Penn Engineering

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Fwd: Editorial Decision on manuscript CELL-REPORTS-D-20-04331

27 messages

Vivek Shenoy <vshenoy@seas.upenn.edu> Tue, Dec 1, 2020 at 6:53 AM
To: Ze Gong <gongze@seas.upenn.edu>, Ovijit Chaudhuri <chaudhuri@stanford.edu>, Eoin McEvoy <emcevoy@seas.upenn.edu>, Katrina Wisdom <kmwisdom@seas.upenn.edu>, Omokolade Olayiwola Adebowale <kaa@stanford.edu>, Julie Chang <jchang39@stanford.edu>

Hopefully we can address the concerns.

---------- Forwarded message ---------
From: **Cell Reports** <em@editorialmanager.com>
Date: Tue, Dec 1, 2020 at 6:29 AM
Subject: Editorial Decision on manuscript CELL-REPORTS-D-20-04331
To: Vivek B. Shenoy <vshenoy@seas.upenn.edu>

Dr. Shenoy,
University of Pennsylvania
Materials Science and Engineering
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UNITED STATES

Dec 01, 2020

Manuscript Number: CELL-REPORTS-D-20-04331
"Recursive Feedback Between Matrix Dissipation and Chemo-mechanical Signaling Drives Oscillatory Growth of Cancer Cell Invadopodia"

Dear Dr. Shenoy,

Thank you for submitting your manuscript to Cell Reports. I am including the reviewer comments, which I hope you will find useful and constructive. As you will see, they express interest in the study, but they also have several criticisms and suggestions. If it is possible to address the concerns raised with additional data and/or discussion, we would be interested in considering a revised version of the manuscript.

Please consult me with any questions you have during the revision process (r.gemayel@cell.com). The timing for revision is flexible. If you anticipate that revisions will take longer than 2-3 months, please contact our editorial office (reports@cell.com) to discuss your anticipated timing for resubmission.

We understand that the global COVID-19 situation has likely caused disruptions for you and your colleagues. If that is the case for you and it has an impact on the revision process, please let me know so we can work with you on a plan for moving your paper forward (r.gemayel@cell.com). We appreciate the professional and personal challenges you and your lab members may be facing due to the pandemic situation, and we want to assure you that Cell Reports is very flexible on the timing for revisions. Please keep us updated on your progress at reports@cell.com, and feel free to contact me with any specific questions or concerns.

IMPORTANT: STAR Methods formatting
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Table using this interactive webform. Please contact me (r.gemayel@cell.com.) if you have any questions about restructuring your manuscript using the STAR Methods format.

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Thanks again for submitting your work to Cell Reports. I look forward to reading your revised manuscript.

Sincerely,

Rita Gemayel, Ph.D.
Associate Editor, Cell Reports
r.gemayel@cell.com

Administrative correspondence:
Andrew Ferrell and David Paradela, Editorial Operations Associate
617-386-2190
email: reports@cell.com

Reviewers' comments:

Reviewer #1: This study provides an exciting model that couples intracellular and invadopodia dynamics with ECM remodeling. This is a timely study, with many recent studies highlighting the importance of ECM viscoplasticity on cell behavior. The study primarily focuses on a novel model, along with experimental data of cells in gels with tunable viscoplastic properties. Overall the model incorporates relevant features, including signaling, cytoskeletal dynamics, and ECM properties, and experimental data appear to support aspects of the model. Additional and closer coupling between experimental and modeling results would be very helpful to further validate the model and derive quantitative insights.

This is an exciting and potentially impactful study that warrants further consideration. Specific comments:

1) More reconciliation between experiments and model should be done, especially for this journal. Currently, most comparisons are qualitative juxtapositions between representative experimental data and representative computational results. There should be better and more rigorous reconciliation between experiments and model, and there should be more quantitative assessments of how well the model matches different experimental data.

2) The authors calibrate their model to some initial experimental data. After this calibration, the authors should then determine how sensitive the model is to different parameters. With the calibrated model and an understanding of the sensitivity to parameters, the model should then be applied to simulate experiments where known parameters are controlled (e.g. drug studies and studies in different gels). Then experimental and "predictive" computational results should be compared to determine how well the model matches experimental findings. Such predictive readouts and sensitivity analyses would provide important insights.

3) This study ends up focusing largely on invadopodia dynamics. However, a central aspect of the paper and one of the unique and exciting aspects of the model is the coupling between invadopodia and matrix remodeling. This coupling is seldom the focus of the figures, and instead invadopodia dynamics is emphasized. Numerous studies already exist about the mechanisms of invadopodia, including models. More emphasis of the coupling between ECM and invadopodia along with direct experimental validation of this coupling is warranted. The relationship between invadopodia dynamics and matrix remodeling, which this model seems to have the capability to explore, should be more extensively explored with complementary experimental and computational readouts. Further assessment on the accuracy of the model should be done.

4) Can the map in Fig. 4F be compared between experimental and computational results?

5) Figure 5 is another example of the juxtaposition between experiments and model without quantitative assessment of model accuracy. It would be helpful if closer comparisons are made and it is quantified how accurate the model is. Additionally, these experimental effects are well known in the literature (e.g. inhibition of ROCK and myosin IIa will lengthen cell protrusions). What are the new insights that this model is able to provide? The authors should more extensively highlight novel insights.

6) Figures 6, S7, S8 are interesting. However, it is not clear how these relate to experimental findings. Can the authors demonstrate examples of the different states in actual cells, and describe in more extensive detail how their model provides insights and predictions to those states?

7) One control experiment that would be helpful is to study how cell protrusion dynamics are with cells on 2D substrates, without any confining matrix. In such cases, cell protrusions also undergo oscillatory dynamics, but without any matrix feedback. Is the model consistent in predicting these dynamics, i.e. with matrix feedback features removed?

8) Expansion of the discussions to include additional relevant recent experimental and computational studies would be helpful in tying the current work to the broader recent literature.

Reviewer #2: This is a carefully performed and thorough study on a timely topic, i.e. how cells enable to orient themselves based on cues they get from the viscoelastic properties of the ECM and how cells can generate meaningful patterning on the ECM. Carefully designed figures and models with excellent explanations of model variables that are briefly explained as they appeared in the text. These models provide a lot of added for future studies. This study requires only minor amendments, as itemized below.

Minor comments:

- Please provide explanation of the creep-recovery tests, and how are they performed.
- Creep-recovery tests were performed to obtain the values to calculate the total strain rate that the viscoelastic matrix has on the invadopodia (formula 2). Unclear how can the sum of all forces on the filament bundle itself can be obtained (formula 1)? Please explain carefully.
- The generality of the observations should be tested with at least some other cell models and not just one highly invasive cell line to ensure that the model can be more broadly applicable.
- For the model, IPN hydrogels have been used. Has the model been tested for other extracellular matrix compositions?
- Has it been confirmed that the measured forces, for example, myosin pulling force is solely associate with force of myosin pulling, without any kind of "bleed-through force" from e.g. adhesion forces?
- Could this model be applied to other types of protrusions, other than invadopodia, such as e.g. filopodia?
- This model was created using an ODE solver in Matlab, would it be possible to re-create it in other programming softwares, such as Rstudios?
- Check the text critically, as a few typos and mistakes were spotted (for example, "(A) something something" vs.