8-30-2013

Collaborative Research: Mechanics of Growing Bodies: A Riemannian Geometric Approach

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Federal Agency and Organization Element to Which Report is Submitted:	4900
Federal Grant or Other Identifying Number Assigned by Agency:	1130252
Project Title:	Collaborative Research: Mechanics of Growing Bodies: A Riemannian Geometric Approach
PD/PI Name:	Alireza S Sarvestani, Principal Investigator
Recipient Organization:	University of Maine
Project/Grant Period:	09/01/2011 - 08/31/2014
Reporting Period:	09/01/2012 - 08/31/2013
Submitting Official (if other than PD\PI):	Alireza S Sarvestani Principal Investigator
Submission Date:	08/30/2013
Signature of Submitting Official (signature shall be submitted in accordance with agency specific instructions)	Alireza S Sarvestani

Accomplishments

*** What are the major goals of the project?**

Our general goal is to determine the underlying physics of the effect of substrate stiffness on

neuronal growth. We believe, however, that the mechanism of rigidity sensing is generic and

controlled by a common pathway in all cell types. Therefore, instead of being focused on

neurons, during this part of the project, we focused our attention on the effect of substrate

rigidity on the formation on focal adhesions in general. By unwrapping the details of this

mechanism, we hope to finally explain why neuronal growth, in particular, is sensitive to the

mechanical stiffness of the underlying substrate.

*** What was accomplished under these goals (you must provide information for at least one of the 4 categories below)?**

Major Activities:

1- A theoretical model for the effect of substrate rigidity on formation of focal complexes

First present a thermodynamic model for the coupling between a flexible membrane and a

compliant bio-adhesive substrate. The local adhesion between the membrane and substrate relies

on the aggregation of transmembrane mobile receptors and their binding to the immobilized

ligands on the substrate. The model predicts that the substrate compliance hampers the energetic

driving force for bond aggregation and entropic repulsion between ligand-receptor bonds

becomes increasingly more dominant as the substrate rigidity decreases. On very compliant

substrates, the rigidity-dependent distance between the nearest neighboring bonds may exceed

the characteristic size of the crosslinking proteins (e.g., talin) connecting the cytoplasmic ends of

clustered integrins. This can prevent the stabilization and reinforcement of the adhesion sites and

lead to development of immature focal adhesion on very compliant substrates, as observed in

experiments.

2- An experimental method to elucidate integrin transport regulates the rigidity sensing by

focal adhesions

The goal here is to show that growth of focal adhesions is largely mediated by integrin transport,

which plays a key role in the interplay between sensing a force in the extracellular matrix (ECM)

and transducing this signal, a process termed mechanotransduction. Through cell-ECM focal

adhesions, integrin mediates the signaling both into and out of the cell, promoting growth of

focal adhesions and subsequent cell spreading and migration. In order to study focal adhesion

dynamics related to force, we seeded the cells on two different substrates: polyacrylamide gels

and polydimethylsiloxane (PDMS) micropillars. The mobility of integrin on the different

substrates was assessed using fluorescent recovery after photo-bleaching (FRAP) and analyzed

along with cell traction force measurements.

Specific Objectives:

Specific Aim 1:

develop a generic physical model that describes how focal complexes perceive

the substrate's mechanical rigidity.

Specific Aim 2

develop empirical methods by which the growth of focal adhesion under the

effect of cytoskeletal traction can be both measured.

Significant Results: In short, the fluorescent recovery results from the different rigidity PA gel tests support our original hypothesis that integrin mobility plays a key role in the regulation of the rigidity and mechanosensing ability of cells. By monitoring the recycling of integrin to adhesion sites, these studies elucidated that cells exhibited more stable focal adhesions on more rigid substrates and more dynamic nascent adhesions on softer substrates. In the future, the tests could be done on a serial range of rigidities in order to further refine this data.

Key outcomes or Other achievements: This project aims to address the role of force, stress, and elasticity in regulation of neuronal growth, based on the fundamental laws of mechanics and soft matter physics. Based on our results, we propose that the mechanosensory nature of growth cones plays the most prominent role in regulation of neuronal growth. The main idea behind this approach is that the force-dependent growth of neurons is a result of formation of a positive feedback loop between the strength of adhesion of the growth cones and the mechanical leverage

developed in axons. Transmitting the axonal force to the environment by the adhering growth cones leads to strengthening of distal focal adhesion sites due to their mechanosensory function. This leads to translocation of the growth cone forward, which in turn further stretches the axon thereby increasing the developed tensile force. Substrate rigidity is a key regulator of this process. This mechanistic contribution, at some point, will be coupled with the biochemical machinery of the neurons and become part of the signal transduction road map.

*** What opportunities for training and professional development has the project provided?**
Nothing to report.

*** How have the results been disseminated to communities of interest?**

The NSF support during this part of the project has helped us to publish a paper

Sarvestani, A.S., 2013. Effect of substrate rigidity on the assembly of specific bonds at biological interfaces.*Soft Matter*, 9, 5927-5932,

and has provided support for one undergraduate student (Jennifer MacDowell) to do her Honors thesis under supervision of the PI:

Jennifer MacDowell (May 2013): A new mechanism for mechanitransduction by endothelial cells. Jennifer has joined the medical School of Tufts University after graduation.

*** What do you plan to do during the next reporting period to accomplish the goals?**

I am no longer affiliated with the University of Maine and wont be supported by this grant any more.

Supporting Files

Filename	Description	Uploaded By	Uploaded On
NSF Report 2013.pdf	Summary of goals an results for this period of the grant.	Alireza Sarvestani	08/30/2013

Products

Books

Book Chapters

Conference Papers and Presentations

Inventions
Nothing to report.

Journals
A. S. Sarvestani (2013). Effect of substrate rigidity on the assembly of specific bonds at biological interfaces.. *Soft Matter*. 9 5927. Status = PUBLISHED; Acknowledgment of Federal Support = Yes ; Peer Reviewed = Yes

Licenses
Nothing to report.

Other Products
Nothing to report.

Other Publications

Patents
Nothing to report.

Technologies or Techniques
Nothing to report.

Thesis/Dissertations
Jennifer MacDowell. *A new mechanism for mechanitransduction by endothelial cells*.. (2013). University of Maine. Acknowledgement of Federal Support = No

Websites
Nothing to report.

Participants/Organizations

What individuals have worked on the project?

Name	Most Senior Project Role	Nearest Person Month Worked
Sarvestani, Alireza	PD/PI	1

Full details of individuals who have worked on the project:

Alireza S Sarvestani
Email: alireza.sarvestani@umit.maine.edu
Most Senior Project Role: PD/PI
Nearest Person Month Worked: 1

Contribution to the Project: Leader

Funding Support: This NSF grant (Award 1130252)

International Collaboration: No
International Travel: No

What other organizations have been involved as partners?
Nothing to report.

What other collaborators or contacts have been involved?

YES

Impacts

What is the impact on the development of the principal discipline(s) of the project?
Nothing to report.

What is the impact on other disciplines?
Nothing to report.

What is the impact on the development of human resources?
Nothing to report.

What is the impact on physical resources that form infrastructure?
Nothing to report.

What is the impact on institutional resources that form infrastructure?
Nothing to report.

What is the impact on information resources that form infrastructure?
Nothing to report.

What is the impact on technology transfer?
Nothing to report.

What is the impact on society beyond science and technology?
Nothing to report.

Changes/Problems

Changes in approach and reason for change
Nothing to report.

Actual or Anticipated problems or delays and actions or plans to resolve them
Nothing to report.

Changes that have a significant impact on expenditures
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 or care of biohazards
Nothing to report.