THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DIVISION OF SCIENCE AND ENGINEERING

EXPRESSION OF MATRIX METALLOPROTEINASES BY INVASIVE BREAST CANCER CELLS

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ABSTRACT

According to the American Cancer Society, breast cancer is the most common cancer in women. As with any cancer, breast cancer becomes most dangerous when the cancerous cells acquire the ability to invade into surrounding tissues. This invasion later leads to metastasis and an increase in the severity of the disease. One of the main tools that cancer cells use to facilitate their invasive behavior is matrix metalloproteinases (MMPs). MMPs are a group of metal-containing enzymes that degrade extracellular matrix (ECM) proteins allowing cancer cells to invade, enter circulatory systems, and eventually spread and form tumors at other locations in the body. We have investigated the expression of MMPs in two breast cancer cell lines using reverse transcription polymerase chain reaction (RT-PCR). One is a non-invasive breast epithelial cancer cell line; the other is an invasive cell line derived from the first by mutagenesis and selection. We have found that both cell lines express several MMPs and some differences in MMP expression are evident between these two cell lines. In addition, we examined the effects of exposing cells to specific MMP inhibitors on their invasive activity. We will present our data on MMP expression and the role of MMPs in the invasive behavior of these breast cancer cell lines.

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Chapter 1

Background

What is Cancer?

Cancer occurs when the regulation of normal cell growth, division, proliferation, and death, become abnormal; instead of going through these steps, cancer cells continue to grow and form new abnormal cells. They can also acquire the ability to invade and penetrate through other tissues.

Unrepaired mutations during DNA replication are the main reason why cells become cancerous. Normally, if the mutated DNA is not repaired, the affected cells will receive death signals and go through apoptosis, or programmed cell death; however, in the few cases in which the DNA is not repaired, cells can become cancerous and not receive death signals. They continue to replicate until they form benign or malignant tumors.

Malignant tumors are able to invade neighboring tissues, something normal cells are not able to do. Cancer cells go through a cascade of events in order to acquire the ability to metastasize to a different area of the body. First, cancer cells must breach the basement membrane and intravasate into lymphatic or blood microvessels. The latter allows the cancer cells to be transported to distant anatomical sites. They then must extravasate from the blood vessels, form micrometastases, and colonize into a secondary tumor.[1]

What is Breast Cancer?

This is the most common type of cancer among women. One in eight women will develop invasive breast cancer in the United States. Most of the time, breast cancer begins in the ducts of the breast. The ducts carry milk from the milk-producing glands, called lobules, to the nipple[2].

These tumors in the breast do not directly cause death; however, if the cells that metastasize to other parts of the body colonize and form large tumors that affect the function of vital organs and tissues, an individual can die. For example, breast tumor metastases can metastasize to the lungs. If the metastases colonize in the lung tissue, lung function will decrease. Eventually if the tumor is not removed or if there are too many colonized metastases, lung function will fail and the affected individual will die.

There is a greater chance of cancerous cells entering into the blood stream if they can get into the lymphatic vessels and travel to the lymph nodes[2]. Once in the lymph nodes, cells can intravasate into the blood stream and metastasize to other areas of the body.

What are Matrix Metalloproteinases?

Matrix metalloproteinases (MMPs), also known as matrixins, are a large family of metal-dependent endopeptidases with activity against many extracellular matrix (ECM) molecules, including collagens, elastins, gelatins, matrix glycoproteins, proteoglycans and the basement membrane. Every component of the ECM can be cleaved by at least one of the 23 members of the human MMP family. ECM degradation is an important feature in normal processes such as morphogenesis, wound healing, tissue repair, and remodeling in response to injury.

MMPs are multi-domain proteins and are part of the zinc metalloprotease family. They consist of four domains. The N-terminal pro-domain (about 80 amino acid residues), directs the secretion of the pro-enzyme[3]. The pro-peptide contains a highly conserved sequence in which a cysteine forms a covalent bond with a catalytic zinc ion that maintains the pro-MMP in latent form[3]. The catalytic domain (about 70 amino acid residues), consists of two modules separated by an active site cleft[3]. Three histidine residues coordinate the binding of catalytic zinc at the active site. The hinge region, which varies in length and is proline-rich, links the catalytic domain to the hemopexin-like domain, which is about 200 amino acid residues[3]. A disulfide bridge connects the ends of the domain, which plays a functional role in substrate binding[3]. Membrane-type matrix metalloproteinases (MT-MMPs) contain an additional transmembrane domain that anchors them to the cell surface.

Depending on their substrate specificity and structural organization, MMPs can be categorized into subfamilies: collagenases, stromelysins, matrilysins, gelatinases, and MT-MMP (Table 1). Collagenases cleave the triple helix of fibrillar collagen type I, II, III, and IV, resulting in ¾ N-terminal and ¼ C-terminal triple-helix fragments[4]. Stromelysins have a similar structure and substrate specificity. They are able to hydrolyze collagen type IV, but do not cleave fibrillar collagen. Matrilysins, which lack the hemopexin-like domain, are able to process collagen type IV. Gelatinases cleave collagen type I and IV and degrade components of the basement membrane[4]. These are characterized by the presence of a collagen-binding domain (CBD) located in the catalytic domain. It binds to fibrillar collagen type 1[4]. MT-MMP, which contains an addition domain at the C-terminal, can cleave fibrillar collagen type I[5].

Class	MMP Number
Collagenases	MMP-1, MMP-8, MMP-13
Stromelysins	MMP-11
Matrilysins	MMP-7
Gelatinases	MMP-2, MMP-9
Membrane Type 1 (MT-MMP)	MMP-15

Table 1. Classification of Examined Matrix Metalloproteinases

MMPs are excreted by a variety of connective tissue and pro-inflammatory cells including fibroblasts, osteoblasts, endothelial cells, macrophages, neutrophils, and lymphocytes[1]. They are initially expressed as zymogens, which are then processed by proteolytic enzymes to generate active forms.

MMP activity is regulated at different levels, including transcription, activation, inhibition, and localization. Generally, hormones, growth factors, cytokines, cell-cell and cell-matrix interactions regulate MMP expression[1]. MMPs that respond to these extracellular stimuli contain an AP-1 binding site[3]. Transcription factors, such as Jun and Fos, bind to the AP-1 binding site and activate the transcription of MMP genes[1,3].

Activation and inhibition of MMPs also regulates MMP activity. Latency of pro-MMPs is maintained by the "cysteine switch," a covalent bond between the cysteine residue in the pro-domain and the Zn^{2+} in the catalytic domain[3]. Proteinases, such as plasmins and trypsins, disrupt this bond and activate the pro-MMPs. Activated MMPs can also activate other pro-MMPs.

Endogenous MMP inhibitors (MMPIs) and tissue inhibitors of MMP (TIMPs) can also control these enzymes. TIMPs assist in negative regulation by binding to MMPs and putting them in an inactive configuration[1].

Another important aspect of MMP activity regulation is localization. Anchoring MMPs to the cell surface prevents them from rapidly diffusing away and keeps them under close regulatory

control. Binding to the cell surface also allows positioning of MMPs for activation, interaction with cell surface molecules or receptors, regulation of their turnover, and focused pericellular proteolysis[3].

How do Matrix Metalloproteinases Assist Cells in Invasion?

Malignant cancer cells have the ability to invade adjacent layers of cells. In order for cancer cells to remodel nearby tissues, the cells must rely on MMPs to create phenotypes associated with epithelial mesenchymal transition (EMT). The cells can exploit the EMT program to profoundly change their own morphology, motility and ability to invade nearby cells[1]. Recruited stromal cells, notably macrophages, mast cells, and fibroblasts, secrete MMPs, most of which are in a soluble form. Initially, these soluble MMPs are all synthesized as inactive pro-enzymes that only function following activation by other proteases. When activated, MMPs mobilize and activate certain growth factors, such as basic fibroblast growth factor (bFGF), transforming growth factor β1 (TGF-β1), platelet derived growth factor (PDGF), epidermal growth factor (EGF) related factors, and interferon 8 (IFN8), which are tethered in inactive form to the ECM or the surface of cells[1]. Growth factors, through a series of signal transduction cascades, signal cells to grow and proliferate.

Chapter 2

Purpose

The purpose of this two-step experiment is to first, determine the difference between expression levels of MMP-1, MMP-2, MMP-7, MMP-8, MMP-9, MMP-11, MMP-13, and MMP-15 in non-invasive (10F) cells and invasive (C5) cells, and then determine how MMP inhibitor, BB-94, affects the mobility of the invasive (C5) cells.

Chapter 3

Hypotheses

In part 1 of the experiment, it is hypothesized that the invasive cancer (C5) cell line will express higher levels of MMP-2, MMP-11, and MMP-15.

In part 2 of the experiment, it is hypothesized that invasive cancer (C5) cells will penetrate less through the Matrigel when exposed to BB-94 MMP inhibitor, compared to invasive cancer (C5) cells not exposed to BB-94 MMP inhibitor.

Chapter 4

Procedures

Cell Culture Procedure

1. Culture non-invasive (10F) and invasive (C5) breast epithelial cancer cell lines
2. Check each petri dish under the microscope to check the confluence of the cells (they are ready to pass when the confluence is around 80-90%)
3. Inside the hood, aspirate the media from the petri dishes with suction
4. Add 5 mL of 0.25% Trypsin and EDTA and incubate at 37°C for 10-15 minutes
5. Check under the microscope for detachment of the cells; if they are not detached wait 5 more minutes
6. Add 5 mL of High Calcium Media and 5% of Horse Serum to each petri dish
7. Mix and transfer to a labeled 50 mL centrifuge tube
8. Add another 5 mL to the petri dishes to wash left over cells
9. Transfer to the centrifuge tube (final volume of liquid should be 15 mL in each tube)
10. Centrifuge for 6 minutes at 4000 RPM
11. Take the centrifuge tube and check for the white pellet at the bottom of the tube
12. Aspirate the media with suction (do not aspirate the pellet)

If you want to continue cell culture:

13. Re-suspend the pellet in 6 mL of High Calcium Media and mix well
14. Add 12-15 mL of High Calcium Media to three new petri dishes
15. Add 2 mL of the cell suspension in each dish
16. Incubate at 37°C and check cells every day

If you want to freeze cells:

13. Create Freezing Media by mixing together 5 mL High Calcium Media, 0.25 mL Glycerin and 0.25 mL DMSO
14. Add 8 mL of Freezing Media to the pellet and mix well
15. Distribute the cell suspension into 5 vials
16. Leave vials for 45 minutes at -20°C
17. Transfer vials to -80°C

TriZol RNA Preparation

Note: Be sure to wear gloves when working with RNA samples.

1. Trypsinize cells and pellet at 4000 RPM for 6 minutes at 4°C
2. Homogenize pelleted cells in 200 μL TriZol by trituration with a pipette tip
3. Incubate for 5 minutes at room temperature
4. Add 40 μL chloroform and shake tube vigorously for 15 seconds
5. Incubate for 3 minutes at room temperature
6. Centrifuge at 12,000 x *g* for 15 minutes at 4°C
7. Remove the upper clear aqueous phase
8. Add 100 μL isopropanol
9. Incubate for 10 minutes at room temperature
10. Centrifuge for 10 minutes at 12,000 x *g* at 4°C
11. Remove supernatant
12. Re-suspend in a small volume (105 μL) of DEPC-dH_2O

PCR Reaction Preparation

1. Prepare 10 μL PCR reactions according to the following:

Taq PCR Master Mix	5 μL
Primer Mix	1 μL

RNase-free Water	3 μL
Template DNA	1 μL

2. Cycles:

Denature	94°C for 3 minutes
30 cycles	94°C for 30 seconds
	Annealing temperature 60°C for 1 minute
	72°C for 1 minute
Final extension	72°C for 5 minutes
Link to file	4°C for 99 hours

3. Prepare a 2% agarose gel in 1xTAE
4. Run samples along with DNA ladder

Procedure for Use of Matrigel™ Matrix for Invasion Assay

Rehydration

1. Remove the package from -20°C storage and allow to come to room temperature
2. Add 0.5 mL warm (37°C) bicarbonate based culture medium to the interior of the inserts and bottom of wells
3. Rehydrate for 2 hours in humidified tissue culture incubator at 37°C and 5% CO_2 atmosphere
4. After rehydration, carefully remove the medium without disturbing the layer of Matrigel™ Matrix on the membrane

Invasion Studies

1. Rehydrate the number of Matrigel inserts to be used as directed above
2. Prepare an equal number of control inserts by using sterile forceps to transfer them to empty wells of the BD Falcon™ TC Companion Plate

3. Prepare cell suspensions in culture medium containing $5x10^4$ cells/mL for 24-well chamber
4. Add High Calcium Medium to the wells of the BD Falcon™ TC Companion Plate
5. Use sterile forceps to transfer the chambers and control inserts to the wells containing the High Calcium Medium (be sure that no air bubbles are trapped beneath the membranes)
6. Immediately add 0.5 mL of cell suspension
7. Incubate the BD BioCoat™ Matrigel Invasion Chambers for 22 hours in a humidified tissue culture incubator at 37°C and 5% CO_2 atmosphere

Measurement of Cell Invasion

Removal of Non-invading Cells

Note: After incubation, the non-invading cells are removed from the upper surface of the membrane by "scrubbing." The attachment of the membrane to the insert housing is quite firm and will not be dislodged during scrubbing nor will cells be dislodged from the bottom surface of the membrane. Scrubbing is very efficient in removing Matrigel™ Matrix and/or non-invading cells from the upper membrane surface. Scrubbing must be accomplished quickly to avoid drying of the cells adhering to the bottom surface of the membrane.

1. Insert a cotton tipped swab into the BD BioCoat™ Matrigel insert and apply gentle but firm pressure while moving the tip over the membrane surface
2. Repeat the scrubbing with a second swab moistened with medium

Staining of Cells

Note: Cells may be fixed and stained with 100% methanol and 1% Toluidine blue, respectively.

1. Add 100% methanol to the appropriate number of wells of a BD Falcon™ TC Companion Plate
2. In a separate plate, add 1% Toluidine Blue in 1% borax to the appropriate number of wells.

3. Add distilled water to two beakers
4. Transfer inserts into the methanol for 2 minutes
5. Transfer inserts into the Toluidine stain for 2 minutes
6. Rinse inserts in the two beakers of distilled water to remove excess stain
7. Allow the inserts to air dry for 10 minutes

Counting of Invading Cells

Note: Cell counting is facilitated by photographing the membrane through the microscope. Direct counting of the cells at the microscope is also acceptable.

1. Remove the membrane from the insert housing by inverting the insert and inserting the tip of a sharp scalpel blade through the membrane adjacent to the housing wall
2. Rotate the insert housing against the stationary blade and the membrane will be released in much the same manner as the lid is cut from a tin can
3. Do not fully release the membrane from the housing but leave a very small point of attachment
4. Use forceps to peel the membrane from the remaining point of attachment and place it bottom side down on a microscope slide on which a small drop of immersion oil has been placed
5. Place a small drop of immersion oil on top of the membrane
6. Place a second slide or cover slip on top of the membrane and apply gentle pressure to expel any air bubbles
7. Observe and/or photograph the invading cells under the microscope at approximately 40-200X magnifications depending on cell density
8. Count cells in several fields of triplicate membranes

Note: Cells will invade through the Matrigel™ Matrix on the 8 μm membrane pores ranging from even distribution to localization in discrete areas notably the center of the membrane and/or

around the periphery of the membrane. When counting cells of the triplicate membranes, choose fields in the center of the membrane as well as fields in the periphery of the membrane for “true” representation of the cell number throughout the membrane.

Chapter 5

Results

When using single gene primers, the non-invasive (10F) and invasive (C5) expressed MMP-2, MMP-8, MMP-11, and MMP-15; however, neither expressed MMP-1 or MMP-13. Invasive (C5) cells expressed higher levels of MMP-8, MMP-11, and MMP15 than the non-invasive (10F) cells.

When using the multiplex PCR primer mix, both types of cells expressed MMP-2; however, the non-invasive (10F) cells also expressed MMP-9, MMP-7, and MMP-14.

When examining the invasion assay slides, cells that were and were not exposed to MMP inhibitor, BB-94, were able to penetrate the Matrigel™ Matrix; however, fewer cells were able to penetrate through the matrix when exposed to BB-94. Preliminary results suggest that MMP inhibitors reduced the ability of cells to invade through Matrigel.

Chapter 6

Discussion

In the first part of the experiment, it was hypothesized that both non-invasive (10F) and invasive (C5) cells would express all the MMPs, but the invasive (C5) cells would have higher expression levels of MMP-2, MMP-11, and MMP-15; however, the invasive cells only expressed higher levels of MMP-8, MMP-11, and MMP-15 (Figure 1).

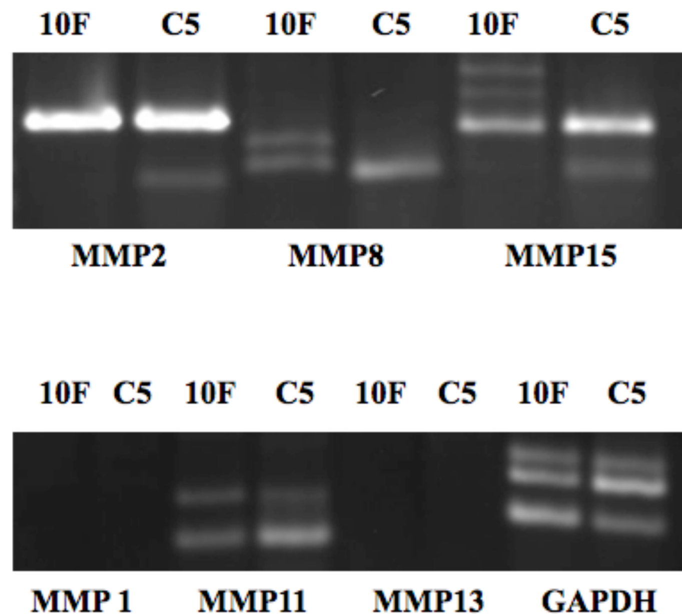

Figure 1. RT-PCR Analysis of MMP-1, MMP-2, MMP-8, MMP-11, MMP-13, and MMP15 Expression

The increased expression of MMP-11 and MMP-15 was expected in the invasive cancer (C5) cells. MMP-11, when activated, assists in the epithelial mesenchymal transition (EMT), which allows cells to acquire the ability to mobilize and invade the surrounding tissues. MMP-11 is also important in the early stages of tumorigenesis by favoring the survival of cancer cells in environments not suitable for tumor growth[3].

Activated MMP-15 also favors cell survival by acting as an anti-apoptotic factor; however, it is predominantly responsible for the activation of inactive zymogens of MMP-2, which plays a role in cleaving collagen type IV[6]. Collagen type IV is a major structural component of basement membrane, and by cleaving the collagen, invasive (C5) cells are able to penetrate through the basement membrane[1,8].

On the other hand, high expression of MMP-8 was not expected in our results. MMP-8 induces interleukin 6 and 8, which decreases cancer cell proliferation, and also reduces the ability of invasion[7].

Another surprising result was the expression of MMP-7, MMP-9, and MMP-14 seen in the non-invasive (10F) cells and not in the invasive (C5) cells (Figure 2). We would expect that the invasive (C5) cells would express these MMPs and the non-invasive (10F) cells would not.

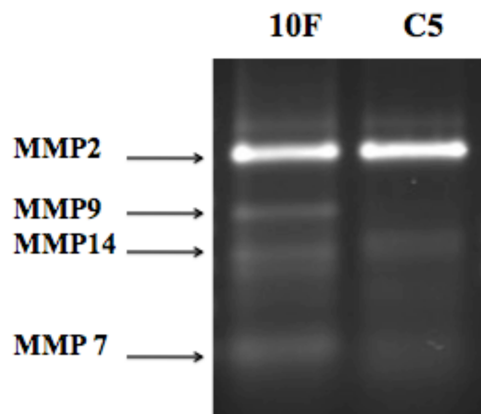

Figure 2. RT-PCR Analysis of MMP-2, MMP-7, MMP-9, and MMP-14 Expression

In the second part of the experiment, we hypothesized that the cancer cells exposed to the MMP inhibitor, BB-94, would decrease invasion of the invasive (C5) cell line through the Matrigel™ Matrix. Higher levels of MMP help cancer cells invade through neighboring tissues. If we inhibit MMPs, we expect fewer cells to invade through the Matrigel™ Matrix (Figure 3).

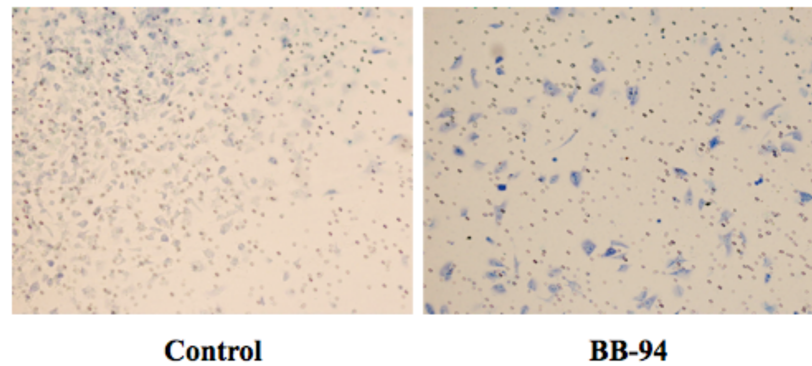

Figure 3. Invasion Assay of C5 Cells With and Without MMP Inhibitor, BB-94

Although we looked at the expression of MMPs, it would be ideal to look at protein expression and enzyme activity in the future. This could tell us why both non-invasive (10F) and invasive (C5) cells did not express MMP-1 or MMP-13, and also why the non-invasive (10F) cells expressed MMP-7, MMP-9, and MMP-14, while the invasive (C5) cells did not.

Appendix A

Abbreviations

MMP – matrix metalloproteinase, ECM – extracellular matrix, RT-PCR – reverse transcription polymerase chain reaction, DNA – deoxyribonucleic acid, MT-MMP – membrane type matrix metalloproteinase, CBD – collagen binding domain, MMPI – matrix metalloproteinase inhibitor, TIMP – tissue inhibitor of MMP, EMT – epithelial mesenchymal transition, bFGF – basic fibroblast growth factor, TGF-β1 – transforming growth factor β1, PDGF – platelet derived growth factor, EGF – epidermal growth factor, IFN8 – interferon 8

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