Colorectal cancer, one of the most prevalent cancers worldwide (1), is the second leading cause of cancer-related mortality in developed countries (1–4). Whereas mortality (rate, ~50%) can be prevented by surgical resection of the involved bowel before tumor cell dissemination (2–5), ~61% of patients have metastatic disease at presentation (Fig. 1A, inset) and ~90% of those patients die within 5 years of diagnosis (Fig. 1A; ref. 2). Moreover, adjuvant chemotherapy for metastatic colorectal cancer increases median survival by only ~14 months (6). These observations highlight the unmet need for rationally designed targeted therapeutic interventions to manage the metastatic process in colorectal cancer patients.

Matrix metalloproteinase 9 (MMP-9) is a zinc-dependent extracellular protease which regulates metastatic progression in colorectal cancer (7–9). Also termed the 92-kDa type IV collagenase or gelatinase B, MMP-9 degrades basement membrane collagen type IV, allowing epithelial cancer cells to invade the adjacent stromal compartment (10, 11). MMP-9 promotes cancer progression by regulating physiologically based processes co-opted during metastasis, including cell adhesion, migration, tissue invasion, intravasation and extravasation, and angiogenesis (7, 12, 13).

Although MMP-9 expression is increased in colorectal tumors compared with normal tissues (14, 15), colorectal cancer cells with high metastatic potential do not express or secrete functional MMP-9 in vitro. Indeed, MMP-9 expression has been localized in the tumor stroma, mainly in fibroblasts and inflammatory cells (15, 16). Thus, the current paradigm suggests that cancer cells stimulate stromal fibroblasts (17)
and tumor-infiltrating inflammatory cells (18, 19) to secrete MMP-9, which in turn contributes to the metastatic activity of the cancer cells. In this model, cancer cells exploit a physiologic mechanism for their metastatic dissemination because stromal cell MMP-9 is central to inflammation (20) and wound healing (21, 22).

Clinical trials with broad-spectrum MMP inhibitors in cancer patients have shown no therapeutic efficacy due, in part, to their lack of specificity for tumor-associated MMPs and tumor-dependent pathophysiologic processes (23, 24). In this regard, the current paradigm, in which MMP-9-mediated metastasis is the product of stromal reaction to tumor formation, may represent an obstacle to the development of effective anti-metastatic therapies by focusing on the inhibition of potentially protective antitumor host-defense mechanisms (20–22) rather than targeting tumor-specific pathophysiologic. In contrast, the present work reveals that human colorectal cancer cells from patients express MMP-9, which mediates discreet processes underlying metastasis, from secretion of functional gelatinase B associated with matrix degradation, through cell locomotion, to the hematogenous seeding of parenchymal organs. Expression of this enzyme by cancer cells, which is central to mechanisms underlying metastasis, provides a previously unrecognized opportunity to develop effective therapeutic approaches against colorectal cancer dissemination specifically targeting cancer cell MMP-9.

Materials and Methods

Cell culture and clinical specimens. T84, SW480, and CaCo2 human colon carcinoma cells (American Type Culture Collection, Manassas, VA) were cultured at 37°C, 5% CO2 with DMEM:Ham’s F-12 medium containing 10% fetal bovine serum. Surgical specimens from 28 patients (Table 1) with adenocarcinomas of the colon or rectum were obtained from the Department Pathology, Anatomy, and Cell Biology of Thomas Jefferson University under a protocol approved by the Institutional Review Board (Thomas Jefferson University, Philadelphia, PA). Adenocarcinomas and normal adjacent tissues were confirmed by histopathology.

Real-time reverse transcription-PCR. Surgical specimens were placed in RNA-Later (Ambion, Inc., Austin, TX) immediately following resection and stored at −80°C until analyses. Total RNA from clinical samples and cells in culture obtained with the Qiagen RNA Easy kit (Qiagen, Valencia, CA) were subjected to one-step reverse transcription-PCR (RT-PCR) on a 7000 Sequence Detection System for 45 cycles (95°C, 5 minutes; 94°C, 20 seconds; 62°C, 1 minute) using TaqMan EZ RT-PCR Core Reagents according to the protocol of the manufacturer (Applied Biosystems, Inc., Foster City, CA). MMP-9 mRNA was detected

Table 1. Clinical data for patients with colorectal cancer

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Median (range)</th>
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<tr>
<td>Gender (%)</td>
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<td>12 (43)</td>
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<tr>
<td></td>
<td>Female</td>
<td>16 (57)</td>
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<tr>
<td>Tumor site (%)</td>
<td>Colon</td>
<td>24 (86)</td>
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<tr>
<td></td>
<td>Rectum</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Dukes’ Tumor stage</td>
<td>A</td>
<td>4 (14)</td>
</tr>
<tr>
<td></td>
<td>B1</td>
<td>5 (18)</td>
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<td></td>
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<td></td>
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<td>8 (29)</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>4 (14)</td>
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<tr>
<td>Differentiation grade (%)</td>
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<tr>
<td>Tumor depth* (%)</td>
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<td>4 (14)</td>
</tr>
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<td></td>
<td>T2</td>
<td>6 (22)</td>
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<td></td>
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<tr>
<td>Distant metastasis (%)</td>
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<td>4 (14)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24 (86)</td>
</tr>
</tbody>
</table>

*T1, limited to mucosa and submucosa; T2, invading the muscularis; T3, invading the serosa or adjacent organs.
and quantified with a commercially available fluorescently labeled primer/probe set (Assay on Demand, Applied Biosystems). Data were analyzed using Sequence Detection Software (Applied Biosystems) with thresholds set at 0.2. Template-negative controls were run on each PCR plate. mRNA levels were normalized to total RNA, quantified by spectrophotometry, rather than to a housekeeping gene, reflecting the variability of gene expression in different cells, tissues, and patients and the general acceptance of normalization to amount of total RNA analyzed (25).

**Laser capture microdissection.** Tissue samples were flash frozen and sectioned on a cryostat. Tissue sections, neither fixed nor stained to preserve nucleic acid integrity, were mounted on a PixCell IIe microscope (Arcturus Bioscience, Mountain View, CA) over a collection vial. A clinical pathologist, trained in laser capture microdissection, identified and captured cells of interest using a focused low-intensity laser (diameter, 4 μm). Laser capture microdissection—collected tumor epithelial and stromal cells (~250 each) were then subjected to realtime RT-PCR to detect MMP-9.

**Colloidal gold-labeled immunoelectron microscopy.** Fresh surgical specimens were fixed in 4% parformaldehyde and 0.2% glutaraldehyde in 0.1 M sodium cacodylate buffer, dehydrated in graded alcohol, embedded in LRWhite resin, and cured at ~20°C under a long wave UV lamp. Ultrathin sections (90 nm) were collected on nickel grids using a Leica FCS microscope and incubated for 1 hour at room temperature with blocking buffer (1% ovalbumin and 0.2% cold water fish skin gelatin in 10 mmol/L sodium phosphate buffer with 0.9% NaCl, pH 7.4). Immunostaining for human MMP-9 was done overnight at room temperature using a rabbit polyclonal antibody (Biomol, Plymouth Meeting, PA; 1:100) or a mouse monoclonal antibody (Chemicon International, Temecula, CA; 1:10). Immunodetection was done for 1 hour at room temperature with 15 nmol/L gold-labeled antirabbit or antimouse immunoglobulin G antibody (Rockland Immunocchemicals, Gilbertsville, PA). Nonimmune rabbit or mouse immunoglobulin G or secondary antibody alone was used as control. Sections were examined with the Joel Jem 1010 electron microscope and images were collected with a Hamamatsu CCD powered by AMT HR-12 software.

**Immunoblot analysis.** Proteins from cell lysates or conditioned media prepared in SDS sample buffer were separated by electrophoresis on 10% acrylamide Tris-glycine gels, transferred on nitrocellulose membranes, and then probed with a rabbit polyclonal antibody directed against human MMP-9 (dilution, 1:1,000) in TBS-Tween (5% milk) overnight at 4°C. After washing the primary antibody (3 × 15 minutes with TBS-Tween), membranes were probed with goat anti-rabbit immunoglobulin G antibody (dilution, 1:2,000) in TBS-Tween (5% milk) for 1 hour at room temperature, and then washed again (3 × 15 minutes with TBS-Tween). Immunostained bands were visualized by autoradiography using horseradish peroxidase and quantified by densitometry.

**Gelatin zymography.** Conditioned media (500 μL) from T84 cell incubations (24 hours in serum-free media) were concentrated using Centricron protein concentration kits (Millipore Corporation, Bedford, MA) and resolved on 0.1% gelatin, 10% acrylamide electrophoretic gels. Proteins were resolved under denaturing conditions, renatured for 1 hour, and incubated for 18 hours (37°C) in buffer containing 50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, and 5 mmol/L CaCl2. Gelatinolytic activity was visualized by Coomassie blue staining and quantified by densitometry (15, 19). Where indicated, the tissue inhibitor of matrix metalloproteinase 1 (TIMP-1; Chemicon International) was dissolved in PBS and included in incubations.

**Cell spreading.** Adherent T84 cells were treated for 24 hours in serum-free media, harvested using 0.05% Trypsin-EDTA, and plated in T25 flasks at 5 × 104/mL. After 6 hours, the number of cells that formed distinct pseudopodia was scored by a blinded evaluator as the fraction of total cell number per microscopic field (~100 cells) of an inverted microscope (10×/1× lens). The specific MMP-9 inhibitor I and MMP-2 inhibitor I (Calbiochem, San Diego, CA) were prepared in DMSO and used at a concentration near the reported Ki [0.9 nmol/L (26) and 17 μmol/L (27), respectively]. Purified human recombinant active (67-kDa form) MMP-9 was purchased from Calbiochem whereas human recombinant pro-MMP-9 was expressed in HeLa cells and purified to homogeneity as previously described (28).

**Tumor cell seeding of mouse lungs in vivo.** T84 cells (~75% confluence) were experimentally treated as indicated. Following incubation, cells were washed (three in PBS), fluorescently labeled (30 minutes, 37°C in serum-free media) with 0.2 μmol/L Mito-Tracker Red CMXRoX (Molecular Probes, Inc, Eugene, OR), washed again (twice in PBS), and harvested with 0.05% trypsin-EDTA. Cells (6 × 105/mL) were resuspended in serum-free medium and injected into the inferior vena cava of anesthetized (Nembutal, Abbott Laboratories, North Chicago, IL) female nu/nu mice (4-6 weeks old; Taconic Farms, Germantown, NY) artificially ventilated by a pressure-controlled ventilator (Kent Scientific Corporation, Torrington, CT) through a tracheotomy. Five minutes after injection, lungs were cleared of blood by gravity perfusion through the pulmonary artery with Kreb-Ringer bicarbonate buffer (5% dextran, 10 mmol/L glucose, pH 7.4), excised and placed onto a slide chamber with ports for the tracheal cannula, and inflated with 5% CO2 in air (29). Fluorescent tumor cells attached to pulmonary vessels were detected using a Leica DMRB inverted fluorescent research microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Germany) and quantified by

**Fig. 2.** Tumor cell and stroma cells from colorectal tumors express equivalent amounts of MMP-9. A, stromal and cancer cells (~250) from primary colorectal tumors were isolated by laser capture microdissection. B, MMP-9 mRNA was quantified by RT-PCR in total RNA recovered from stromal and epithelial cells isolated by laser capture microdissection from primary colorectal tumors. Values represent relative copies of MMP-9 mRNA quantified as 2(ΔΔCt)/250 cells, where 41.32 is the y intercept of the standard curve for MMP-9 generated with serial dilution of T84 human colon carcinoma cells and Ct is the sample threshold cycle number. NTC, nontemplate control.
scanning 45 consecutive fields (OpenLab program, Improvison, Boston, MA) obtained with 10×/1× lens (1.1 mm² of field/picture) from the left lobe of the lung.

**Statistical analysis.** Unless otherwise indicated, data were expressed as the mean (SD) of at least three independent experiments. Statistical analyses were done employing the Student’s *t* test.

**Results**

All 28 patients (Table 1) expressed MMP-9 mRNA by real-time RT-PCR in tumor and normal adjacent tissues (Fig. 1B, left). In most (~82%) patients, MMP-9 expression was, on average, ~4-fold greater in tumors compared with matched normal mucosa (410.30 ± 140.10 versus 93.76 ± 36.20 × 10³ copies of MMP-9 mRNA; *P* < 0.05; Fig. 1B, right). Harvesting specific cell populations within colorectal tumors employing laser capture microdissection (Fig. 2A) revealed that epithelial and stromal cells expressed equivalent quantities of MMP-9 mRNA (Fig. 2B). Moreover, colloidal gold-labeled immunoelectron microscopy employing rabbit polyclonal antibody raised against a pro-MMP-9 peptide revealed MMP-9 protein in normal (Fig. 3A and B) and neoplastic (Fig. 3D) epithelial cells but not in mucin-enriched goblet cells (Fig. 3A). In colorectal cancer cells (Fig. 3C), MMP-9 distributed throughout the cytoplasm and brush border membrane (Fig. 3D) in a pattern that resembled that of normal colonocytes (Fig. 3B). Intracellular MMP-9 immunostaining of colonocytes and colorectal cancer cells also was obtained with a mouse monoclonal antibody against the catalytic domain of MMP-9 (data not shown). Conversely, MMP-9 could not be detected in sections stained in the absence of primary antibody (Fig. 3E), highlighting the specificity of this technique. Taken together, these observations show that, in contrast to the current paradigm, MMP-9 mRNA and protein are expressed in human colorectal cancer cells.

Consistent with the finding in the tumor samples, human colorectal cancer cell lines in vitro expressed MMP-9 mRNA (Fig. 4A), resulting in the synthesis and secretion of pro-MMP-9 (92 kDa in Fig. 4B; only T84 cells shown). Active MMP-9 (84 kDa) also was detected in the media as determined by gelatin zymography (Fig. 4C). The gelatinolytic activity of MMP-9 secreted by colorectal cancer cells, involved in matrix degradation, was inhibited in a concentration-dependent fashion by the specific endogenous inhibitor TIMP-1 (Fig. 4D). Moreover, TIMP-1 and a specific small-molecule inhibitor of MMP-9, MMP-9 inhibitor I, significantly reduced locomotory organelle (pseudopodia, lamellipodia)–driven cell spreading (12) in colorectal cancer cells (Fig. 4E), suggesting that MMP-9 activity is involved in this process associated with the metastatic phenotype. Indeed, exogenous administration of either the pro or active form of MMP-9 rescued the ability of colorectal cancer cells to extend lamellipodia whereas the specific inhibitor of MMP-2, MMP-2 inhibitor I, had no effect (Fig. 4E). Interestingly, addition of the active form of MMP-9 did not further promote the spreading of colorectal cancer cells (Fig. 4E), indicating that the catalytic activity of endogenous MMP-9 is sufficient for maximum cancer cell locomotion.

Whereas specific adhesion of circulating cancer cells to select tissue components accessible in the microvasculature of parenchymal organs is central to metastatic dissemination of tumors (Fig. 5A; ref. 29), a role for MMP-9 in hematogenous seeding by human colorectal tumor cells has not been explored previously. Indeed, human colorectal cancer cells attached to the microvasculature in lungs following injection into the inferior vena cava of mice (Fig. 5B and C). However, treating cancer cells in vitro with small-molecule inhibitors of MMP-9 or TIMP-1 blocked their ability to seed mouse lungs in vivo, an effect that was rescued by the addition of purified human pro-MMP-9 (Fig. 5D). These observations reveal a role for catalytically active MMP-9 produced by tumor epithelial cells in hematogenous seeding of parenchymal organs, a critical step in the metastatic progression of colorectal cancer.

![MMP-9 expression in colorectal cancer](image-url)
Discussion

Colorectal cancer progression reflects at least two mechanistically discreet and clinically distinct processes, including local proliferation and metastasis. Whereas the former can be effectively treated surgically, the latter defines the primary pathogenetic mechanism associated with mortality, and the vast majority of patients with distant metastases die within 5 years of diagnosis (Fig. 1A; refs. 2–5). Metastasis is mediated by discreet sequential rate-limiting steps, including invasion and migration; intravasation and systemic distribution of cancer cells; and seeding, colonization, and proliferation in capillary...

Fig. 4. Human colon cancer cells secrete functional MMP-9. A, MMP-9 mRNA was quantified by RT-PCR in three human colon carcinoma cell lines. Relative copy numbers of MMP-9 mRNA were quantified as $2^{\Delta C_{\text{t}}}$, where $\Delta C_{\text{t}}$ is the y intercept of the standard curve for MMP-9 generated with serial dilution of T84 human colon carcinoma cells and Ct is the sample threshold cycle number. Further, Western blot (B) and gelatin zymography (C) showed that T84 cells synthesize the 92-kDa pro-MMP-9 (B), which is secreted into the extracellular space (B and C) and converted into the active 84 kDa form (C). Quantification of bands in the zymogram by densitometry (D) revealed that the endogenous MMP-9 inhibitor TIMP-1 suppresses the gelatinolytic activity of T84 cell MMP-9 in a dose-dependent fashion. **, $P < 0.01$; ***, $P < 0.001$, two-tailed paired t test. E, development of locomotory organelles by T84 cells was quantified as the ratio of cells extending lamellipodia versus the total cell number per microscopic field with a 10×/1× lens of an inverted microscope. The specific synthetic MMP-9 inhibitor I (\(\text{iMMP-9}, 0.9\) nmol/L), but not the MMP-2 inhibitor I (\(\text{iMMP-2}, 17\) μmol/L), and the endogenous MMP-9 inhibitor TIMP-1 (40 ng/mL) attenuated the ability of cells to extend lamellipodia. MMP-9-mediated cell spreading was rescued by addition of 500 ng/mL of either the pro form (\(\text{MMP-9}\)) or the active form (\(\text{aMMP-9}\)) of MMP-9. Data are from a representative experiment done in triplicate and repeated thrice, and represent percent inhibition of cell spreading obtained with the respective vehicle-treated control cells. ***, $P < 0.001$, two-tailed unpaired t test.

Fig. 5. MMP-9 regulates hematogenous seeding of mouse lungs by human colon cancer cells in vivo. A, schematic representation of the subpleural vasculature of mouse lungs. A, arteriole; V, post-capillary venule; C, capillary; ALV, alveolus. B and C, MitoTracker-stained T84 cells (arrows) attach to the endothelium of mouse lung pre-capillary arteriole (B) and capillary (C) 5 minutes after injection into the inferior vena cava. D, treatment of T84 human colon cancer cells in vitro (24 hours in serum-free media) with a broad MMP inhibitor (BB94, 60 nmol/L), the endogenous MMP-9 inhibitor TIMP-1 (40 ng/mL), or the selective MMP-9 inhibitor I (\(\text{iMMP-9}, 0.9\) nmol/L) reduced their ability to seed mouse lungs in vivo, an effect that was reversed by addition of purified human pro-MMP-9 during the last 2 hours of incubations (MMP-9, 500 ng/mL; D, bottom). D, top, representative inverted fluorescence microscope fields of control cancer cells and of cells treated with MMP-9 inhibitor I. Bar, 32 μm (B and C) and 200 μm (D). ***, $P < 0.001$, two-tailed unpaired t test.
MMP-9 Is a Target in Colorectal Cancer Metastasis

Pihl E, Hughes ES, McDermott FT, Milne BJ, Price  

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The central importance in mechanisms underlying metastasis suggests that MMP-9 could be a key therapeutic target in patients with colorectal cancer. Surprisingly, MMP-directed therapies generally have been unsuccessful in inhibiting metastatic progression (23, 24). One obstacle to this therapeutic approach may be the current paradigm in matrix biology that fibroblasts and macrophages of the tumor stroma express MMP-9 rather than cancer cells that seed distant organs (14–19). Indeed, the stromal reaction to tumor formation may represent a potentially protective antitumor host-defense mechanism (20–22), and general MMP-directed therapies that are otherwise untargeted with respect to the source of enzyme may abrogate those critical adaptive antitumor mechanisms.

In contrast to the prevailing paradigm, the present observations reveal that human cancer cells in colorectal tumors from patients express MMP-9 mRNA and protein. Absence of MMP-9 expression in colorectal cancer cells in earlier studies likely reflects the relative insensitivity of standard immunohistochemical and Northern blot analyses which cannot precisely determine the cellular source of the protein expression (14, 16). Here, MMP-9 mRNA expression was quantified specifically in cancer cells isolated from tumors by laser capture microdissection employing RT-PCR. Further, MMP-9 protein was visualized directly within cancer cells in tumors by immunogold electron microscopy. Moreover, MMP-9 produced by tumor cells was catalytically active and mediated formation of locomotory organelles associated with cell spreading and the hematogenous seeding of mouse lungs, all critical steps in metastasis. The present results are particularly significant because they reveal a previously unrecognized mechanism-based tumor-specific target, MMP-9 expressed in cancer cells, for treating metastasis in colorectal cancer patients. In that context, disruption of MMP-9 expression and/or function specifically in cancer cells may represent a more specific therapeutic strategy to prevent the metastatic process than the use of general MMP-9 inhibitors, which may also abrogate adaptive antitumor mechanisms (20–22). Indeed, strategies to target tumor-produced, but not stroma-produced, MMP-9 are being developed in this laboratory.

Beyond processes central to invasion and extravasation of cancer cells in primary colorectal tumors, the precise role of MMP-9 in establishing metastases at distant sites has not been clear, particularly because those cells presumably do not express that enzyme. However, tumorigenic rodent cells transiently expressing MMP-9 established significantly more metastatic colonies than parent MMP-9-null cells in a mouse model of hematogenous metastasis to lung (7). Similarly, infusion of the MMP-9 inhibitor TIMP-1 with melanoma cells reduced the number of pulmonary metastases developed by hematogenous dissemination in mice (33). Taken together, these observations suggest that MMP-9 expressed by cancer cells plays a role in early events establishing parenchymal metastases (7). The earliest events in metastatic seeding involve adherence of tumor cells to exposed basement membrane components and their subsequent spread on the endothelium in the vasculature of target parenchymal organs (30, 34). Here, MMP-9 was required for maximum hematogenous seeding of human colorectal cancer cells in mouse lungs. Indeed, inhibitors of MMP-9 blocked the ability of colorectal cancer cells to adhere to the pulmonary vasculature within a 5-minute window. Further, adherence to the pulmonary vasculature blocked by inhibitors was rescued by addition of purified MMP-9. Although the precise molecular mechanisms remain undefined, these observations reveal an unexpected central role for colon cancer cell MMP-9 in hematogenous seeding of parenchymal organs, specifically by affecting the earliest events underlying vascular adherence. Moreover, they bridge an unfilled gap by providing a novel in vivo model to explore the role of MMP-9 expressed by cancer cells and its suitability as a therapeutic target in the progression of metastases in colorectal cancer (23).

In summary, the present observations that the catalytic activity of endogenously expressed MMP-9 regulates the ability of cancer cells to degrade extracellular matrix components, mobilize locomotory organelles, and seed distant organs independently of components contributed by stromal cells offer an ideal candidate for targeted antimetastatic therapy for colorectal cancer. Indeed, pharmacologically silencing MMP-9 expressed by colorectal tumor cells inhibits discreet indices which contribute to their malignant phenotype. Interventional strategies that selectively disrupt cancer cell MMP-9 expression and/or function may reduce the mortality, and improve the management, of patients with colorectal cancer.

References
