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Date: 16th November 20 05:12:36
Last Sent: 16th November 20 05:12:36
Triggered By: Redacted
BCC: Redacted
Subject: Decision on Nature Materials submission NM19124277A-Z
Message: 16th November 2020

Dear Professor Chaudhuri,

We apologise for the delay in processing your manuscript.

Thank you for submitting your manuscript, "Enhanced substrate stress relaxation promotes filopodia-mediated cell migration". The manuscript has been seen by 2 referees, whose comments are attached below. You will see that whereas they find your work of potential interest, they have raised substantive points that in our view preclude the publication of the manuscript in its present form in Nature Materials.

Should future experiments allow you to address these criticisms in full, we would be happy to look at a revised manuscript (unless, of course, a similar paper is published elsewhere or is accepted for publication in Nature Materials in the meantime). In particular, the concerns regarding the claims made without thorough justification should be addressed in full.

It is only fair to say, however, that we would be reluctant to trouble our referees again unless we thought that their comments had been largely addressed.

When you are ready to submit a revised version, please use the link below to submit the manuscript files, including (in a separate document from the cover letter) a point-by-point response to all referees' comments and a clear description of the changes and additions that you have made (we suggest highlighting the changes in the main text).

Link Not Available

Nature Materials is committed to improving transparency in authorship. As part of our efforts in this direction, we are now requesting that all authors identified as 'corresponding author' on published papers create and link their Open Researcher and Contributor Identifier (ORCID) with their account on the Manuscript Tracking System (MTS), prior to acceptance. This applies to primary research papers only. ORCID helps the scientific community achieve unambiguous attribution of all scholarly contributions. You can create and link your ORCID from the home page of the MTS by clicking on 'Modify my Springer Nature account'. For more information please visit please visit www.springernature.com/orcid.

We hope that you find the referees' comments helpful when preparing a revised manuscript. If you have any questions, please feel free to contact me at materials@nature.com.

With kind regards,

Amos

Amos Matsiko, PhD
Senior Editor
Nature Materials

REFEREE REPORTS

Reviewer #2 (Remarks to the Author):

I have studied the revised manuscript and the detailed responses by the authors. I am pleased to see that major points of the criticisms raised in the original version of the manuscript has been substantially addressed. The data and analysis presented in the revision are consistent with the model presented. Nevertheless, I have a number of comments for this version which, while, not particularly major, are also non-trivial, that I hope the authors will be able to address:
1. In general, the fluorescence micrographs in this manuscript are on the low-resolution and less detailed side of things, which was attributed by the authors in the rebuttal to the high thickness of the gel (>500 um) that exceed the working distance of high NA objective lens. I'm wondering if the authors have tried to "flip" the gel, i.e. place the sample upside down so that the cells will be much closer to the coverglass, and thus making high-resolution, high-NA imaging possible. For fixed specimen, perhaps there might be a way to do this. I'm raising this comment because high-resolution imaging is one of the central tools of cell migration field, and from which many discoveries have been made. As the authors are proposing a new modality of cell migration, I think some high-resolution characterization will be reassuring. Furthermore, the manuscript makes strong claim on the key roles of filopodia whose width is sub-diffraction, and the independence of the lamellipodia, which are very thin structures. A concern is that with too low resolution, one may not be able to observe these structures well enough.

Alternatively, Scanning EM would be another viable technique to visualize these structures convincingly under the key conditions (fast/slow vs elastic vs glass, etc.).

2. Fig. 4a, the authors refers to pPaxY113. However, paxillin is tyrosine-phosphorylated at residue 118. Residue 113 of paxillin is glutamic acid (at least in human). The authors seem to confuse Y113 (the clone name of the monoclonal anti-paxillin antibody from) with phosphorylation at the non-existent residue Y113 (e.g. line 257,260, and so on). The Y113 antibody is detecting paxillin in general and not phosphorylated paxillin. This seems to be correctly described in the Methods but incorrectly described in the revised main text/figure.

3. The mechanism of how fast relaxation support migration is predicted by modelling to be due to 'increased bond lifetime and/or bond number' on fast-relaxing substrates. In Fig. 6, the authors quantify filopodia lifetime on different substrates which is consistent with this. However, there is still a gap here since a filopodia is not a single 'bond' but an ensemble of many 'bonds'. If the authors can experimentally demonstrate 'increased bond lifetime' perhaps by FRAP or similar techniques, this will go a long way toward bridging the gap between cellular scale and molecular scale events.
4. 'Fast' or 'slow' stress relaxation are concepts that may not be universally intuitive especially for biologists. In the discussion, it might help to give concrete example in a few sentences (e.g. what are the numbers for some well-known tissues). In this version of the text, the authors just cite the references and leave it to the reader to go search for it themselves.

Reviewer #3 (Remarks to the Author):

The authors have very convincingly addressed all my comments. I would happily recommend for publication.