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TITLE: Decoding the Mechanoregulation of Breast Tumor Organoid Invasion, One Cell at a Time

PRINCIPAL INVESTIGATOR: Bo Sun

CONTRACTING ORGANIZATION: Oregon State University

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The vast majority of breast cancer deaths are related to metastasis, during which cell migrate and invade surrounding tissue. Attempts to design effective drug treatments for metastasis have largely failed. A major reason for this failure is the plasticity of migrating cancer cells: they are able to rapidly switch between different modes of migration when faced with different extracellular environment. As a consequence, drugs that target a single migration mode will not be effective in stopping metastasis. This plasticity is poorly understood but depends strongly on the mechanical properties of the extracellular matrix (rigidity, fiber alignment, pore size, etc.). In this project, we will carry out quantitative experiments which determine the modes of migration as a function of the extracellular matrix properties, quantify the transitions between migration modes, and determine how the remodeling of the extracellular matrix couples back to the migration mode and mode transitions.

15. SUBJECT TERMS

NONE LISTED

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We aim to address the overarching challenge to understand why some breast cancers become metastatic. Metastasis is enabled by cell migration during which cancer cells navigate through and negotiate space within the extracellular matrix (ECM). During metastasis, cancer cells can dynamically switch migration modes and these transitions between modes may significantly contribute to the invasive properties of tumors. To directly address the overarching challenge, we hypothesize that bidirectional and mechanical interactions in the cell-ECM system regulate the migration mode switching of breast cancer cells, which ultimately determines the metastatic potential of breast tumors. We will employ a combination of quantitative experiments, automated algorithmic data analysis, and computational modeling. Our project has two specific aims:

Aim 1: To quantify how breast cancer cell migration mode transitions are determined by extracellular matrix properties and mechanotransduction pathways.

Aim 2: To determine how the invasiveness and migration mode transitions of disseminating breast cancer cells depend on collective extracellular matrix remodeling and tumor geometry.

Cancer, metastasis, migration, morphology, migration modes, modeling

What were the major goals of the project?

The major goals of this project are to quantify how breast cancer cell migration mode transitions are determined by extracellular matrix properties and mechanotransduction pathways and to determine how the invasiveness and migration mode transitions of disseminating breast cancer cells depend on collective extracellular matrix remodeling and tumor geometry.

Aim 1: To quantify how breast cancer cell migration mode transitions are determined by extracellular matrix properties and mechano-transduction pathways

Major Task 1: To quantify the ECM micromechanical control of migrational mode transitions
Milestone of Major Task 1: establish how ECM micromechanical rigidity and anisotropy modulate the migration mode transition rates of breast cancer cells of different subtypes.
Major Task 1 is 100% accomplished.

Major Task 2 To identify main molecular pathways that regulate cell migrational mode transitions
Milestone of Major Task 2: establish how mechanosensing pathways modulate the migration mode transition rates of breast cancer cells. Examine the pathways with different subtypes of breast cancer cells
Major Task 2 is 70% accomplished

Major Task 3: Development of a comprehensive cell motility model
Milestone of Major Task 3: develop a validated cell motility model that can be validated using experimental data and that can generate experimentally testable predictions.
Major Task 3 is 60% accomplished

Aim 2: To determine how the invasiveness and migration mode transitions of disseminating breast cancer cells depend on collective extracellular matrix remodeling and tumor geometry

Major Task 4: To determine individual cell migrational mode transitions in disseminating tumor organoids
Milestone of Major Task 4: establish the spatial-temporal pattern of cancer cell migration mode transitions disseminating from tumor organoids. Test the effects of ECM micromechanics remodeling in modulating cell migration mode transitions in these dissemination processes.
Major Task 4 is 30% accomplished

Major Task 5: Development of a computational model for collective ECM remodeling and tumor organoid invasion

Milestone of Major Task 5: validate an efficient computational model for collective ECM remodeling and tumor organoid invasion

Major Task 5 is yet to begin.

What was accomplished under these goals?

Major Task 1: To quantify the ECM micromechanical control of migrational mode transitions

Milestone of Major Task 1: establish how ECM micromechanical rigidity and anisotropy modulate the migration mode transition rates of breast cancer cells of different subtypes.

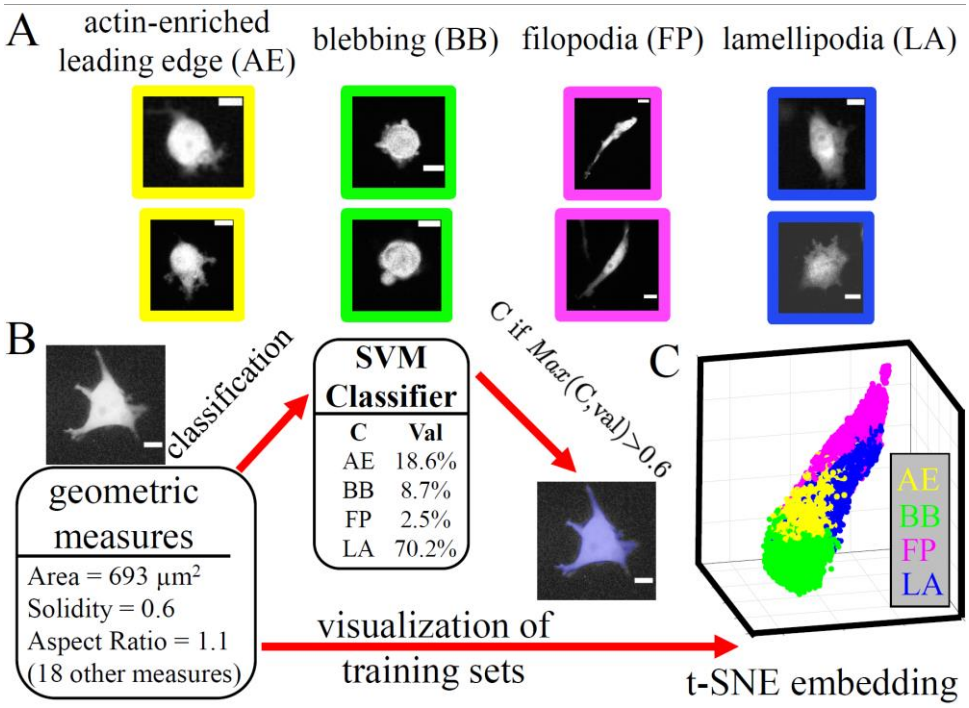

Fig. 1 This Figure shows the development of a supervised machine learning model to classify cells into morphological phenotypes corresponding to different migration modes. (A) MDA-MB-231 cells in 3D collagen matrices exhibit multiple morphological phenotypes that are characteristic of four distinct migration modes: actin-enriched leading edge (AE), small blebbing (BB), filopodial (FP), and lamellipodial (LA). (B) The cell images are quantified using a total of 21 geometric measures such as area, solidity, and aspect ratio. With 3800 manually labeled single cell images we have trained a supported vector machine (SVM) to calculate probability scores (Val) for a cell to belong to each morphological phenotypes (classes). In (B) a sample cell image is classified as a lamellipodial cell (LA), because LA class has a score of greater than 0.6. (C) To better visualize the high dimensional geometric measures, we apply t-SNE method to generate a 3D projection of the geometric cell shape space. 15,000 unseen data set is presented here. Different morphological phenotypes are well separated. AE (yellow): actin-enriched leading edge. BB (green): small blebbing. FP (magenta): filopodial. LA (blue): lamellipodial.

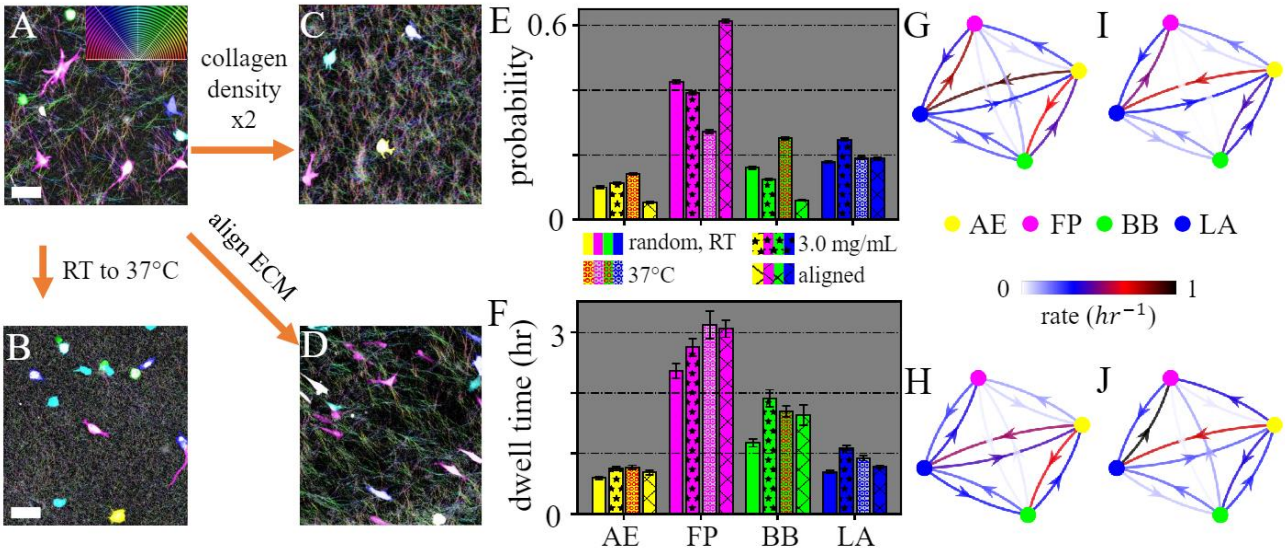

Fig. 2 This figure shows how physical properties of collagen ECM regulate the morphological phenotype homeostasis of breast cancer cells. (A-D) Confocal reflection images and pseudo colored breast cancer cells for collagen matrices prepared at varying conditions. A: collagen ECM prepared at room temperature (RT, or 25 Celsius) and collagen concentration of 1.5 mg/mL. B: collagen ECM prepared at 37 Celsius and= 1.5 mg/mL. C: collagen ECM prepared at RT and concentration of 3.0 mg/mL. D: collagen ECM prepared with flow-aligned collagen fibers. (E) Fraction of cells in each morphological phenotype. 8,000 single cell images are analyzed under each ECM condition. (F) Dwell time of cells in each morphological phenotype. Errorbars in (E-F) represent 95% confidence intervals calculated from 1000 bootstrap iterations. (G-J): The transition matrix -- morphological phenotype transition rates under varying ECM conditions. G: collagen ECM prepared at room temperature and concentration of 1.5 mg/mL. H: collagen ECM prepared at 37 Celsius and concentration of 1.5 mg/mL. I: collagen ECM prepared at RT and concentration of 3.0 mg/mL. J: collagen ECM prepared with flow-aligned collagen fibers. Under each ECM condition a total of more than 2,000 hours of single cell trajectories are analyzed.

During the past reporting period, we made progress towards major task 1. In one published report, Eddy et al, **Morphodynamics facilitate cancer cells to navigate 3D extracellular matrix**, Scientific Reports, 2021, 11:20434, we examined the migration phenotype of breast cancer cells in 3D extracellular matrix. We developed a computer algorithm that quantified the morphology of cells using a set of 18 values such as aspect ratio, solidity and circularity. Based on these shape measures, we trained a machine learning model to classify the cell into four established migration phenotypes based on cell morphology (Fig.1). We showed that breast cancer cells exhibit multiple mode of migration and the transition between these modes

are highly dependent on the extracellular matrix (ECM) physical properties. In particular, we showed that collagen matrices with homogeneous structure enriched the population of blebbing cells (BB). The enrichment of blebbing cells was directly related with the reduced transition rate from BB to Actin Enriched Leading Edge (AE) state, and also indirectly contributed by the mesenchymal-to-amoeboidal transition through lamellipodial (LA) and AE states. Similarly, collagen matrices with structural anisotropy enriched the population of filopodial (FP) cells. The enrichment was directly attributed to an increased LA to FP rate, and indirectly contributed by the amoeboidal-to-mesenchymal transition mediated by LA and AE states (Fig.2).

Major Task 2 To identify main molecular pathways that regulate cell migrational mode transitions

Milestone of Major Task 2: establish how mechanosensing pathways modulate the migration mode transition rates of breast cancer cells. Examine the pathways with different subtypes of breast cancer cells

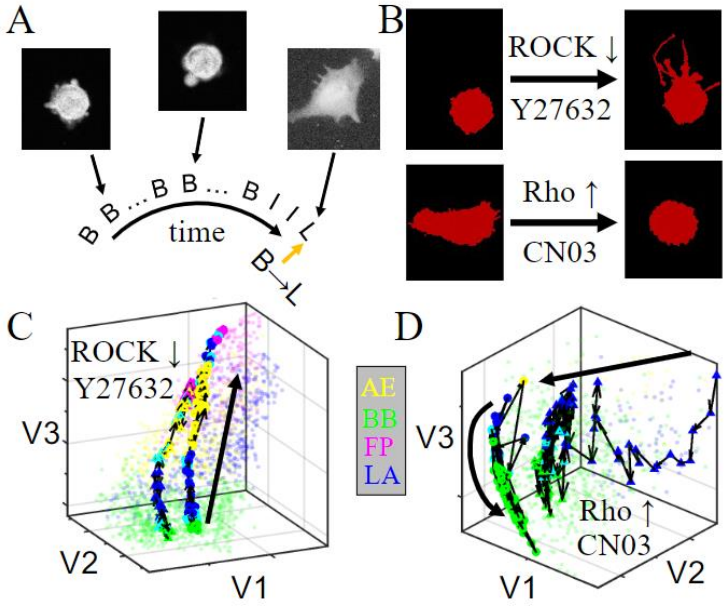

Fig. 3 This Figure shows how Rho/ROCK-signaling internally controls mesoscale morphodynamics of 3D cultured breast cancer cells. (A) A sample time series of morphological phenotype. Insets: three snapshots showing the GFP-labeled cell morphology. Abbreviations: B -- blebbing, I -- intermediate state, L -- lamellipodial. (B) Representative morphological changes under treatment of Y27632 and CN03, which downregulates and upregulates Rho/ROCK signaling respectively. (C-D) Characteristic morphodynamic trajectories of cells in the t-SNE embedded shape space. The trajectories start immediately after introducing Y27632 or CN03, and ends after 12 hours of incubating with the drugs. The forward time directions are shown as thick curves with arrows as guide to the eyes. Two representative trajectories (one with circular symbols, and another one with triangular symbols) per each treatment are shown as colored symbols connected by black lines, where color represents the instantaneous phenotype.

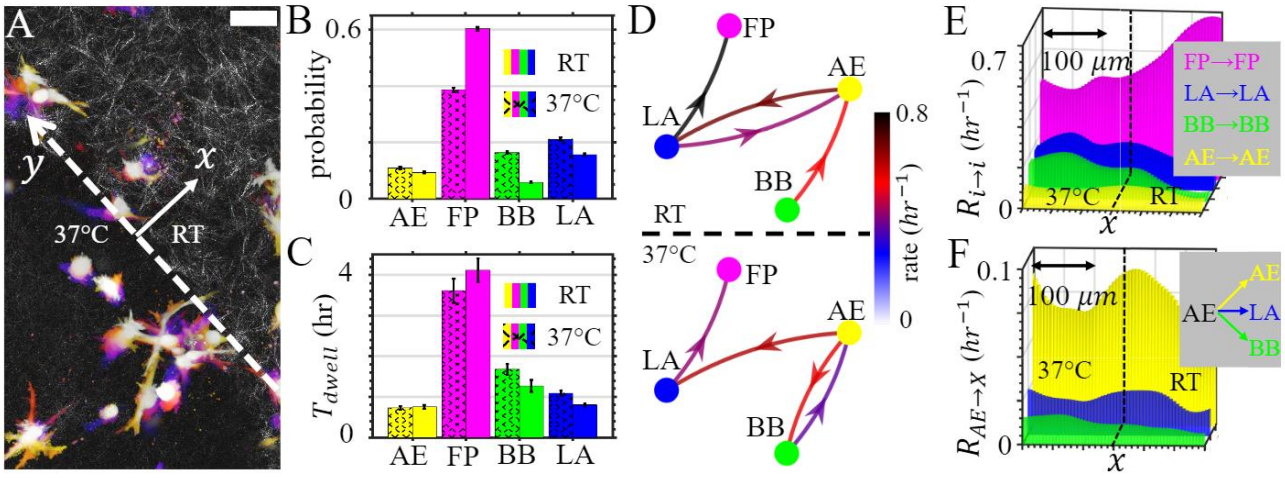

Fig. 4 This Figure shows morphological phenotype transition facilitates cell migration in heterogeneous ECM. (A) Time-lapse projection of 3D migrating breast cells navigating engineered heterogeneous ECM. The ECM contains two adjacent layers that are prepared at room temperature (RT) and 37 Celsius respectively. A confocal reflection image shows the ECM structure next to the interface. (B) Fraction of cells of each morphological phenotype in both sides of the interface. (C) Dwell time of cells of each morphological phenotype in both sides of the interface. (D) Phenotype transition rates in both sides of the interface. (E) Spatial frequency of of dwell events. (F) Spatial frequency of AE to AE, AE to LA and AE to BB events. A total of 3,800 hours of single cell recordings from three independent experiments have been used to calculate the results in (B-F).

During the past reporting period, we made progress towards major task 2. In one published report, Eddy et al, **Morphodynamics facilitate cancer cells to navigate 3D extracellular matrix**, Scientific Reports, 2021, 11:20434, we examined the migration phenotype of breast cancer cells in 3D extracellular matrix. We showed perturbations of Rho/ROCK-signaling altered the migration mode transition rates. In particular, down regulating Rho led to overall amoeboidal-to-mesenchymal transition that routed through AE and LA states. Activation of Rho, on the other hand, led to strongly fluctuating morphodynamics that enriched blebbing cells(Fig. 3 and Fig.4). Taking together, we showed that the migration of cancer cells in 3D ECM was a hidden Markov process, where morphodynamics facilitated cancer invasion because phenotype transitions allowed cancer cells to search for and commit to a more effective migration program in the presence of mechanical heterogeneity of the ECM.

Major Task 3: Development of a comprehensive cell motility model

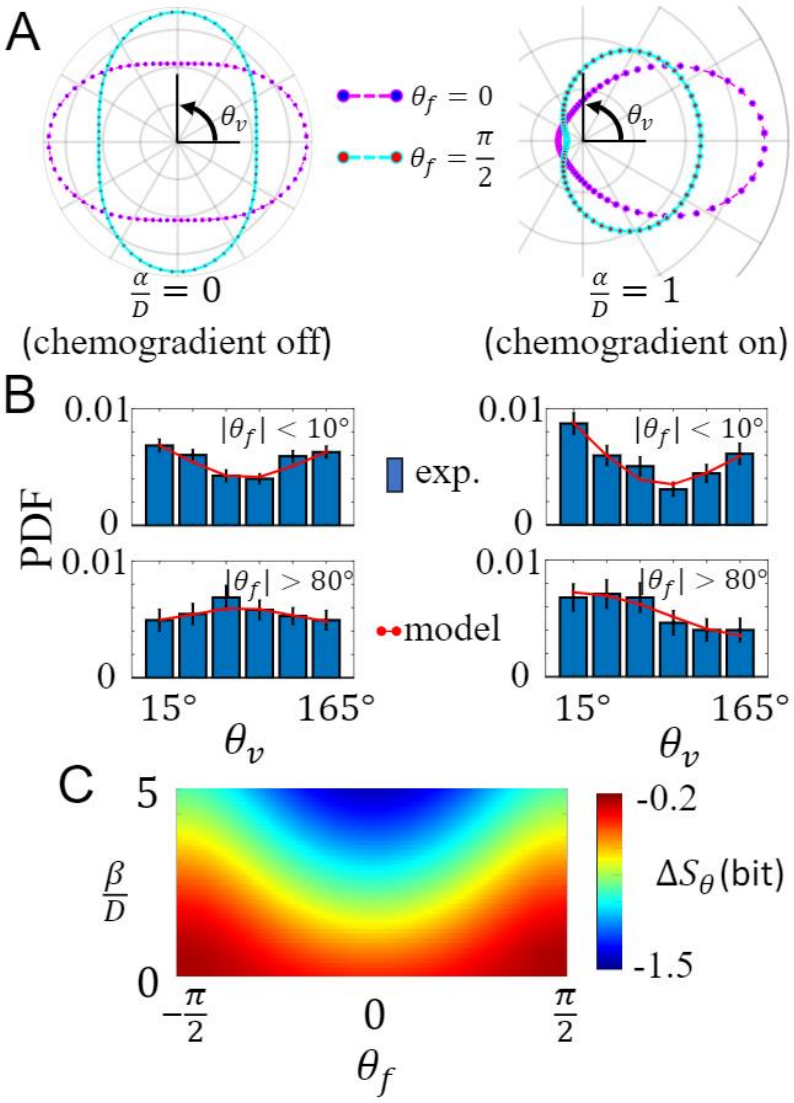

Fig. 5 This figure shows that our theoretical model predicts cancer cell motility in response to dual mechanochemical guidance. (A) Probability distribution of cell velocity direction when cues agreement is maximal (magenta), and when cues agreement is minimal (cyan). Left: only the mechanical cue is present. Right: both chemical and mechanical cues are present. (B) Typical experimental results corresponding to scenarios shown in (A). Abbreviations: PDF: probability distribution function; exp. experiments. For each histogram, N>1000 data points are included. Error bars are obtained from standard deviation of 100 bootstrap iterations. (C) Uncertainty of cell migration direction quantified by the differential entropy of migration angle. The heat map shows the change of differential entropy in comparison with the case without external guidance.

During the past reporting period, we made progress towards major task 3. In a published report, Esfahani et al, **Three-dimensional Cancer Cell Migration Directed by Dual Mechanochemical Guidance**,

Physics Review Research 2022, 4, L022007, we examined the 3D migration of breast cancer cells in the presence of both chemical and mechanical cues and developed a theoretical model to predict and verify with experiments. There the chemical cue was a serum gradient that drove chemotactic motion, and the mechanical cue originated from the alignment of ECM that forced contact guidance of migration. We showed that in this more realistic situation that modeled physiological conditions, the chemotaxis of cells was complicated by the presence of contact guidance as the microstructure of extracellular matrix (ECM) varied spatially. In the presence of dual guidance, the impact of ECM alignment was determined externally by the coherence of ECM fibers, and internally by cell mechanosensing Rho/Rock pathways. When contact guidance was parallel to the chemical gradient, coherent ECM fibers significantly increased the efficiency of chemotaxis. When contact guidance was perpendicular to the chemical gradient, cells exploited the ECM disorder to locate paths for chemotaxis. We have constructed a mathematical model of guided stochastic cell motility, which agrees with the experimental observations (Fig. 5) Our results underscored the importance of fully characterizing the cancer cell microenvironment in order to better understand invasion and metastasis.

Major Task 4: To determine individual cell migrational mode transitions in disseminating tumor organoids

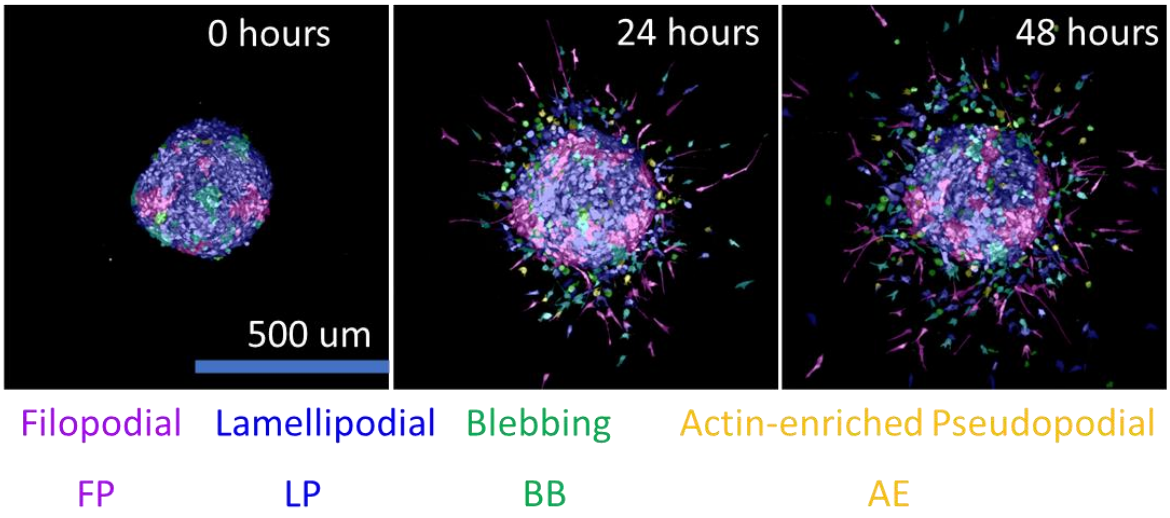

Fig. 6 The figure shows the AI-assisted segmentation and classification of breast cancer cells disseminating from tumor spheroids. Individual cells are colored by the migration phenotypes.

During the past reporting period, we made progress towards major task 4. We have developed a deep-learning based algorithm to segment and classify the migration phenotype of individual cells disseminating from tumor spheroids (Fig. 6). We have conducted experiments for varying ECM concentration (1.5mg/mL, 3mg/mL, 4 mg/mL and 6 mg/mL), with and without crosslinking. Additional experiments and analysis will be performed during the next reporting period.

In an additional published report (Ghabache et al, **Coupling traction force patterns and actomyosin wave dynamics reveals mechanics of cell motion,** Molecular systems biology, 17, e10505, 2022), we used traction force microscopy and fluorescent labeling of actin and myosin to quantify and correlate traction force patterns and cytoskeletal distributions in motile eukaryotic cells that move and switch between keratocyte-like fan-shaped, oscillatory, and amoeboid modes. We found that the wave dynamics of the cytoskeletal components critically determine the traction force pattern, cell morphology, and migration mode. Furthermore, we found that fan-shaped cells can exhibit two different propulsion

mechanisms, each with a distinct traction force pattern. Finally, we showed that the traction force patterns can be recapitulated using a computational model, which uses the experimentally determined

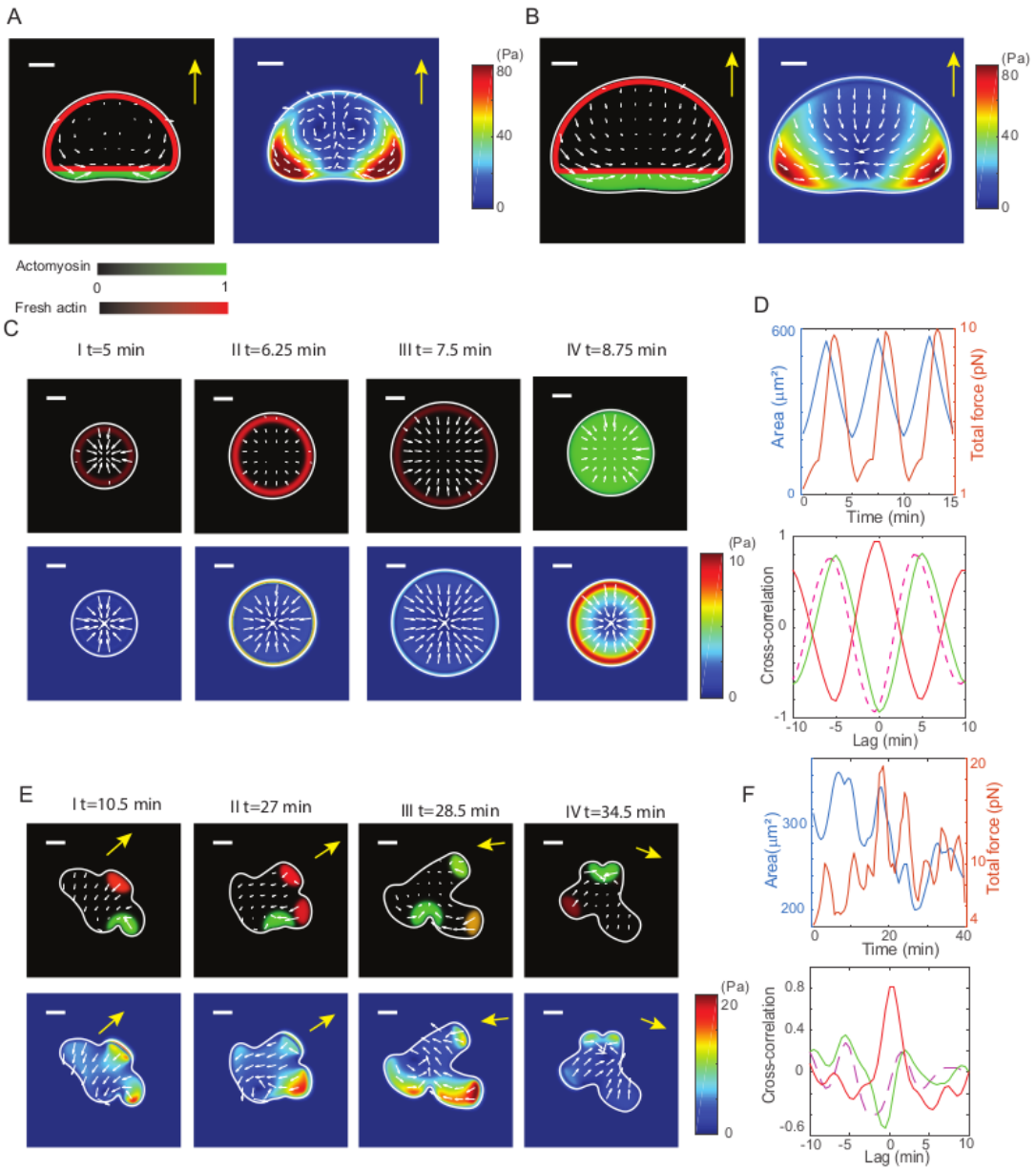

Fig. 7 This figure shows that a computational model can reproduce the different migration modes as well as the traction force patterns generated by migrating eukaryotic cells. Shown here are the keratocyte-like (A and B), oscillatory (C-D), and amoeboid mode (E and F).

spatiotemporal distributions of actin and myosin forces and a viscous cytoskeletal network. This is shown in Fig. 7 where we have plotted the three different migration modes obtained in the simulations, along with the

distributions of actin and myosin (in red and green, respectively), and their traction force patterns (using the indicated color scale). This figure also shows, for the oscillatory and amoeboid mode, the area as a function of time (D and F) as well as the cross correlation between myosin and actin (D and F). Our results suggest that cell motion can be generated by friction between the flow of this network and the substrate.

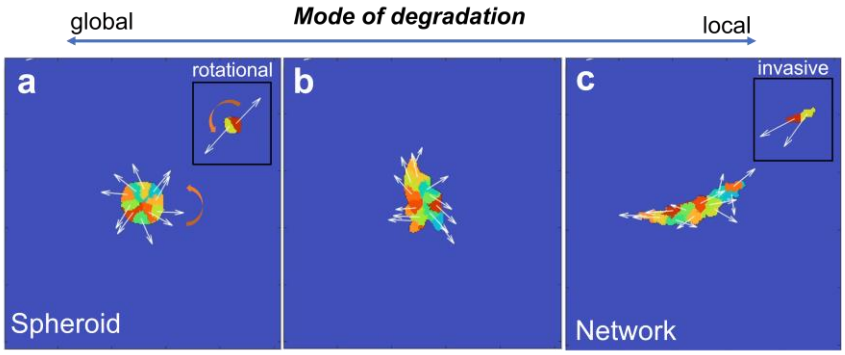

Fig. 8 Results of a computational model shows that global ECM degradation results in rotating spheroid structures (left panel) while local ECM degradation leads to network-like structures (right panel).

In preliminary work, we also studied the migration modes of cancer cells seeded in an ECM with varying properties. Specifically, we determined when, after multiple divisions, cancer cells for a network structure in which they become elongated, form strands of cells, and invade the ECM, and when they form a compact spheroidal structure that rotates. In experimental work, we found that high density ECM results in a large proportion of cells becoming spheroidal and not invasive. To probe potential mechanisms that may be responsible for this finding, we developed a computational model that takes into account cell morphology, cell polarity, cell-cell adhesion, and cell-ECM interaction. This model predicted that the degree of localization of the ECM degradation plays a crucial role in the resulting migration phenotype. Specifically, local degradation, present at the front of the cells, favored the formation of network structures while global degradation resulted in spheroid structures, as presented in Fig. 8. In this figure, cells are embedded in the ECM (shown in blue) and are given different colors for visualization purposes. The white arrows represent

the polarity of the cells. This prediction was then verified using novel experiments that quantified the localization of degraded matrix fibers.

What opportunities for training and professional development has the project provided?

As part of this project, Dr. Christopher Eddy, a postdoc at Oregon State University, was trained in carrying out experiments and analyzing data. Furthermore, this project offered him training in writing scientific manuscripts. Mr. Pedram Esfahani, a graduate students at Oregon State University was involved in the project. He was trained in conducting live cell experiments, extracellular matrix engineering and data analysis. He was trained in writing and presenting his scientific communication skills that helped him to get ready to defend his PhD thesis soon.

In addition, Dr. Ghabache, Dr. Karmakar, and Dr. Elmi, post-doctoral researchers at UC San Diego, were supported by this grant and were able to further develop their modeling and analysis skills. Finally, all participants were given the opportunity to improve their presentation skills during our group meetings.

How were the results disseminated to communities of interest?

One study has been published in a prestigious, peer-reviewed journal (Morphodynamics facilitate cancer cells to navigate 3D extracellular matrix, Scientific Reports, 2021, 11:20434, and Three-dimensional Cancer Cell Migration Directed by Dual Mechanochemical Guidance, Physics Review Research 2022, 4, L022007). Dr. Eddy and Mr. Esfahani both presented the research at the American Physical Society meeting. Dr. Eddy additionally presented the research at Allen Institute, and Oregon Health and Science University. In addition, another study was published in the high-impact, peer reviewed journal Molecular Systems Biology (Coupling traction force patterns and actomyosin wave dynamics reveals mechanics of cell motion, Ghabache et al., Molecular systems biology. 2021 17 e10505).

Impact

What was the impact on the development of the principal discipline(s) of the project?

Our results, reported in Eddy et al Scientific Reports, 2021, provide insights into breast cancer cell metastasis in 3D extracellular matrices (ECMs). Breast cancer cells and are known to exhibit multiple mode of migration,

which poses significantly challenges to the treatment of metastasis disease. Our results demonstrate that even at single cell level, cancer cells are able to switch between different migration modes. Therefore, the migration of cancer cells in 3D ECM should be considered as a hidden Markov process, where the ECM regulates the cell motility by modulating the mode transition dynamics. This new perspective of cancer cell motility sheds light to the mechanism and therapeutics of metastatic solid tumors.

Our results, reported in Esfahani et al Physical Review Reports, 2022, provide insights into the directed motility of breast cancer cells. In physiological conditions multiple external cues often exist simultaneously. Our results demonstrate how cells integrate mechanical and chemical cues together to decide on the direction of motility. These results offer a generalizable framework to under stand and predict the metastasis of breast cancer cells in complex physiological environment.

The published report Ghabache et al, Molecular systems biology, 2021, presents a computational model that can address how motile cells can use and switch between different modes of migration. We showed how this model can be critically compared to quantitative experimental data, including data from traction force microscopy and fluorescent labeling of actin and myosin. Furthermore, we showed that this model can reproduce the experimental data and can provide further insights into the correlation between signaling and force generation. These results indicate that cell motion is critically dependent on the flow of the cytosolic actomyosin network and that friction between this flow and the substrate can generate the required traction for movement.

What was the impact on other disciplines?

Our project is highly disciplinary and involves, aside from cancer biology, the field of cell biology and mathematical modeling. It will thus have an impact on these disciplines. For cell biology, for example, our experimental studies provide deeper insights how cell morphologies and cell migration are internally controlled by Rho/Rock signaling and externally by extracellular matrix geometry and mechanics. Our result also provides an image-based algorithm to automatically classify cell morphological phenotypes, which can be applied to essentially any types of mammalian cells. In addition, our mathematical models are able to address morphological changes in migrating cells and should be extendable to a wide variety of cell biology problems.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

4. Changes/Problems

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Due to the COVID-19 pandemic, the lab operation still encounters frequent disruption such as due to lab member being infected or exposed. In addition, many research supporting functionality, such as shipping of reagents, staff hiring, facility access, and equipment maintenance were occasionally impacted. As such, even with our best effort to address the challenges, we expect delays in the research output.
We are making our best efforts to prioritize the health of lab members while at the same time keeping research on pace. For instance, we have been working with multiple vendors to reduce delays of key experimental reagents. We have also been utilizing non-regular business hours to access key facilities.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

5. Products

Publications, conference papers, and presentations.

Journal publications.

Morphodynamics facilitate cancer cells to navigate 3D extracellular matrix, Christopher z Eddy, Helena Raposo, Aayushi Manchanda, Ryan Wong, Fuxin Li, Bo Sun, Scientific Reports, 2021, 11:20434 *acknowledgement of federal support: yes*

Three-dimensional Cancer Cell Migration Directed by Dual Mechanochemical Guidance, Pedram Esfahani, Herbert Levine*, Mrinmoy Mukherjee, Bo Sun*, Physics Review Research 2022, 4, L022007 *acknowledgement of federal support: yes*

The Mechanics of Fibrillar Collagen Extracellular Matrix, Bo Sun, Cell Reports Physical Science, 2021, 2, 100515 *acknowledgement of federal support: yes*

Coupling traction force patterns and actomyosin wave dynamics reveals mechanics of cell motion, Elisabeth Ghabache, Yuansheng Cao, Yuchuan Miao, Alex Groisman, Peter N. Devreotes, and Wouter-Jan Rappel. Molecular systems biology, 17 2021, p.e10505. *acknowledgement of federal support: yes*

6. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Participants at Oregon State University

Name:	Bo Sun
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	0000-0001-7001-8781
Nearest person month worked:	1
Contribution to Project:	Oversee overall project progress, analyze data, write manuscript,

	coordinate with collaborating labs
Funding Support:	DOD, NSF, NIH

Name:	Christopher Eddy
Project Role:	Postdoc Scholar
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	conduct experiment, analyze data, write manuscript
Funding Support:	DOD W81XWH-20-1-0445

Name:	Pedram Esfahani
Project Role:	Graduate student
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	conduct experiment, analyze data, write manuscript
Funding Support:	DOD, NIH

Name:	Elisabeth Ghabache
Project Role:	Postdoctoral Scholar
Researcher Identifier (e.g. ORCID ID):	0000-0001-9832-9354
Nearest person month worked:	1
Contribution to Project:	Dr. Ghabache is responsible for data analysis
Funding Support:	DOD, NSF, Human Frontiers Program

Name:	Richa Karmakar
Project Role:	Postdoctoral Scholar
Researcher Identifier (e.g. ORCID ID):	0000-0002-9741-6816
Nearest person month worked:	5
Contribution to Project:	Dr. Karmakar is involved in the development of the model that can address how cells can use and switch between different migration modes
Funding Support:	DOD, NSF, NIH

Name:	Wouter-Jan Rappel
Project Role:	Collaborating PI

Researcher Identifier (e.g. ORCID ID):	0000-0003-3833-7197
Nearest person month worked:	2
Contribution to Project:	Dr. Rappel is the collaborating PI on the project and responsible for the modeling efforts
Funding Support:	DOD, NSF, NIH

Name:	Dorsa Elmi
Project Role:	Postdoctoral Scholar
Researcher Identifier (e.g. ORCID ID):	0000-0002-9741-6816
Nearest person month worked:	5
Contribution to Project:	Dr. Elmi is responsible for model development for cells in ECMs with varying composition
Funding Support:	DOD, NSF, NIH

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

We collaborated the project with Dr. Herbert Levine from Northeastern University, Dr. Joe Gray from Oregon Health and Science University, and Dr. Peter Devreotes from Johns Hopkins University

7. Special Reporting Requirements

8. Appendices