to inhibition of peritoneal implantation. These data suggest that the CD44 molecule plays an important in vivo role in ovarian cancer cell implantation and that strategies to inhibit CD44 function may represent a novel approach to limiting the intra-abdominal spread of this highly lethal tumor.

Introduction

Ovarian cancer frequently metastasizes throughout the abdominal cavity, resulting in widespread tumor implants involving the peritoneal mesothelium (1). As a result of this unique pattern of spread, most patients experience abdominal pain and eventual death due to mechanical bowel obstruction. Because most ovarian cancers extend to the surface of the ovary, it is likely that tumor cells are shed from the primary ovarian mass into the peritoneal cavity, followed by attachment of cells onto the peritoneal mesothelial surfaces that line the bowel and abdominal wall. In view of the extreme degree of morbidity and mortality resulting from this pattern of spread, strategies to inhibit the implantation of ovarian cancer cells onto the peritoneal mesothelium would be expected to significantly improve the outcome of patients with this highly lethal disease.

Our previous studies have suggested that the CD44H molecule, a major receptor for hyaluronic acid, may be partly responsible for mediating the adhesion of ovarian cancer cells to peritoneal mesothelium (2, 3). In vitro binding of ovarian cancer cells to peritoneal mesothelial monolayers is partly inhibited by neutralizing anti-CD44 antibody (2). Ovarian cancer cell lines that bind effectively to peritoneal mesothelium predominantly express the 90-kDa CD44H molecule, whereas ovarian cancer lines that bind poorly to mesothelium express either absent or relatively low levels of CD44H (2, 3). Furthermore, transfection of weakly binding ovarian cancer cells with CD44H cDNA is capable of restoring their ability to bind to mesothelium in vitro (3). Finally, treatment of mesothelial monolayers with hyaluronidase abolishes the CD44 component of ovarian cancer cell binding (2). Taken together, these data suggest a possible role for the CD44H molecule in the process of ovarian cancer metastasis.

The in vitro binding assay that we developed to quantitate ovarian cancer cell attachment to mesothelium is performed by allowing peritoneal mesothelial cells obtained from ascitic fluid to grow to confluence in microrot well plates. The use of these antibodies in indirect immunofluorescence analysis by flow cytometry has been described previously (2, 3). Anti-CD44 antibody clone 515 has been previously shown to neutralize CD44-mediated binding of cells to mesothelium and to hyaluronic acid-coated wells in vitro over a concentration range of 1-50 μg/ml (data not shown; Refs. 2 and 3). Anti-CD44 antibody clone 515 has been previously shown to neutralize CD44-mediated binding of cells to mesothelium and to hyaluronic acid-coated wells in vitro (2, 3). This antibody does not induce tumor cell clumping of the 36M2 human ovarian cancer cell line (described below) in suspension culture under conditions that prevent plastic adherence. The use of these antibodies in indirect immunofluorescence analysis by flow cytometry has been described previously (3). All antibodies were affinity-purified using Affi-Gel Protein A agarose (Bio-Rad Laboratories, Hercules, CA). The BBA1O antibody (IgG2a, pan-CD44; R&D Systems, Minneapolis, MN) was used in immunoblot analysis to characterize the molecular masses of CD44 species present on 36M2 cells and its subclones as described below.

Materials and Methods

Source of Reagents and Antibodies. Murine monoclonal antibodies used in the characterization of ovarian cancer cell lines and for i.p. treatment are anti-D144 (nonreactive IgG1; Ref. 2), anti-DF3 (reactive IgG1, a kind gift of Dr. Donald Kufe, Dana-Farber Cancer Institute, Boston, MA), and anti-CD44 (reactive IgG1, clone 515, a kind gift of Dr. Geoffrey Kansas, Northwestern University, Chicago, IL). As expected, both anti-D144 and anti-DF3 are incapable of inhibiting ovarian cancer cell binding to mesothelium in vitro over a concentration range of 1-50 μg/ml (data not shown; Refs. 2 and 3). Anti-CD44 antibody clone 515 has been previously shown to neutralize CD44-mediated binding of cells to mesothelium and to hyaluronic acid-coated wells in vitro (2, 3). This antibody does not induce tumor cell clumping of the 36M2 human ovarian cancer cell line (described below) in suspension culture under conditions that prevent plastic adherence. The use of these antibodies in indirect immunofluorescence analysis by flow cytometry has been described previously (3). All antibodies were affinity-purified using Affi-Gel Protein A agarose (Bio-Rad Laboratories, Hercules, CA). The BBA1O antibody (IgG2a, pan-CD44; R&D Systems, Minneapolis, MN) was used in immunoblot analysis to characterize the molecular masses of CD44 species present on 36M2 cells and its subclones as described below.

Cell Lines. Human ovarian cancer cell lines used in this study were cultured in RPMI 1640 (Sigma Chemical Co., St. Louis, MO) supplemented with 7.5% FCS (Hyclone, Logan, UT) unless otherwise specified. The UPN36T human ovarian cancer cell line was originally derived from a patient...
with papillary serous ovarian cancer by injecting 100 × 10⁶ cells from malignant ascites into the peritoneal cavity of a female Swiss nu/nu mouse, with subsequent selection of a peritoneal tumor nodule for \textit{in vitro} propagation. This line has been previously shown to be partly dependent upon the CD44 molecule for its ability to bind peritoneal mesothelium in \textit{vitro} (2, 3). To obtain a line that resulted in highly efficient implantation in nude mice, the original UPN36T line was passaged a second time by injecting 100 × 10⁶ cells i.p. into a Tac-Cr:(NCR)-nu/BR female athymic nude mouse 24 h after irradiation of the animal with 300 R. After 5 weeks, the animal was sacrificed, and a peritoneal tumor nodule was aseptically removed, dissociated with DNase/collagenase, and expanded in \textit{vitro} in 20% FCS/Iscove’s modified DMEM (Sigma) containing 5 ng/ml recombinant human EGF (culture grade; Amgen, Thousand Oaks, CA). After subcloning, the line was referred to as 36M2 (M, mouse-selected; 2, second passage). Like the parent UPN36T line, 36M2 cells strongly express both CD44 and DF3 molecules as assessed by flow cytometry (94 and 83% specific reactivity, respectively; data not shown). In pilot studies we determined that the mesothelial binding properties of 36M2 cells were similar to those of parent UPN36T cells and that neither anti-D144, anti-DF3, nor anti-CD44 antibodies were capable of inhibiting cell growth in \textit{vitro} at a concentration of 10 μg/ml for 5 days in culture (data not shown). The SW626 ovarian cancer cell line was used as a positive control for the presence of CD44 splice variants in immunoblot analysis (3) and was purchased from the American Type Culture Collection (Rockville, MD).

\textbf{In Vivo Assessment of Ovarian Cancer Cell Implantation.} To determine the effects of anti-CD44 antibody on ovarian cancer cell implantation in vivo, athymic female nude mice [Tac-Cr:(NCR)-nu/BR] were preirradiated (300 R), followed 24 h later by i.p. inoculation with 10 × 10⁶ 36M2 cells/mouse in the presence of either anti-D144, anti-DF3, or anti-CD44 antibody. For each mouse, the cells were initially incubated in the appropriate antibody at a concentration of 45 μg of antibody/0.5 ml of PBS for 30 min at 4°C to ensure adequate antibody coating before i.p. injection. After resuspension, the cells were injected i.p. in the continued presence of antibody (0.5 μl). We have previously determined in pilot studies that maximum inhibition of CD44-mediated binding in \textit{vitro} occurs at anti-CD44 antibody concentrations of ~1.0 μg/ml. Therefore, a dose of 45 μg i.p. injection was used to achieve a final \textit{in vivo} concentration of 1.5 μg/ml, assuming an average nude mouse weight of 30 g and therefore a possible maximum volume of distribution of 30 ml. Thereafter, antibody treatment was repeated for a total of 10 i.p. doses/mouse (45 μg of antibody in 0.5 ml) equally spaced over a 20-day duration. After 5 weeks, the mice were sacrificed, and nodules on the peritoneal mesothelial surfaces of the abdominal cavity and the underside of the diaphragm were quantified under low-power magnification using a micrometer (Manostar). For some experiments, UPN36T cells were injected s.c. as indicated to exclude the possibility of a direct antiproliferative effect of antibody on the growth of CD44-positive tumor cells in vivo.

\textbf{In Vitro Assessment of Ovarian Cancer Cell Binding to Mesothelium.} The \textit{in vitro} binding characteristics of 36M2 ovarian cancer cells to mesothelium were characterized using a previously described ⁵¹Cr-based binding assay (2). Mesothelial cells (1.5 × 10⁶) obtained from ascitic fluid were added to flat-bottom microtiter wells (Nunc, Roskilde, Denmark) in 100 μl of 20% FCS/Iscove’s modified DMEM supplemented with 5 ng/ml EGF and 0.5 μg/ml hydrocortisone to permit cell growth to confluence (2–3 days). On the day of the binding assay, mesothelial monolayers were washed twice in 1% FCS/MEM (Life Technologies, Inc.) to remove EGF and hydrocortisone. Ovarian cancer cells (2–5 × 10⁶) were then labeled with 0.10 μl of ⁵¹Cr (1 mCi/ml, 200 Ci/g; DuPont New England Nuclear, Boston, MA) for 1 h at 37°C, followed by washing twice in HBSS. Cells were subsequently treated (30 min at 4°C) with either control or anti-CD44 (clone 515) antibodies (10 μg/ml), followed by the addition of 50–100 × 10⁵ cells/well to microtiter wells containing a confluent layer of mesothelial cells in the continued presence of antibody. After the addition of cells, the plates were spun at 800 rpm for 5 min, and binding was allowed to occur for 30 min at 37°C. After incubation, the nonadherent cells were removed by three washes with 1% FCS/MEM, followed by lysis of bound cells with 0.1% NP40. The radioactivity of each lysate was measured in a gamma counter. The mean cpm for each treatment group was determined for quadruplicate wells. The percentage of cells specifically bound was calculated as follows: % specific binding = 100 × [mean cpm (mesothelial monolayer) − mean cpm (plastic)/cpm (total)].

\textbf{Immunoblotting.} Lysates (50 μg/lane) were resolved by one-dimensional SDS-PAGE under reducing conditions, followed by transfer onto a 0.45-μm polyvinylidene difluoride membrane (Millipore Corporation, Bedford, MA) in transfer buffer at 0.2 amperes for 2 h. After transfer, residual binding sites were blocked by incubating the membrane in TBS containing 10% nonfat dry milk for 1 h at RT. The blots were then incubated with a pan-CD44 antibody (BBA10; 2 μg/ml) in TBS containing 5% nonfat dry milk for 1 h at 4°C. The blots were then washed 3 times for 10 min in TBST, followed by incubation with sheep anti-mouse immunoglobulin conjugated to horseshadish peroxidase (Amersham, Arlington Heights, IL) in TBST containing 5% nonfat dry milk for 1 h at RT. After 3 washes for 10 min in TBST, the blots were developed using the enhanced chemiluminescence detection system (Amersham) according to the manufacturer’s protocol and exposed to X-ray film (Eastman Kodak).

\textbf{Immunohistochemistry Analysis.} In some experiments, the APAAP technique was used to assess the bioavailability of murine antibody to s.c. tumor nodules by detecting the presence of murine monoclonal antibody (2). Briefly, s.c. tumor was processed 1 h after i.p. injection of either anti-D144 or anti-CD44 antibody by snap-freezing in isopentane, followed by cryostat sectioning (6–8 μm), and fixation in acetone for 10 min at RT. Fixed slides from cryostat sections were then treated for 30 min at RT with 50 μl of rabbit anti-mouse immunoglobulins (1:25 dilution in TBS; DAKO) and incubated for 30 min at RT, followed by washing. APAAP complexes (50 μl of a 1:50 dilution in TBS; DAKO) were added and incubated for 30 min at RT, followed by washing. The alkaline phosphatase substrate was freshly prepared and consisted of 2 mg of naphthol AS-MX phosphate, free acid, 0.2 ml of dimethylformamide, 9.8 ml of 0.1 m Tris buffer (pH 8.2), 1 ml levamisole, and 10 mg of Fast-Red TR salt (Sigma). Each slide was flooded with substrate and incubated for 20 min at RT. After washing, the slides were counterstained with hematoxylin and mounted with Glycergel (DAKO).

\textbf{Statistical Analysis.} Data are expressed as mean ± SE when appropriate. Significance levels for comparison of binding between cell lines were determined using the two-sided Student’s \textit{t} test for unpaired samples.

\textbf{Results and Discussion} To determine the effects of anti-CD44 antibody on ovarian cancer cell implantation in vivo, athymic female nude mice [Tac-Cr:(NCR)-nu/BR] were preirradiated with 300 R, followed 24 h later by i.p. inoculation with 10 × 10⁶ 36M2 cells/mouse in the presence of either nonreactive control antibody (anti-D144), reactive control antibody (anti-DF3), or anti-CD44 antibody as stated above. Anti-D144 antibody was a control for the presence of mouse IgGl antibody, and anti-DF3 was an isotype-identical control for the possibility that cell coating with murine antibody might induce a cytotoxic response in vivo through ADCC. Thereafter, antibody treatment was repeated for a total of 10 i.p. doses/mouse (45 μg of antibody in 0.5 ml of each dose) equally spaced over a 20-day period. Each treatment group was comprised of 10 mice, with each mouse receiving a total of 450 μg of the appropriate antibody (45 μg × 10 doses) by the completion of therapy.

Five weeks after i.p. tumor cell inoculation, the mice were sacrificed, and nodules on the peritoneal mesothelial surfaces of the abdominal cavity and the underside of the diaphragm were quantified under low-power magnification. All mice were alive and healthy at the time of sacrifice, with no differences observed in the mean weight of mice in each treatment group (mean weight, 23.7 ± 0.5 g; n = 10/group; \textit{P} > 0.2). Treatment with either D144 or DF3 did not affect implantation or growth of peritoneal tumor compared with untreated animals (data not shown). In contrast, there was a significant decrease in the total number of nodules observed in the anti-CD44 antibody treatment group compared to either of the control groups (35 ± 4 nodules/mouse; \textit{n} = 10;
Three groups of 10 athymic female nude mice each were preirradiated with 300 R and inoculated 24 h later i.p. with 10 x 10^6 36M2 cells in the presence of antibodies as indicated, followed by continued treatment for a total of 10 i.p. doses of antibody (45 pg/dose) over a 20-day period. The mice were sacrificed after 5 weeks, and tumor implants were quantitated under low-power magnification. Peritoneal implantation of 36M2 cells is expressed as mean ± SE nodules in the indicated locations (n = 10/group). Peritoneal, nodules present on all serosal surfaces, excluding dia-

The localization of antibody delivery to tumor implants in vivo was consistent with the fact that the mean size of tumor implants was identical in the treatment groups. To determine whether the reduction in the number of tumor nodules observed in anti-CD44-treated animals was due to selection of cells with diminished proliferative capacity, tumor cell implants were excised in each of the three treatment groups and expanded in vitro, with subsequent determination of the growth rate in culture over a 5-day period. No difference in proliferative rate was observed between 36M2 subclones derived from the anti-D144, anti-DF3, or anti-CD44 antibody treatment groups (data not shown), an observation consistent with the fact that the mean size of tumor implants was identical in the three groups of animals. In addition, CD44 was expressed by 93, 94, and 89% of cells in 36M2 subclones derived from anti-D144, anti-DF3, or anti-CD44 antibody-treated mice, respectively, as assessed by flow cytometry. Immunoblot analysis revealed that the predominant CD44 species expressed by 36M2 subclones had a molecular mass of 90 kDa, consistent with CD44H (Fig. 3A). Finally, each line demonstrated equivalent levels of CD44 function as manifested by CD44-dependent binding to mesothelium in vitro (Fig. 3B). These data suggest that residual tumor cell implants present in anti-CD44-treated animals are not due to selection of CD44-negative cells or cells that preferentially express CD44 species with decreased affinity for hyaluronic acid (3).

To further exclude a direct cytotoxic effect of anti-CD44 antibody in vivo, we determined whether antibody treatment was capable of inhibiting the growth of ovarian cancer cells grown s.c., as opposed to i.p., in nude mice. Two groups of 10 preirradiated mice each received a s.c. injection of 0.5 x 10^6 UPN36T ovarian cancer cells, which strongly express CD44H, into the right flank and were allowed to form a palpable tumor nodule measuring ~5 mm^2 (occurring after a mean of 18 days). The mice were then treated with 40 μg of either anti-D144 or anti-CD44 antibodies i.p. in 0.5 ml of PBS for a total of 10 doses equally spaced over a 3-week period during which tumor measurements were made. As shown in Fig. 4, there was no difference in the growth rate of s.c. tumor nodules in either treatment group, suggesting that the presence of anti-CD44 antibody by itself did not mediate an antiproliferative or cytotoxic effect in this system. To ensure that antibody delivered via the i.p. route was bioavailable to the tumor cells in these experiments, tumor nodules were excised 1 h after i.p. antibody injection, and the presence of tumor-associated anti-CD44 antibody was determined by staining cryostat sections with rabbit anti-mouse antibody, with subsequent detection by the APAAP technique (2). Strong reactivity of rabbit anti-mouse antibody was observed only in tumor tissue obtained from anti-CD44-treated mice, demonstrating that anti-CD44 antibody is bioavailable to tumor cells within the subcutis and that localization is CD44-specific (data not shown).

A possible role for CD44H in mediating ovarian cancer metastasis was first suggested by its ability to promote in vitro attachment of tumor cells to peritoneal mesothelial monolayers through the recognition of mesothelial-associated hyaluronic acid (2). Because adhesion of tumor cells to the peritoneal mesothelium is a critical early step in ovarian cancer cell metastasis, we were interested in determining the physiological relevance of these observations for the process of peritoneal implantation in vivo. Although many epithelial carcinoma cell lines are capable of growing within the murine peritoneal cavity, they often produce a dominant intra-abdominal mass and ascites, resulting in animal death due to bowel obstruction within a few weeks after inoculation. We have found that this short period of time is often insufficient for producing the numerous and easily quantifiable nodules typical of human ovarian cancer. In contrast, the 36M2 human ovarian cancer cell line used in this study was selected for its ability to diffusely implant onto murine peritoneal mesothelium in the absence of a dominant mass or ascites, resulting in the formation of nodules that could be easily quantitated at 5 weeks (Fig. 2). This xenograft model has allowed us to demonstrate an important role for the CD44 molecule in ovarian cancer cell metastasis and to show that it is feasible to limit ovarian cancer cell implantation through the use of neutralizing anti-CD44 antibody.

The ability to significantly reduce the number of implants in mice treated with anti-CD44 antibody most likely represents a specific effect on implantation for several reasons: (a) treatment with a reactive isotype-identical antibody (anti-DF3) exerted no effect on tumor implant formation, thus excluding an important role for ADCC in this phenomenon (Figs. 1 and 2). The absence of ADCC is also consistent with the use of IgG1 isotype antibodies in these studies; (b) the lack of effect of anti-CD44 antibody on the growth of CD44-positive tumor nodules grown s.c., as opposed to i.p., again argues against a major role for either ADCC or natural killer cell-mediated cytotoxicity (Fig. 4); and (c) none of the antibodies used in this study inhibited the growth of ovarian cancer cells in vitro, reducing the likelihood of a direct antiproliferative effect of anti-CD44 antibody on tumor nodular formation in vivo. This conclusion is also supported by the observation that the size of tumor nodules present in anti-CD44 antibody-treated mice was equivalent to those present in control animals, suggesting that once implantation occurred, the growth of
NOVEL ROLE FOR CD44 IN PERITONEAL TUMOR IMPLANTATION

Fig. 3. Characterization of 36M2 subclones derived from residual implants in treated mice. Implants were excised and expanded in vitro as described in the text to determine whether differences existed in CD44 expression and function between 36M2 cells derived from the three treatment groups. 36M2 (original) refers to the line used at the time of the initial i.p. inoculation. 36M2 (D144), 36M2 (DF3), and 36M2 (CD44) refer to subclones later isolated from anti-D144, anti-DF3, and anti-CD44 antibody-treated mice, respectively. A, immunoblot developed with anti-CD44 antibody, showing predominant expression of a 90-kDa species characteristic of CD44H in 36M2 cells and the presence of higher molecular weight CD44 species characteristic of splice variants in SW626 as described previously. B, in vitro binding of 36M2 subclones to confluent layers of mesothelial cells, revealing equivalent amounts of CD44-dependent binding in cells derived from each of the three treatment groups.

ovarian cancer cells proceeded normally despite the presence of anti-CD44 antibody.

We have previously shown that it is not possible to completely inhibit ovarian cancer cell adhesion to mesothelium in the presence of anti-CD44 antibody, suggesting that other adhesion molecules may be involved in the implantation process (2, 3). We therefore considered the possibility that treatment with anti-CD44 antibody might select for tumor implants that are relatively deficient in CD44 expression and that bind to mesothelium through a CD44-independent mechanism. However, 36M2 subclones obtained from each treatment group showed equivalent levels of CD44H expression and of CD44-dependent adhesion to mesothelium in vitro (Fig. 3). These data suggest that the presence of tumor implants in mice treated with anti-CD44 anti-
UPN36T ovarian cancer cells, which strongly express CD44H(2), into the right flank and group. Data are expressed as mean ± SE tumor surface area at the indicated time points in the presence of overlying skin necrosis in the majority of animals from each treatment area, at the indicated time points. The experiment was discontinued after 55 days due to the product of perpendicular tumor diameters, which is proportional to the tumor surface area, as described in the text, followed by determination of antibody proceeded over 3 weeks as described in the text, followed by determination of the product of perpendicular tumor diameters, which is proportional to the tumor surface area, at the indicated time points. The experiment was discontinued after 55 days due to the presence of overlying skin necrosis in the majority of animals from each treatment group. Data are expressed as mean ± SE tumor surface area at the indicated time points (n = 10/group).

body reflects incomplete inhibition of CD44 rather than selection of cells with diminished CD44 expression or function. The fact that anti-CD44 antibody was less efficient at inhibiting the formation of diaphragmatic implants compared to other peritoneal sites suggests that the effectiveness of neutralizing antibody may be dependent upon the distribution of this reagent within the peritoneal cavity.

Previous investigators have suggested that CD44 may be involved in the hematogenous spread of malignant cells (5–7). For instance, CD44H-expressing transfecants of Namalwa cells exhibit an increased rate of metastasis when the cells are injected i.v., and this effect is inhibited in the presence of soluble CD44H-immunoglobulin fusion protein (5, 6). Interestingly, certain splice variants of the CD44 molecule, such as CD44E, do not seem to enhance hematogenous metastasis, suggesting that the standard 90-kDa CD44H protein is a major determinant of malignant potential in at least certain animal tumor models (5). Nevertheless, other studies have suggested that expression of certain forms of CD44 splice variants, such as those containing exon 6, may increase the likelihood of distant metastasis (8–10). Also, CD44 splice variant expression may be associated with a worse prognosis in certain forms of human malignancy such as lymphoma (9) and colorectal cancer (11), although this is not a universal phenomenon (12, 13). Taken together, these data suggest that both standard CD44H and its splice variants may contribute to the process of distant metastasis, although the mechanism by which these molecules mediate hematogenous or lymphatic spread is not fully understood. It is important to note that ovarian cancer is distinct from many other epithelial malignancies in that it typically remains confined to the peritoneal cavity and does not usually spread via the hematogenous route. Thus, in contrast to previous reports, the data presented in this paper suggest a novel and distinct role for the CD44 molecule in the metastatic process, specifically by mediating an early step (implantation) in ovarian cancer spread.

In summary, our data suggest that the CD44 molecule plays an important role in human ovarian cancer metastasis and that i.p. administration of agents that inhibit CD44 function may represent a potentially useful strategy for the treatment of patients with this disease. Because most patients present with disseminated tumor at the time of diagnosis, it is possible that this approach might be most beneficial as an adjunct to surgery and chemotherapy in an attempt to prevent or delay recurrence of peritoneal implants. Although not the goal of the present study, it will be important to determine which dose and schedule of anti-CD44 antibody treatment will produce optimal inhibition of implantation and whether anti-CD44 antibody treatment can affect the survival of mice with pre-established intra-abdominal tumor.

References

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