Targeting Matrilysin and Its Impact on Tumor Growth In vivo: The Potential Implications in Breast Cancer Therapy


Abstract

Introduction: Matrilysin (MMP-7) is a metalloproteinase that is involved in the degradation of extracellular matrix, invasion, and tumor progression. The current study examined if targeting matrilysin using retroviral ribozyme transgenes may have an impact on breast cancer cells and may have clinical implications.

Experimental Design: Retroviral hammerhead ribozyme transgenes were designed to specifically target human matrilysin mRNA. The breast cancer cell MDA-MB-231 was transfected with either a retroviral matrilysin transgene or a control retroviral transgene. Stably transfected cells were tested for their invasiveness and migratory properties in vitro. The cells were also used in creating a tumor model in athymic nude mice in which the growth of tumors and levels of matrilysin were assessed. In addition, levels of both protein and mRNA of matrilysin were investigated in a cohort of human breast tumors.

Results: Expression of matrilysin in MDA-MB-231 was successfully eliminated by the retroviral hammerhead ribozyme transgene for matrilysin as revealed by reverse transcription-PCR. Matrilysin transgene – transduced cancer cells (MDA-MB-231ΔMatrilysin) exhibited a significantly lower degree of invasion (number of invading cells 16.0 ± 2.5) compared with wild type (MDA-MB-231WT, 26.2 ± 6.2, P < 0.05) or control transgene-transduced cancer cells (MDA-MB-231ΔRevTRE, 25.3 ± 4.2, P < 0.01). However, the rate of growth of the cells in vitro was not significantly affected. In the in vivo tumor model, MDA-MB-231ΔMatrilysin tumors, which had very low levels of immunoreactive matrilysin, grew at a significantly lower rate (0.24 ± 0.03 cm³, 4 weeks after inoculation) compared with the wild-type MDA-MB-231WT (1.46 ± 0.04 cm³) and MDA-MB-231ΔRevTRE (1.12 ± 1.0 cm³) tumors. In human breast tumors, breast cancer cells stained matrilysin at a significantly higher density, compared with normal mammary epithelium. The highest level of matrilysin was seen in high-grade tumors and that from patients with moderate and poor prognosis. Finally, high levels of matrilysin were significantly linked with a poor long-term survival (P = 0.0143).

Conclusion: Matrilysin, which is aberrantly expressed in human breast tumors, can be effectively eliminated from breast cancer cells by way of hammerhead ribozyme transgene. Elimination of matrilysin is associated with low invasiveness and slow tumor growth. Taken together, the study suggests that targeting matrilysin may have important therapeutic implications.

Matrilysin (MMP-7, putative metalloproteinase I, PUMP1) gene was identified through studies of collagenase-related connective tissue–degrading metalloproteinases produced by human tumors (1). MMP-7, by acting as a proteolytic enzyme, has been indicated in the invasiveness and progression of cancer cells. Matrilysin cleaves extracellular matrix and basement membrane proteins, such as fibronectin, collagen type IV, laminin, and, particularly, elastin, entactin, osteopontin, and cartilage proteoglycan aggregates. Furthermore, matrilysin seems to mediate the proteolytic processing of other molecules (e.g., tumor necrosis factor α precursor, urokinase plasminogen activator; refs. 2, 3).

The promoter region of the matrilysin gene contains typical MMP promoter elements, such as AP-1 and PEA3, which mediate responsiveness to growth factors, oncoproteins, and phorbol esters. The transcription relation of matrilysin also requires the LEF-1/β-catenin pathways (4, 5). Matrilysin protein localizes to secretory and ductal epithelium in the endometrium and in various exocrine glands. In the mouse, high constitutive levels of matrilysin mRNA are found in epithelial cells in the uterus, small intestine, and extratesticular ducts, suggesting that matrilysin may have a specific role in normal gland and organ function, a
possibility that can be explored further by the genetic manipulation of matrilysin levels in vivo. Antisense oligonucleotide to matrilysin has been shown to reduce the metastasis of colon cancer to liver in a mouse model (6).

Matrilysin is also able to cleave integrins on the surface of cancer cells, including breast cancer cells (7). Matrilysin forms a complex with CD44 at the cell surface of cancer cells, possibly to coordinate the matrix degradation process by cancer cells (8). Matrilysin can also cleave E-cadherin to induce the invasive potential of cancer cells (9, 10). Matrilysin is involved in the development of mammary gland (11, 12). In breast cancer, matrilysin was claimed to have no association with other classic clinical parameters, such as age, menopausal status, stage, size, nodal status, vascular infiltrate, necrosis, steroid receptors, metastasis, and survival (n = 81, follow-up 40 months; ref. 13). In breast tissues, matrilysin was expressed by morphologically normal epithelial ducts within tumors and in tissue from reduction mammoplasties and by epithelial-derived tumor cells (14).

Despite the progress in this area, the potential role of MMP-7 in human breast cancer, and particularly in clinical breast cancer, has not been thoroughly investigated. For example, the limited information available in the literature was based on a small cohort and a short period of follow-up. There have been no conclusive reports to show the link between matrilysin and clinical outcome. In addition, no reports are yet available on attempting to target matrilysin using ribozyme transgenes. In the current study, we have shown that by knocking-down the expression of matrilysin from breast cancer cells using ribozyme transgenes, the invasiveness of the cancer was greatly reduced. Furthermore, the matrilysin knockdown cells displayed a significant reduction in the growth in a nude mouse model. The study went on to show that patients with breast cancer had a significantly poor long-term (10 years) survival when matrilysin was expressed at a higher level.

**Materials and Methods**

Human mammary cancer cells, MDA-MB-231 was from the European Collection of Animal Cell Culture (Salisbury, England) and were routinely maintained in DMEM F12 with 10% FCS. Recombinant human hepatocyte growth factor/scatter factor was a gift from Dr. T. Nakamura (Osaka University Medical School, Osaka, Japan). Matrigel (reconstituted basement membrane) was purchased from Collaborative Research Products (Bedford, MA). Doxycycline was from Clontech Laboratories (Palo Alto, CA) and Sigma (Poole, Dorset, England, United Kingdom), respectively. A chemiluminescence detection kit for Western blotting conjugated anti-IgG were from Santa Cruz Biotechnologies (Santa Cruz, CA) and Sigma (Poole, Dorset, England, United Kingdom). DNA gel extraction and plasmid extraction kits were from Qiagen (Crawley, England, United Kingdom). DNA and protein A/G conjugate were from Santa Cruz Biotechnologies. A chemiluminescence detection kit for Western blotting (reconstituted basement membrane) was purchased from Collaborative Research Products (Bedford, MA). Doxycycline was from Clontech Laboratories (Palo Alto, CA) and Sigma (Poole, Dorset, England, United Kingdom). DNA gel extraction and plasmid extraction kits were from Qiagen (Crawley, England, United Kingdom).

Primary breast cancer tissues (n = 120) and normal tissues that were away from tumor tissues and free from cancer cells (n = 32) were collected immediately after surgery and stored in the deep freezer until use. Patients were routinely followed clinically after surgery. The median follow-up period was 120 months. The presence of tumor cells in the collected tissues was verified by examination of frozen sections using H&E staining. Details of the samples were previously described (15).

**Construction of retroviral hammerhead ribozyme transgenes targeting human matrilysin and generation of active viral hammerhead ribozymes.**

The procedure has been previously reported (16, 17). Briefly, the secondary structure of human matrilysin was generated using Zuker's RNA mFold software (18). A suitable GUC site within the matrilysin mRNA was identified. Touch-down PCR was used to generate PCR-based ribozyme (17) using the following primers: 5'-CGACTTG-CAGTAGGTCTGAGTTGCGCTCTGAGAAGACGCCATTTGCCGATGGCTCA-3' and 5'-CCATCACATGCATTTTGGCTCCTGCCGACTGATAGGC-3'. PvuI and SpeI restriction sites were introduced during the PCR reaction.

![Fig. 1](https://example.com/figure1.png)

**Fig. 1.** A, retroviral ribozyme transgenes successfully eliminated expression of matrilysin transcript from breast cancer cells. MDA-MB-231 wild-type cells expressed matrilysin transcript (top). A pREV-TRV-Matrilysin transgene successfully knocked down the expression of the transcript from the cells. B, matrilysin and invasiveness of breast cancer cells.
The above-generated antisense-hammerhead ribozymes, flanked by PstI and SpeI sites, were first T-A cloned into a pCR2.1 TOPO cloning vector (Invitrogen, Paisley, Scotland, United Kingdom), followed by amplification in the OneShot E. coli (Invitrogen). Bacterial clones with correct oriented insert were verified using PCR. Plasmid was subsequently purified from the bacterial preparation and dually digested using PstI and SpeI. The digests were separated on a 2% agarose gel, followed by purification of the respective ribozyme inserts from the gel.

Gel purified ribozymes (with PstI and SpeI overhangs) were then ligated into either pLXSN (RetroX, K1060) or pRevTRE292 vector (RevTet-On, K1267, Clontech Laboratories) using T4 DNA ligase. These vectors were modified in our laboratory by inserting a U1 promoter in front of the multicloning site from our previous work (a generous gift from Dr. J. Laterra, Department of Neurology, Kennedy Krieger Institute and Johns Hopkins School of Medicine, Baltimore, MD; ref. 19). Ligated products were used to transform JM109 E. coli. Bacterial clones with correctly ligated antimatri lyisin ribozyme, termed here as pRevTRE-MAT, and control plasmid (termed pRevTRE-cont) was subsequently identified. pRevTRE carried a tetracycline-responsive gene and were used throughout the in vitro and in vivo studies. pLXSN ribozymes were not used in the subsequent studies. The direction and sequence were verified using a plasmid-specific primer LXSNF, 5'-CCCTTGAACTCCTCCTCGTTCCACC-3', and U1-specific primers 5'-GGATCCGGCAACCGAAAAGT-3' (UBAMHR) and 5'-GTACGATTACAACCTAAGA-3' (UBAMHR).

Retroviral packaging and transduction of cells. Plasmid, extracted and purified using a plasmid extraction kit (Qiaprep, Qiagen), was introduced to a retroviral packaging cell line, PT67, using electroporation as previously described (19), followed by selection with G418 containing-medium for over 3 weeks. Viral titers from stably transduced PT67 cells were tested using NIH3T3 cells, and were found to be on average 8 × 10^5 cfu/mL. Active viral stocks (a combination of pRevTRE-MAT or control stock) and the pRevTet-On viral stock (separately generated from PT67) were used to transduce MDA-MB-231 mammary cancer cells in the presence of polybrene (8 μg/mL final concentration). Each transduction lasted 24 hours and three consecutive transductions were carried out. Transduced cells were subject to dual selection with G418 (for pRevTRE-MAT) and hygromycin (for pRevTet-On; Calbiochem, Nottingham, England, United Kingdom), each at 100 μg/mL for over 3 weeks to obtain stably transduced strains that carried both the

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Fig. 2. Reduction of tumor growth by the retroviral ribozyme transgene. A, growth of tumor cell variants over a 72-hour period. Shown are absorbances from stained cells. No difference was seen between three variant cells. B, tumor weight in grams at the end of the experiment. C, the volume of tumors over the experimental period. *, P < 0.05 versus tumor from MDA-MB-231WT. D, immunohistochemical staining of matrilysin in nude mouse tumors. a, tumor from MDA-MB-231WT; b, tumor from MDA-MB-231pRevTRE; c, tumor from MDA-MB-231Matrilysin.
inducing vector, pRevTet-On and expression vector pRevTRE-MAT (or control). These stably transduced and subsequently verified cell variants were designated the following names and are used throughout the text: MDA-MB-231 WT, MDA-MB-231 wild type; MDA-MB-231 pRevTRE, MDA-MB-231 transduced with pRevTRE empty vector; MDA-MB-231Dmatrilysin, MDA-MB-231 transduced with pRevTre-Matrilysin ribozyme transgene.

RNA preparation and reverse transcription-PCR. RNA from cells and tissues was extracted using an RNA extraction kit (AbGene, Ltd., Surrey, England, United Kingdom) and quantified using a spectrophotometer (Wolf Laboratories, York, England, United Kingdom). cDNA was synthesized using a first-strand synthesis with an oligo(dT) primer (AbGene). PCR primers were as follows: for matrilysin, MATF1, 5′-ATGCGACTCACCGT-3′, and MATR1, 5′-TGAATTACTTCTCTTTT-3′. The PCR was done using sets of primers with the following conditions: 5 minutes at 95°C, and then 20 seconds at 94°C to 25 seconds at 56°C, 50 seconds at 72°C for 36 cycles, and finally 72°C for 7 minutes. β-actin was amplified simultaneously using the following primers 5′-GCTGATTTGATGGAGTTGGA-3′ and 5′-TCAGCTACTTGTTCTTGAGTGAA-3′. PCR products were then separated on a 0.8% agarose gel, visualized under UV light, photographed using a Unisave camera (Wolf Laboratories) and documented with Photoshop software.

Quantitative analysis of matrilysin. The level of matrilysin transcripts from the above-prepared cDNA was determined using a real-time quantitative PCR, based on the Amplifluor technology, modified from previous reports (15, 20). Briefly, pairs of PCR primers were designed using the Beacon Designer (Palo Alto, CA) software (version 2), but to one of the primer, an additional sequence, known as the Z sequence (5′-ACTGAACCTGACCGTACA-3′), which is complementary to the universal Z probe (Intergen, Inc., Oxford, England, United Kingdom). A Taqman detection kit for β-actin was purchased from Perkin-Elmer (Beaconsfield, Bucks, England, United Kingdom). The reaction was carried out using the following: Hot-start Q-master mix (AbGene), 10 pmol of specific forward primer (5′-CTACAGTGGGAA-CAGCCTCAG-3′, mmp71s), 1 pmol reverse primer that has the Z sequence (underlined; 5′-ACTGAACCTGACCGTACAATTCCTTGAGTTGCCCTC-3′, mmp7ZR), 10 pmol of FAM-tagged probe (Intergen), and cDNA from ~50 ng RNA. The reaction was carried out using iCyclerIQ (Bio-Rad, Hemel Hempstead, Herfordshire, England, United Kingdom), which is equipped with an optic unit that allows real-time detection of 96 reactions using the following conditions: 94°C for 12 minutes, 50 cycles of 94°C for 15 seconds, 55°C for 40 seconds, and 72°C for 20 seconds. CK19 was used for comparison of cellularity during the analysis and primers for CK19 were 5′-CAGGTCCGAGGTTACTGAC-3′ and 5′-ACTGAACCTGACCGTACACTTTCTGCCAGTGTGTCTTC-3′, respectively (21). The levels of the transcripts were generated from a standard that was simultaneously amplified with the samples. The levels of matrilysin transcript was also normalized by CK19 and is shown as matrilysin/CK19 ratio here.

In vitro invasion analysis and cell growth assay. This was done as previously reported and modified in our laboratory (22). Briefly, transwell inserts (upper chamber) with 8 μm pore size were coated with 50 μg/insert of Matrigel and air-dried before being rehydrated. Twenty thousand cells were added to each well with or without hepatocyte growth factor/scatter factor. After 72 hours, cells that had migrated through the matrix and adhered to the other side of the insert were fixed and stained with 0.5% (w/v) crystal violet. Cells that had invaded and stained with crystal violet were extracted with 10% (v/v) acetic acid and absorbance was obtained using a multiplate reader.

![Fig. 3. Immunohistochemical staining of matrilysin in human mammary tissues. Left, normal tissue; middle, tumor tissue; right, negative control. Magnifications, from top to bottom, ×40, ×100, ×200, and ×400, respectively.](image-url)
For cell growth assay, MDA-MB-231 WT, MDA-MB-231 pRevTRE, or MDA-MB-231 ΔMatrilysin cells were plated into a 96-well plate at 2,500 cells/well. Cells were fixed in 10% formaldehyde at the day of plating; days 1, 2, 3, 4, 5, and 6 after plating; and then stained with 0.5% (w/v) crystal violet. Following washing, stained crystal was extracted with 10% (v/v) acetic acid and absorbance determined using a multplate reader (using wavelength 560 nm). The growth of cells are shown here as absorbance (mean ± SD).

In vivo development of mammary tumor. Athymic nude mice (Nude CD-1) of 4 to 6 weeks old were purchased from Charles River (Margate, Kent, England, United Kingdom) and maintained in filter-topped units. One hundred microliters of cell suspension (in 0.5 mg/mL Matrigel) were injected s.c. at the left scapula area. Each tumor group was divided into those receiving twice weekly injection of doxycycline or injection of buffers. Mice were weighed and tumor sizes measured twice weekly for 4 weeks. Mice with weight loss over 25% and tumor size larger than 1 cm in any dimension were terminated according to the United Kingdom Home Office and the United Kingdom Coordinating Committee on Cancer Research guidelines. The volume of the tumor was determined using the following formula: tumor volume = 0.523 × width² × length (19). At the conclusion of the experiment, animals were terminally anesthetized and primary tumors were dissected, weighed, and frozen at −80°C. Part of the primary tumors was fixed for histologic examination.

Immunohistochemical staining of matrilysin. Frozen sections of tissues (32 paired normal and tumor tissues as well as dissected tumor tissues) were cut at a thickness of 6 μm using a cryostat (15). The sections were mounted on superfrost plus microscope slides, air dried, and then fixed in a mixture of 50% acetone and 50% methanol. The sections were then placed in Optimax wash buffer for 5 to 10 minutes to rehydrate.

Sections were incubated for 20 minutes in 10% horse serum of blocking solution and probed with the primary antibody. Following extensive washings, sections were incubated for 30 minutes in the secondary biotinylated antibody (Multilink Swine anti-goat/mouse/rabbit immunoglobulin; DAKO, Inc., Kidlington, Oxford, England, United Kingdom). Following washings, avidin-biotin complex (Vector Laboratories, Peterborough, England, United Kingdom) was then applied to the sections followed by extensive washings. Diaminobenzidine chromogen (Vector Laboratories) was then added to the sections that were incubated in the dark for 5 minutes. Sections were then counterstained in Gill’s hematoxylin and dehydrated in ascending grades of methanol before clearing in xylene and mounting under a coverslip. Cytoplasmic staining of the respective proteins was quantified using Optimas 6.0 software as we previously described (23, 24) and is shown here as relative staining intensity.

Statistical analysis was carried out using Mann-Whitney U test and significant difference was taken at P < 0.05.

Results

Elimination of matrilysin expression in breast cancer cells affects the in vitro invasiveness and migration of breast cancer cells. MDA-MB-231 cells expressed matrilysin as shown by reverse transcription-PCR (Fig. 1A). Two sublines were generated by infecting the wild-type MDA-MB-231 (MDA-MB-231 WT) with pRevTRE-MAT and pRevTRE-cont active viral stocks and termed MDA-MB-231 ΔMatrilysin and MDA-MB-231 pRevTRE, respectively. MDA-MB-231 ΔMatrilysin cells almost completely lost...
the expression of matrilysin, compared with the wild-type MDA-MB-231WT and MDA-MB-231pRevTRE (Fig. 1A). This suggests that the retroviral transgene was highly active in targeting matrilysin mRNA (Fig. 1A). It is interesting to note that in the pRevTet-On ribozyme transgene system created, the knockout was highly effective, with or without doxycycline, indicating that the U1 promoter inserted in the pRevTRE292 worked well, independent of the tetracycline response elements.

All three cell variants were subject to in vitro testing. Figure 1B reveals that MDA-MB-231ΔMatrilysin cells had significantly reduced invasiveness into Matrigel in response to hepatocyte growth factor (number of invading cells 16.0 ± 2.5). In contrast, MDA-MB-231WT (26.2 ± 6.2, P < 0.05 versus MDA-MB-231ΔMatrilysin) and MDA-MB-231pRevTRE (25.3 ± 4.2, P < 0.01 versus MDA-MB-231ΔMatrilysin) cells responded equally to hepatocyte growth factor. Addition of doxycycline did not significantly increase the effectiveness of the ribozyme transgene. Neither ribozymes nor control plasmid significantly altered the growth rate of MDA-MB-231 cells. Over a period of 72 hours, MDA-MB-231WT, MDA-MB-231pRevTRE, and MDA-MB-231ΔMatrilysin cells showed a similar rate of growth (absorbances were 1.56 ± 0.21, 1.61 ± 0.47, and 1.57 ± 0.36, respectively; Fig. 2A). Addition of doxycycline did not affect the growth rate of the cells.

Reduced tumor growth of breast tumors after elimination of matrilysin. In the nude mouse model, MDA-MB-231WT, MDA-MB-231pRevTRE, and MDA-MB-231ΔMatrilysin cells were s.c. injected. Figure 2 shows that whereas MDA-MB-231WT and MDA-MB-231pRevTRE tumors grew at similar rate, growth of MDA-MB-231ΔMatrilysin tumors were significantly slower (Fig. 2C). In addition, the weight of tumors at the conclusion of the experiment indicated the same trend, where MDA-MB-231ΔMatrilysin tumors were the smallest (Fig. 2B). The size and rate of growth of tumors from MDA-MB-231WT and MDA-MB-231ΔMatrilysin cells were similar, with or without the injection of doxycycline (Fig. 2B and C). Primary tumors were further analyzed histologically. MDA-MB-231ΔMatrilysin tumors displayed substantially weaker staining of matrilysin (Fig. 2D) compared with MDA-MB-231WT and MDA-MB-231pRevTRE tumors (Fig. 2D-B versus C, respectively).

Aberrant expression of matrilysin in human breast cancer. Matrilysin was seen to be present primarily in the mammary epithelial cells and very little in stromal cells (Fig. 3, left). In breast cancer tissues, the staining became markedly stronger, again in cancer cells (Fig. 3, middle). In both cases, stromal cells showed no or very little staining.

We went on to analyze the transcript levels of matrilysin, using quantitative real-time PCR. There were higher levels of matrilysin transcript in breast tumors compared with normal tissues (P < 0.05; Fig. 4A). Interestingly, the levels of matrilysin transcript were high in high-grade tumors (P < 0.05, grade 3 versus grade 1; n = 23, 41, and 56 for grades 1, 2, and 3 respectively; Fig. 4C) and in node-positive tumors (n = 55; P = 0.05 versus node-negative tumors, n = 65; Fig. 4B). A similar trend was seen when matrilysin transcript was normalized by CK19 (Fig. 4, inset).

Here, we have used two methods to assess the clinical relevance: the Nottingham prognosis index (with good, moderate, and poor predicted prognosis, for the respective index <3.4, 3.4-5.4, and >5.4) and with clinical outcome: patients who remained disease-free, with metastatic disease, with local recurrence and with mortality (Fig. 4D). Tumors from patients with predicted moderate and poor prognosis had higher levels (Fig. 4D). Tumors from patients who died of breast cancer (n = 20) had significantly higher levels of matrilysin transcript (Fig. 4E), compared with those who remained disease-free (n = 81). The same was seen when matrilysin transcript was normalized by CK19 (Fig. 4, insets).

Expression of matrilysin is linked with clinical outcome. A Kaplan-Meier survival analysis indicated that high levels of Matrilysin were significantly associated with reduced survival (P = 0.0143; Fig. 5A), in that patients with higher levels of matrilysin had a median survival of 107.5 months (95% confidence interval, 85.1-129.9 months), compared with patients with low levels of matrilysin, 140.5 months (95% confidence interval, 131.5-150.0). High levels of matrilysin was also linked to shorter disease-free survival although this is not statistically significant (P = 0.0892; Fig. 5B) in that patients with higher levels of matrilysin had a median survival of
and, secondly, pointed the potential value of targeting the MMP in cancer therapy.

In the current study, we have used ribozyme transgene as a means to manipulate the expression of matrilysin in cancer cells and to create a cell model to test if targeting matrilysin is of value in cancer intervention. As shown in Fig. 1, the ribozyme has successfully knocked out the expression of matrilysin mRNA from MDA-MB-231 cell, the wild type of which highly expresses matrilysin. Using the cells thus generated (MDA-MB-231 Δmatrilysin), we have shown that loss of matrilysin in the breast cancer cell MDA-MB-231 Δmatrilysin is accompanied by the significant reduction of invasiveness of breast cancer cells in vitro. This is largely expected, given the role of matrilysin in matrix degradation. The same cells were further tested in a in vivo model and have shown a convincing slower growth rate, compared with control and wild-type tumor cells. It is also noteworthy that insertion of a U1 promoter in the pRevTRE vector has enabled the Tet-On system independent of doxycycline.

The success of the ribozyme transgene to matrilysin has been further verified from the in vivo model in that the MDA-MB-231 Δmatrilysin tumors have also displayed low levels of matrilysin staining in the tumor. As well as assisting invasion by degradation of matrix proteins, matrilysin has also been shown to potentially activate angiogenic factors or factors that may facilitate angiogenesis (32, 33), affecting the growth of endothelial cells (34), degradation of matrix thus facilitating the angiogenic process (35). These factors may collectively contribute to the reduced growth of the breast tumors in the in vivo model.

In conclusion, the current study has shown a potential aberrant level of matrilysin in human breast cancer and that the high levels of are linked to a poor clinical outcome. In addition, the current study has also shown that manipulating the expression of matrilysin in breast cancer cells can reduce the invasiveness in vitro and tumor growth in vivo. This indicates that targeting matrilysin may be an effective way to intervene the aggressiveness of breast cancer.

References
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Wen G. Jiang, Gaynor Davies, Tracey A. Martin, et al.