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14. ABSTRACT

This final report covers the three years of work on the Statement of Work with particular focus on the third year of research. This report covers the major accomplishments of this research, including the development of reagents to detect the secreted form of ADAM9, the development of a model system to investigate the isoforms of ADAM-9 in breast cancer cell migration, and the use of this model system to discover novel functions for both isoforms of ADAM9. We have confirmed the presence of the secreted form of ADAM9, ADAM9-S in breast cancer cell lines and tumor lysates,. We have also confirmed the role of ADAM9-S in promoting breast cancer cell migration and shown that this is through the proteolytic function of the protein. In addition, we have shown that the alternatively spliced, membrane-bound isoform of ADAM9, ADAM9-L, suppresses cell migration in a proteolysis-independent manner. These differences are significant as ADAM9 has been identified as a druggable target for breast cancer, and the potential side-effects of an ADAM9 inhibitor will depend on the functional domain targeted and isoform prevalence in disease.

15. SUBJECT TERMS
ADAM9, Tumor-Stromal Interactions, Breast Cancer, metastasis, migration

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Introduction

The purpose of this research project is to evaluate the molecular mechanisms by which the isoforms of ADAM9 participate in breast cancer progression. Based on previous work [1], we hypothesized that ADAM9 participates in tumor-stromal interactions in breast cancer, acting to enhance tumor progression by mediating HB-EGF shedding and EGFR signaling, and participating in the epithelial-mesenchymal transition (EMT) through its integrin binding function. Our 2007 and 2008 annual summaries detailed the development of isoform specific ADAM9 antibodies and the specific detection of ADAM9 isoforms in breast cancer cell lines. We also described the discovery of ADAM9-L suppression of breast cancer cell migration, and established that the protein cleavage function of the protein was not necessary to reconstitute suppression after protein silencing. This data led us to revise our statement of work to explore this mechanism and signaling, including the evaluation of functional domain mutants of ADAM9-L for their role in breast cancer cell migration. In addition, our studies have also shown that two isoforms of ADAM9 play opposing roles in breast cancer cell migration, and this report will summarize those results. The results of this research will provide us with a new mechanism by which the ADAM9 isoforms present in breast tumors and stroma influence cell migration, lending insight into tumor progression and metastasis. Increased understanding of these mechanisms will lead to new strategies for therapy targeted specifically to advanced stage tumors. Over the course of this grant this research has also prepared the Prinicpal Investigator for her career in breast cancer research, including oral presentations at national meetings, poster presentations, and attendance at multiple symposia dedicated to breast cancer work. We are currently preparing this work for publication.

Body

The following tasks from the Statement of Work for this project were the focus for the research period from 31 March 2008 – 31 March 2009:

Task 1: To characterize the expression of ADAM9 in breast cancer tissues and cell lines representing different stages of the disease (months 1-13).

Task 2: Determine the role of ADAM9 in HB-EGF shedding and EGFR signaling in breast carcinoma cells (months 7-26).

Task 3: Evaluate the role of ADAM9 in the migration of breast carcinoma cells (months 24-36).

This final report will summarize the research conducted on each of these tasks as reported in previous annual reports, and describe in detail the results and subsequent experiments of the past 12 months. Many figures from previous reports have been refined for publication, and those updated will be reproduced in this document.

Task 1:

The goal of this Task is to develop immunohistochemical tests to determine the presence of the isoforms of ADAM9 in breast cancer cell lines and tissue arrays, and to ultimately evaluate the isoform distribution in the tumors and stroma of breast cancers with different clinical profiles. While Year one progress in this task included the development and testing of isoform-specific antibodies to both ADAM9-L and ADAM9-S, and the identification of breast cancer cell lines that endogenously express ADAM9-L and –S (Fig 1). Year two research focused on using isoform specific antibodies for immunocytochemistry in preparation for staining tissue arrays. Unfortunately, we were not able to sufficiently lower the background to obtain signal for the ADAM9-S antibody for use in immunohistochemistry, rendering us unable to proceed to tissue arrays. We are proceeding by evaluating breast cancer tumor lysates for ADAM9-L and ADAM9-S expression by Western Blot.

Current Data:

An ADAM9-S antibody suitable for immunohistochemistry is currently unavailable. To analyze the expression of ADAM9-S in patient samples, we obtained breast cancer tumor lysates from Dr. Gerburg Wulf [2] and ran them on an SDS-PAGE gel. Preliminary blotting with ADAM9-S specific antibody shows that ADAM9-S is expressed in tumor lysates (Fig 2). We are currently obtaining matched normal/tumor samples through our collaboration with Dr. Wulf to analyze expression of ADAM9-S during different disease states.

Summary:

During the three years of research on this grant we have used our isoform-specific ADAM9 antibodies to show for the first time that ADAM9-S is expressed both in breast cancer cell lines and in patient samples. This proof of expression supports our work in Tasks 2 and 3, as determining the isoform specific migratory effects of ADAM9 is relevant to the study of breast cancer metastasis.

Task 2:

The overarching goal of Task 2 is to evaluate the role of ADAM9 in EGFR signaling in breast cancer cell lines, with the sub-goal of evaluating the role of the EGFR pathway in breast cancer cell

migration/invasion. Due to our difficulty in originally evaluating breast cancer cell lines for ADAM9 isoform expression, and the promising preliminary migration data presented in our 2007 Annual Update and repeated here, we began this task with the evaluation of the role of ADAM9 in breast cancer cell migration. My original hypothesis, based on data from our lab in which both recombinant stimulation with ADAM9-S and transfected and expressed ADAM9-S enhances invasion of breast cancer cells through a matrigel-coated transwell[1], was that overexpression of ADAM9-S in breast cancer cells would enhance migration, and that overexpression of ADAM9-L would either replicate this phenotype or would have no migratory effect, indicating that the secreted form of ADAM9 was escaping regulation normally imparted through the cytoplasmic domain. Past annual summaries have described our data showing that ADAM9-L and –S have opposing migratory phenotypes and this story will be repeated here. This task further specifies that we will look at the EGFR pathway, as membrane bound EGF is the major known substrate of ADAM9 cleavage[3, 4], as the mechanism for action of ADAM9 mediated migration, and we are in the process of completing these experiments in the context of ADAM9-S metalloprotease mediated migration.

Current Data:

Overexpression of ADAM9 isoforms results in different migration phenotypes

Upon the discovery that both ADAM9 and ADAM9-S are expressed in migratory breast cancer cell lines (Task 1), PCDNA constructs of ADAM9-L, metalloprotease-deficient ADAM9L.EA, ADAM9-S, and ADAM9S.EA were transfected into BT549 breast cancer cells and their chemotactic migration evaluated using an uncoated transwell assay. Consistent with previous results [1], ADAM9-S overexpression causes a significant increase in migration, with no change seen in ADAM9-L overexpressing cells. Furthermore, overexpression of a metalloprotease-deficient ADAM9S.EA mutant has no migratory phenotype, indicating that the metalloprotease activity of ADAM9-S is responsible for increasing cell migration (Fig 3).

ADAM9 Silencing Increases Breast Cancer Cell Migration

To evaluate the role of endogenous ADAM9 in cell migration, an siRNA oligonucleotide pool targeting various sequences in ADAM9 was purchased from Dharmicon Research Inc. Transient transfections of these oligonucleotides into BT549 cells, chosen for their high expression of ADAM9 and migratory capacity, resulted in a surprising increase in migration of the ADAM9-silenced cells through an uncoated transwell assay system (Fig 4). To further confirm this phenotype, two lentiviral shRNA constructs were designed to target the 3' untranslated region of ADAM9 mRNA (ADAM9 shRNA.1) and the cysteine rich domain (ADAM9 shRNA.2). After lentiviral infection and selection, robust silencing of ADAM9-L by both sequences was confirmed by western blot. Silencing of ADAM9 by

both sequences in BT549 cells resulted in an increase in migration in a transwell migration assay (Fig 4). To confirm that ADAM9 silencing was responsible for the increase in migration phenotype, a reconstitution experiment was performed by introducing murine ADAM9-L via transient transfection for 24 hours after silencing of ADAM9 in BT549 cells using ADAM9 shRNA.1. A rescue of the phenotype is observed, implying a direct ADAM9-L phenotype correlation (Fig 5). ADAM9 shRNA.1 was chosen to use in subsequent experiments.

Silencing of both ADAM9 isoforms leads to an increase in cell migration, which is rescued by introduction of wild-type ADAM9-L. To determine the ability of ADAM9-S to contribute to the migration of cells in the presence or absence of endogenous ADAM9 isoforms, lentivirally-infected and selected BT549 cells were transfected with wild-type (hADAM9S) or metalloprotease-deficient (hADAM9S.EA) human ADAM9-S constructs. Consistent with previous literature[1], transfection of ADAM9-S into cells with endogenous ADAM9 results in an increase in cell migration, which is not seen upon overexpression of the metalloprotease-deficient mutant, implicating the metalloprotease domain in this mechanism (Fig 6). Furthermore, the increase in migration is greatly enhanced upon the silencing of endogenous ADAM9, whereas the metalloprotease-deficient mutant behaves similarly to vector controls. These data indicates different and opposing roles for the two ADAM9 isoforms in breast cancer cell migration. At this point, we revised our statement of work to break this work on ADAM9 migration into two sections – task 2 encompasses work on ADAM9-S and the mechanism by which ADAM9-S is enhancing cell migration through its metalloprotease domain. Task 3 continues our work on the role of ADAM9-L in suppressing cell migration via functional domain studies.

ADAM9-S acts as a chemoattractant

To confirm that ADAM9-S is acting as an enhancer of cell migration through its metalloprotease activity and that overexpression is not causing an off-target phenotype we assayed the chemoattractant ability of ADAM9-S and metalloprotease-deficient ADAM9S.EA. First we overexpressed these constructs in HEK-293T cells, and collected serum-free supernatant containing ADAM9-S and ADAM9S.EA. This supernatant was then put in the bottom chamber of a transwell and BT549 breast cancer cells were placed in the top chamber of the transwell and allowed to migrate overnight. Due to the absence of serum in the chemoattractant medium, migration was not robust, but we can see a significant increase in the migration of BT549 cells migrating toward ADAM9-S containing medium in comparison to PCDNA and metalloprotease-deficient ADAM9S.EA medium (Fig 7). This result, coupled with the earlier overexpression data, convincingly shows that ADAM9-S mediates breast cancer cell migration through its metalloprotease activity, and our next step is to evaluate the known substrates of ADAM9, beginning with EGF for activity upon ADAM9-S stimulation.

Summary and Current Work

These studies support our initial hypothesis that ADAM9-S enhances the migration of breast cancer cell lines. By using both chemoattractant and overexpression studies we have shown this to be true despite evidence that suppression of migration by ADAM9-L is the predominant mechanism of ADAM9-mediated migration upon silencing in our system. This indicates that cells may switch the predominant isoform from ADAM9-L to ADAM9-S depending on mitigating signaling pathways in the cell. For example, ADAM9 transcription is responsive to oxidative stress [5], and ADAM9-L is a phosphorylation target of PKCδ [6]. Given that EGF and HB-EGF are both major substrates of ADAM9 cleavage, we are currently assaying function of the EGF receptor in response to ADAM9-S as a potential mechanism in ADAM9-S mediated cell migration, which will fulfill our goals in task 2.

Task 3 :

The goal of task 3 is to evaluate the role of ADAM9 in breast cancer cell migration. As outlined in the task 2 update, we have shown that the different isoforms of ADAM9 have opposing effects on breast cancer cell migration. ADAM9-S enhancing through its metalloprotease activity, and ADAM9-L suppressing via a mechanism we are exploring in this task. This task requires that we evaluate the key functional domains of ADAM9-L, the metalloprotease, integrin-binding disintegrin, and cytoplasmic signaling domains for a role in breast cancer cell migration. Previous updates on this area of our research have indicated a cell-type specific role for ADAM9-L in migration (2008 update, Fig. 2), however subsequent experiments have shown this to be an experimental artifact related to selection protocols used after infection, which was not rescued by reintroduction of wild-type ADAM9-L.

Current Data

Rescue of ADAM9 Silencing Using Functional Mutations

To determine the contribution of each functional domain of ADAM9 to the mechanism by which ADAM9 inhibits migration in a transwell assay, mutations in each functional domain were constructed in a murine ADAM9-L background to allow for rescue of lentiviral-induced silencing in BT549 cells. BT549 cells infected with lentiviral vector alone experience no change in migration phenotype when overexpressing wild-type murine ADAM9-L (mA9L). However, when overexpressing the metalloprotease-deficient mA9L.EA, these cells experience an increase in migration. In the absence of endogenous ADAM-9, we see the increased migration phenotype expected in BT549 cells, which is rescued by wild-type mA9L. It is interesting that this phenotype is also rescued by mA9L.EA, indicating that the metalloprotease-deficient mutant may interfere with the mechanism of endogenous

ADAM9-L, but in silenced conditions is able to act in lieu of the endogenous protein (Fig 8) This indicates that the metalloprotease activity is not critical to the function of ADAM9 in cell migration. Deletion of the cytoplasmic signaling domain (mA9L.delcyt) also results in a rescue of the phenotype, indicating that cytoplasmic signaling is not critical for the action of the protein (Fig 9). This points to the disintegrin domain as the major functional domain involved in migration, and current experiments are focused in this direction.

Assaying migration after gene reconstitution with the disintegrin domain mutant has proved to be impossible. Deletion of the entire domain results in the expression of a protein that cannot be processed in the golgi by furin (Fig 10). In addition, we mutated the ECD amino acids which comprise the integrin-binding motif in ADAM disintegrin domains, which also results in failure of the protein to process appropriately (Fig 10). This highlights a previously unknown critical role for the disintegrin-domain region of ADAM-9 in maintaining protein function.

Summary and Current Work

The progress on this task has led to the confirmation that ADAM9-L is suppressing breast cancer cell migration. Our original hypothesis that this would be via signaling initiated by the protein-cleavage function of the protein was disproven by the rescue of increased migration by addition of a metalloprotease-deficient mutant. Additional mutants of the functional regions of ADAM9-L have shown that the upstream or downstream signaling mediated by the cytoplasmic tail are not critical for suppression of migration, and that the disintegrin domain function is critical for proper protein processing. Our current hypothesis is that the disintegrin domain function is responsible for suppressing migration. To confirm the requirement for the disintegrin domain, we are using ECD-containing peptides (peptides which will block the interactions of the disintegrin domain and integrins) to block the rescue of the silencing phenotype by ADAM9-L. Other possibilities are the cysteine-rich and EGF-like domains, however little is known about the function of these domains in ADAM9 or other ADAMs.

Key Research Accomplishments

- Our isoform specific antibody experiments show for the first time the expression of ADAM9-S in breast cancer cell lines and tumor lysates.
- Analysis of both isoforms of ADAM9 in cell migration shows that ADAM9-L and ADAM9-S have different and opposing roles in cell migration.

- Multiple breast cancer cell lines show enhanced migration upon the silencing of ADAM-9. This enhancement is eliminated when exogenous ADAM9-L is introduced into the silenced cell, confirming the specificity of this phenotype.
- Reconstitution of ADAM9-L signaling in BT549 cells by introduction of a metalloprotease-deficient ADAM9L.EA construct as well as a membrane-tethered cytoplasmic deletion rescues the enhanced migration phenotype in silenced BT549s, indicating that cytoplasmic signaling and cleavage of proteins are not the primary functions mediating cell migration.

Bibliography

Personnel Receiving Pay For This Research Effort:

Jessica L. Fry – Principal Investigator This research effort was the primary focus of the PI's graduate work and Curriculum Vitae, included in the appendix.

PI Training and Development (2008-09)

In addition to the reportable outcomes of this project associated with the career development of the PI, the PI has also presented a poster at one departmental retreat and oral presentations of this work at departmental data clubs as well as 4 dissertation committee meetings.

Reportable Outcomes (2008-09) Meeting Abstracts/Publications

- Invited Presentation: Era of Hope Meeting, June 2008
- Poster Presentation: Era of Hope Meeting, June 2008
- Poster Presentation: Beth Israel Deaconess Cancer Center Symposium, October 2008
- Poster Presentation: FASEB Experimental Biology – ASBMB Principles of Receptor Signaling April 2009. Recipient of the ASBMB Poster Award.
- Manuscript in Preparation
- Principal Investigator expects to attain her Ph.D. in the fourth quarter of 2009

Conclusion

This final summary encompasses the entirety of the Statement of Work for this project. This project marks the first time the secreted isoform of ADAM9, ADAM9-S, has been detected endogenously, specifically in breast cancer tumors and cell lines. The development of a lentiviral shRNA system for silencing ADAM9 allows us to silence endogenous ADAM-9 in human breast cancer cell lines and to identify the migration phenotype. Our results indicate that ADAM9-L suppresses migration of breast cancer cells, while ADAM9-S increases cell migration. Reconstitution experiments using wild-type ADAM9-L eliminate this phenotype, while ADAM9-S enhances migration in both the presence and absence of both ADAM9 isoforms, which is analogous to what was observed in overexpression experiments. We are also the first to propose a mechanism for ADAM9-S function in cell migration, via the metalloprotease activity, and we build upon work in the field linking the disintegrin domain of

ADAM9-L to migration in other cell types [7]. This detailed work is especially important given the identification of ADAM9 as a potential target of breast cancer therapy [8]. Studies that consider the functional role of each isoform in different genotypic contexts, *in vitro* as well as *in vivo*, will be important for the development of safe and effective treatments that target both tumorigenesis and metastasis. Our work has lent insight into the functions and putative mechanisms of both isoforms of ADAM-9, and our future work in this area will further define the relevant signaling pathways which participate in ADAM9 mediated cell migration, paving the way for future studies and possible interventions in breast cancer invasion and metastasis.

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Figure 1

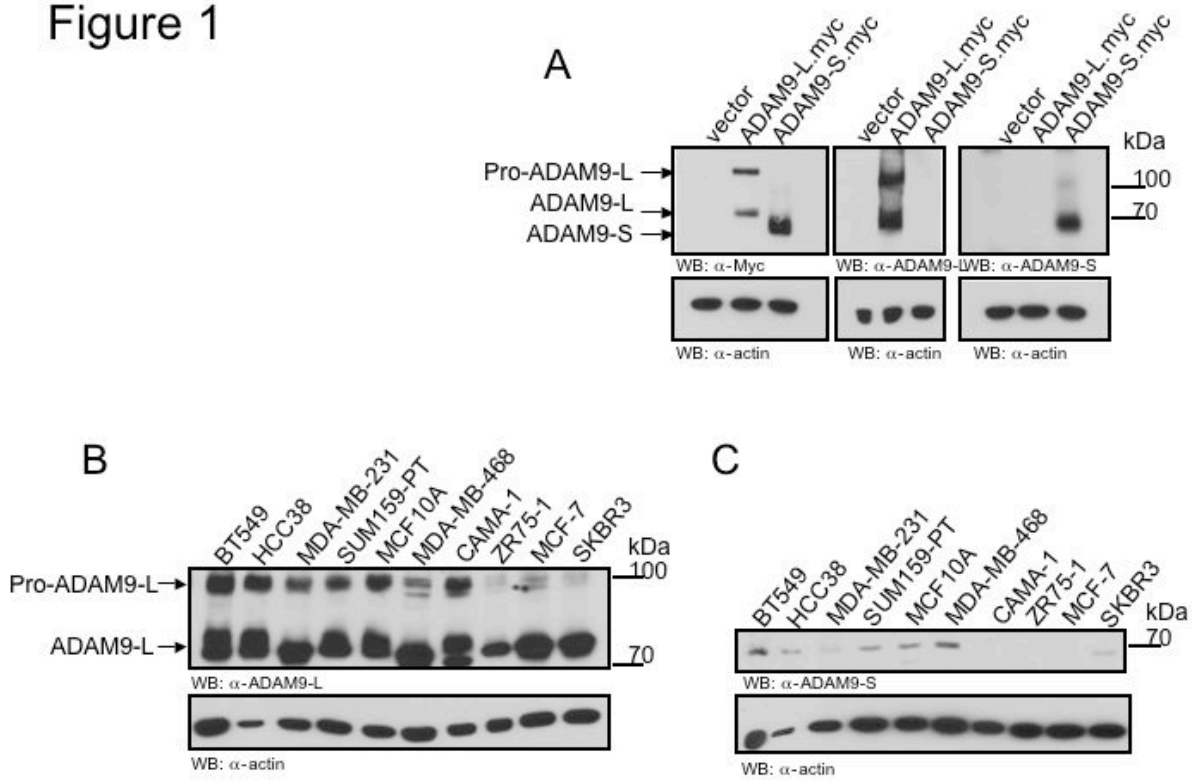


Figure1: *Isoform specific antibodies to ADAM9-L and –S* A) Lysates from transfected myc-tagged murine ADAM9-L and human ADAM9-S constructs are run on an SDS-PAGE gel and blotted with myc and isoform specific antibodies to confirm antibody specificity. B) Lysates from a panel of breast cancer cell lines of multiple genetic subtypes are blotted to evaluate relative expression of ADAM9-L. C) The same panel as in B, analyzed for relative expression of ADAM9-S

Figure 2

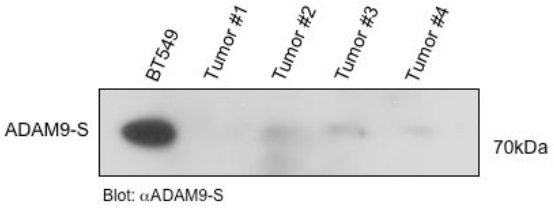


Figure 2: *Endogenous expression of ADAM9-S in breast cancer tumor lysates* SDS-extracted lysates from frozen tumor blocks were run on an SDS-PAGE gel and ADAM9-S detected using isoform specific antibody. BT549 cell lysate was used as a control.

Figure 3

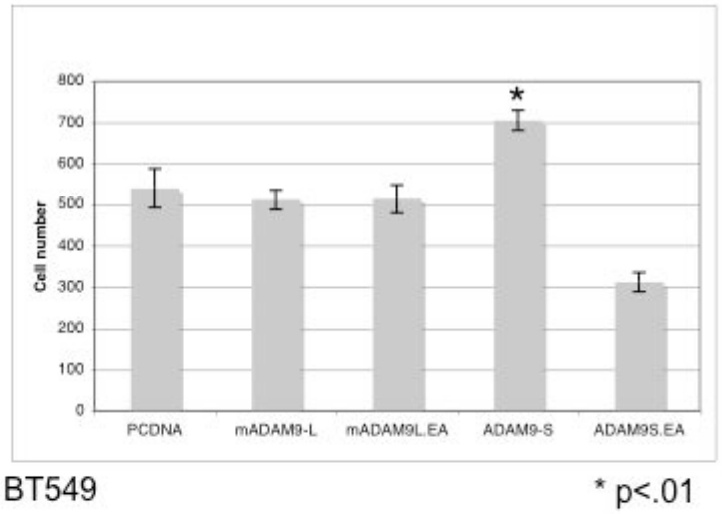


Figure3: *ADAM9-S Overexpression leads to increased breast cancer cell migration* ADAM9 constructs were co-transfected with β-galactosidase into BT549 breast cancer cells. Cells were migrated 16 hours through an 8um transwell chamber toward NIH3T3 supernatant as a chemoattractant. Migrated cells were stained and transfected cells were counted and normalized to the transfection efficiency for each condition. Transfection with an ADAM9-S, but not the metalloprotease deficient ADAM9S.EA constructs resulted in an increase in migration.

Figure 4

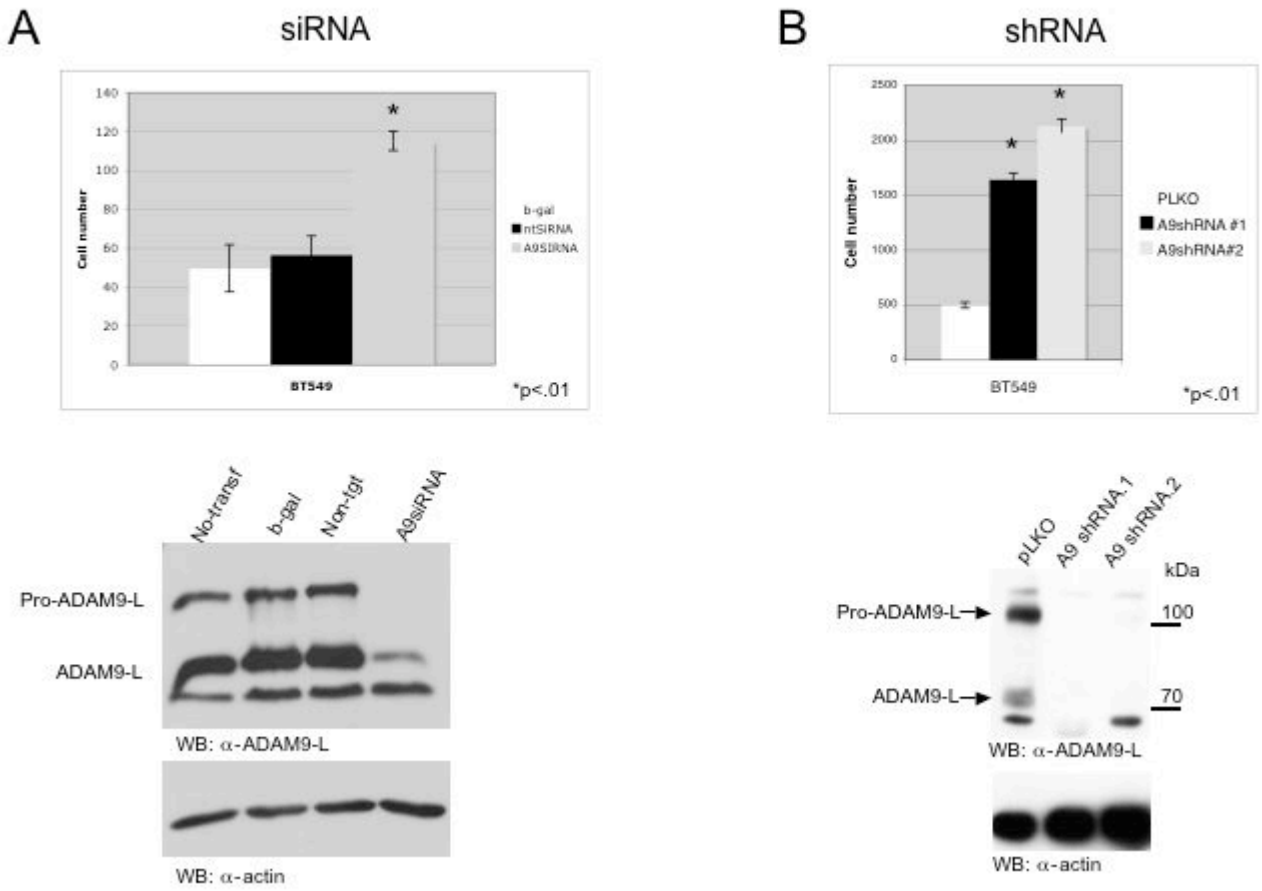


Figure 4 *Breast cancer cell lines lacking ADAM9 show an increase in cell migration* A) BT549 cells transfected with β-galactosidase alone, or in combination with non-targeting or ADAM9-specific siRNA pools purchased from Dharmacon Inc are migrated for 16 hours through an 8um transwell chamber and stained and counted as in previous experiments. The western blot shows silencing with the ADAM9siRNA pool, and otherwise equal expression of ADAM9-L in transfected and non-transfected controls. B) Virus produced from two lentiviral sequencing constructs in the PLKO.1 vector was used to infect BT549 cells for 24 hours. Cells were selected in 2ug/ml puromycin for 24 hours, and subsequently migrated for 4 hours through an 8um transwell chamber toward 3T3 medium. Migrated cells were stained with crystal violet, counted, and normalized to plating efficiency. The western blot shows knockdown of ADAM9-L using both lentiviral sequences.

Figure 5

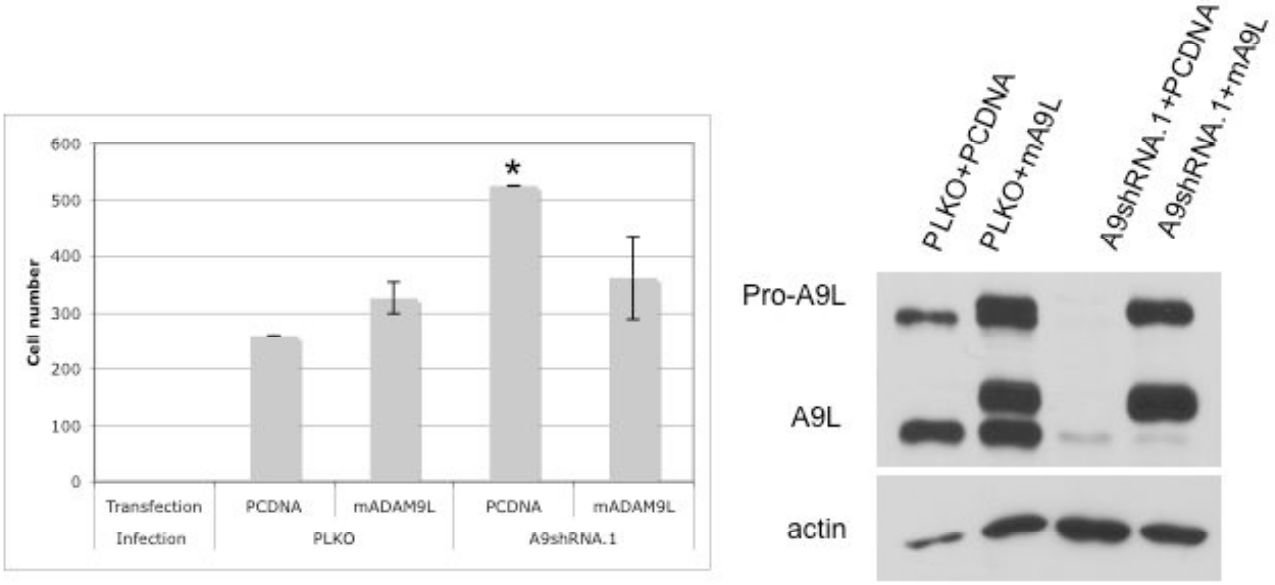


Figure 5 *Increased migration upon silencing of ADAM9 is rescued by introduction of wildtype ADAM9-L* Cells were infected with PLKO vector or ADAM9-silencing virus and selected as described previously. After 24 hours of selection, cells were transfected with PCDNA vector or mADAM9L wildtype construct and β-galactosidase. Migration assays were conducted and scored as described previously. The western blot shows silencing of ADAM9-L, as well as reconstitution with wildtype murine ADAM9-L (which runs higher than endogenous human ADAM9-L).

Figure 6

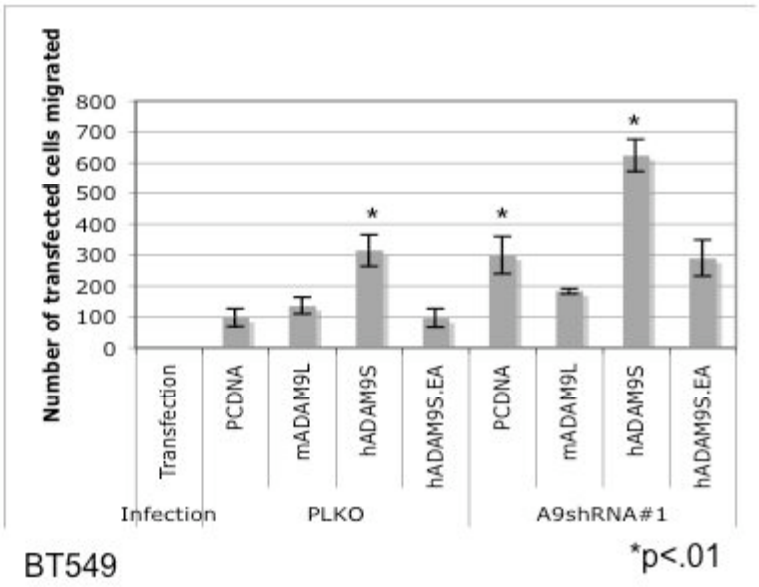
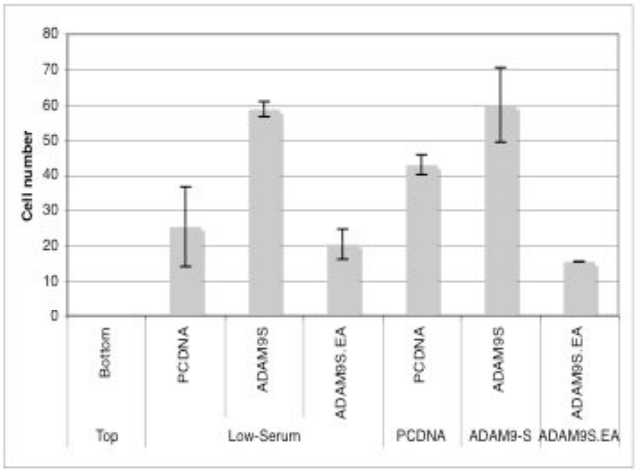


Figure 6 *The increased migration of cells with silenced ADAM9 is unaffected by reconstitution with ADAM9-S.* BT549 cancer cells were infected with PLKO or ADAM9-silencing lentivirus, selected, and transfected with ADAM9 constructs as described previously. While reconstitution with ADAM9-L restores cells to their original level of migration, transfection of ADAM9-S into either vector infected or silenced cells enhances migration. Transfection of the metalloprotease-deficient ADAM9S.EA recapitulates the effect seen on PCDNA control cells.

Figure 7



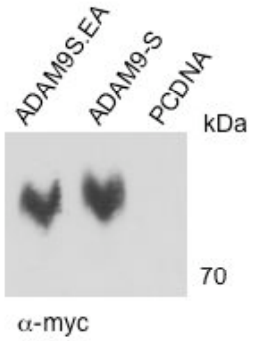
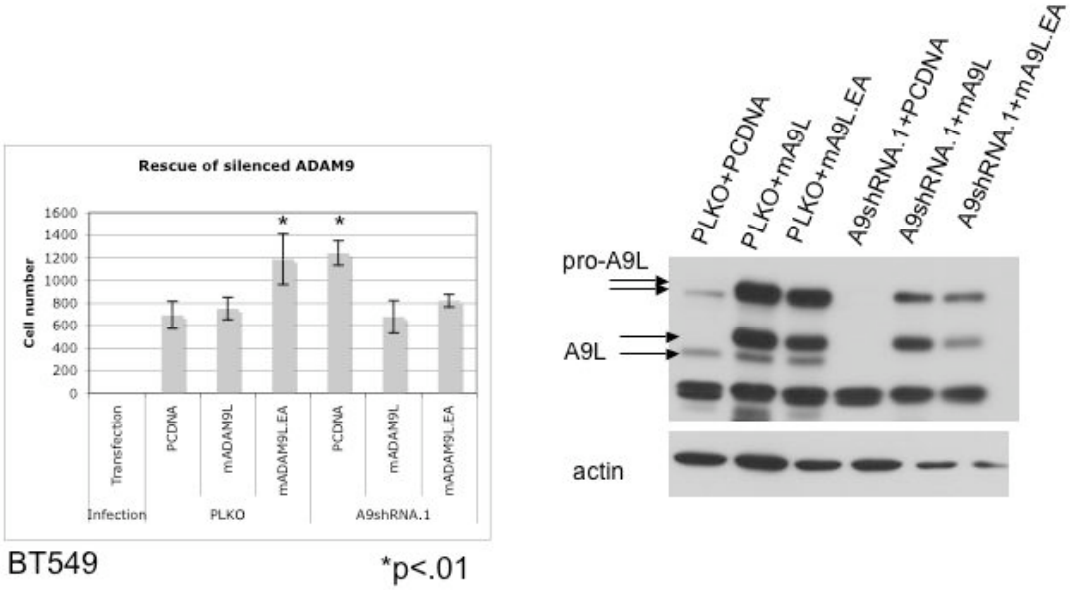


Figure 7 *ADAM9-S acts as a chemoattractant* Myc-tagged ADAM9-S and ADAM9S.EA constructs were expressed in HEK293T cells and serum-free supernatant was collected after 48 hours. This supernatant was placed in the bottom, or both bottom and top, of an 8um transwell chamber. BT549 cancer cells were plated in the upper well, and allowed to migrate for 16 hours before staining with crystal violet and counting. The western blot shows ADAM9-S and –S.EA in the cell supernatant.

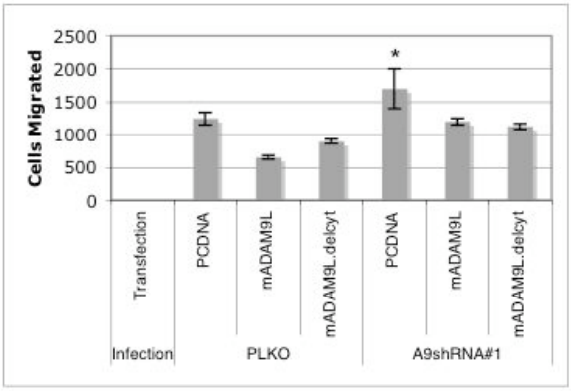
Figure 8



BT549 *p<.01

Figure 8 *The metalloprotease domain is not required for suppression of migration* BT549 cells were infected, selected and transfected with wildtype ADAM9-L, metalloprotease-deficient ADAM9-L, or vector control with β-galactosidase as described previously. Cells were migrated for 16 hours through an 8um transwell chamber and stained and counted as described in previous experiments. The western blot shows silencing of ADAM9-L as well as reconstitution with the wildtype and metalloprotease-deficient constructs.

Figure 9



BT549 *p<.01

Figure 9 *The cytoplasmic domain of ADAM9-L is not required for suppression of cell migration.* BT549 cells were infected and transfected with vector control, wildtype ADAM9-L and mADAM9L.delcyt as previously described. Cells were migrated for 16 hours in an uncoated 8um transwell chamber, and were stained and counted as previously described. Cells reconstituted with the ADAM9L.delcyt protein recapitulate the phenotypic rescue seen in the wildtype transfection.

Figure 10

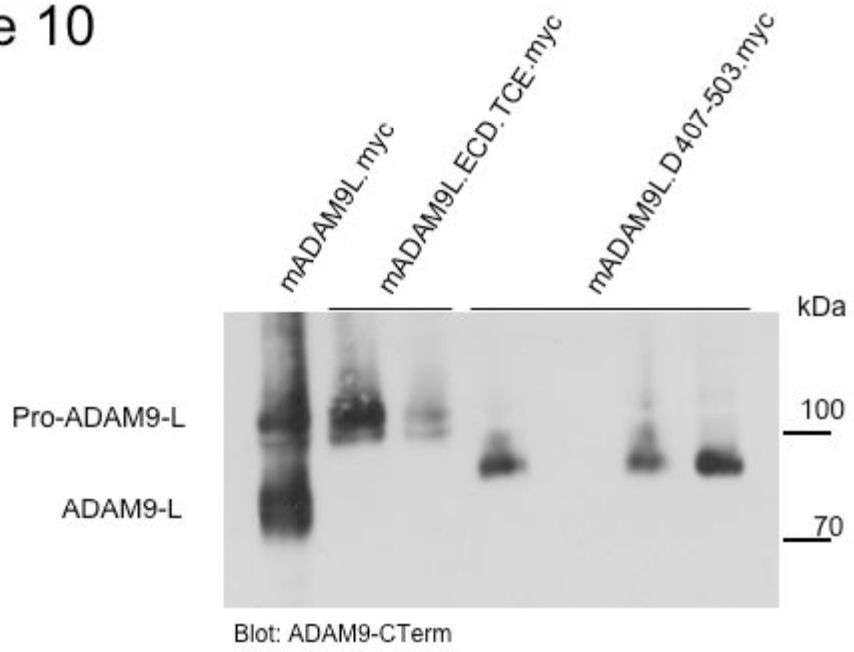


Figure10 *Alterations in the disintegrin domain result in aberrant protein processing.* Western blot using ADAM9-L specific antibody shows normal processing of HEK293T transfected ADAM9-L plasmid, but absence of furin-processing in the point mutant ECD.TCE construct. A larger deletion of the disintegrin domain D407-503, also shows absence of furin-processing.

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330 Brookline Ave, CLS 528-E
Boston, MA 02215
617. 735.2489

EDUCATION

Harvard University, Division of Medical Sciences — Boston, MA
Ph.D. Candidate, Biological and Biomedical Sciences — 2003-present

Massachusetts Institute of Technology — Cambridge, MA
S.B. Biology — 2003

RESEARCH EXPERIENCE

Harvard University, Beth Israel Deaconess Medical Center — Boston, MA
Graduate Researcher; Advisor: Alex Toker, Ph.D. — 2005-Present

The differential roles of A Disintegrin and Metalloprotease (ADAM)-9 isoforms in breast cancer cell migration and invasion.

- Confirmed the expression of the secreted isoform of ADAM9 (ADAM9-S) in breast cancer cell lines and tumors and the role of this protein as a chemoattractant.
- Identified opposing roles for membrane-bound ADAM9-L and ADAM9-S in cancer cell migration
- Tested the role of the metalloprotease function of ADAM9-S in cell migration
- Explored the mechanism by which ADAM9-L suppresses cell migration using gene reconstitution experiments and mutants in key functional domains, peptide blocking of the integrin-binding domain, and basic biochemistry.

Massachusetts Institute of Technology — Cambridge, MA
Undergraduate Researcher; Advisor: Tyler Jacks, Ph.D. — 2001-2003

Characterization of a GFP fusion to the N-terminus of the Neurofibromatosis Type 2 tumor suppressor protein, Merlin.

Techniques/Skills*:*
Retroviral vector construction and infection, flow cytometry, tissue culture and transfection, murine colony organization and husbandry, murine embryonic fibroblast collection, tumorigenicity assays – proliferation, focus formation, soft agar colony formation, and tumor formation in nude mice, co-immunoprecipitation, Western blotting, molecular biology techniques such as site-directed mutagenesis and cloning.

GRANTS AND AWARDS

Pre-Doctoral Traineeship Award — 2006-2009
Department of Defense Breast Cancer Research Program

ASBMB Poster Award – FASEB Experimental Biology 2009

PUBLICATIONS

Research articles

Fry, J.L., Toker, A. (2009). The two isoforms of ADAM9 differentially modulate breast cancer cell migration. (In Preparation)

Johnson, K.C., Kissil, J.L., **Fry, J.L.**, and Jacks, T. (2002). Cellular transformation by a FERM domain mutant of the Nf2 tumor suppressor gene. Oncogene 21, 5990-7

CONFERENCE PRESENTATIONS

Oral Presentations

- **Department of Defense Breast Cancer Research Program Meeting**
  Era of Hope, Baltimore, MD, June 2008
  Fry, JL, Toker A. The role of ADAM-9 in breast cancer cell migration.

Poster Presentations

- **FASEB – Experimental Biology 2009**
  ASBMB Principles of Receptor Signaling, New Orleans, LA, April 2009
  J.L Fry, A.Toker ADAM9 isoforms in breast cancer cell migration.

- **Dana-Farber/Harvard Cancer Center - Program in Breast Cancer**
  Sixth Annual Symposium, Boston, MA, March 2009
  Jessica L. Fry and Alex Toker The two isoforms of ADAM9 differentially modulate breast cancer cell migration.

- **Beth Israel Deaconess Cancer Center Symposium**
  Defining New Frontiers to Eradicate Cancer, Boston, MA, October 2008
  Fry, JL, Toker A. The role of ADAM-9 in breast cancer cell migration.

- **Department of Defense Breast Cancer Research Program Meeting**
  Era of Hope, Baltimore, MD, June 2008
  Fry, JL, Toker A. The role of ADAM-9 in breast cancer cell migration.

TEACHING EXPERIENCE

Harvard University	Boston, MA
Teaching Assistant, Pathology 211	2005
Mentor, Mentoring for Science program	2005
Tutor, Cell Biology 201	2005-present
Cochise Community College	Sierra Vista, AZ
Tutor, Calculus I-III, Biology I, Chemistry I	1999-2000

REFEREES

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