FUNDING PROGRAM FOR NEXT GENERATION WORLD-LEADING RESEARCHERS

Project Title: Elucidation of mechanosense cell signaling by fluorescence single-molecule imaging of actin polymerizing machinery	
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1. Background of research

Cells that constitute our body move, proliferate and determine their fate, sensing the stiffness of their outer environment and the force exerted on their surface. Disintegration of this cellular mechanosense causes abnormal proliferation and metastasis of cancer cells and diseases such as atherosclerosis. While cell signaling mechanisms including calcium ion and protein phosphorylation cascades are thought to play a crucial role in mechanosense, it is largely unknown how these signals are transduced to cell morphogenesis.

2. Research objectives

Our research group has been leading the area of research which uses fluorescence single-molecule imaging in live cells. We have elucidated the detailed actin polymerization and depolymerization kinetics regulating the cell shape, and captured the images of formin homology proteins rapidly elongating an actin filament like a 'linear motor'. By extending our single-molecule imaging approach, this project aims at elucidating the mechanism of cellular response to physical stress and its disorder.

3. Research characteristics (incl. originality and creativity)

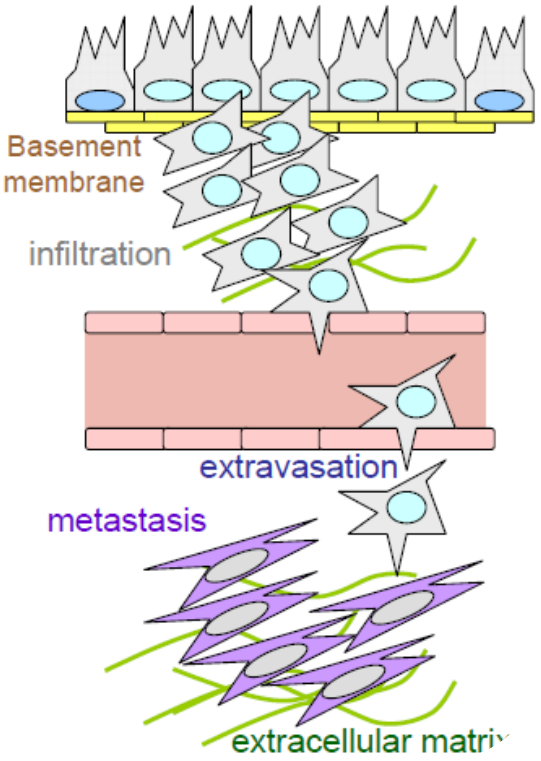
We have recently captured the images of formin homology proteins rapidly polymerizing actin filaments in response to the mechanical stress applied to the cell on the order of a second. This observation implies a new molecular mechanism that allows cells to rapidly regenerate cytoskeletal polymers under physically stress. Real time imaging of molecular behavior thus allows direct viewing of the fast responding phase of the cellular mechanosense.

4. Anticipated effects and future applications of research

We anticipate that this project elucidates how physical stress regulates proliferation and metastasis of cancer cells and pathophysiology of the disorders in cells which support bone and blood vessels. This project will also provide a new application of single-molecule imaging to rapid laboratory testing of the drugs against physical stress-associated diseases.

Migration, Proliferation and Fate of the Cell Are Determined by the Physical Property of Outer Environment.

- Loss of anchorage dependent growth is characteristic of CANCER cells.
- ‘Durotaxis’: cell migration toward more rigid surface.
- Mesenchymal stem cells change their fate by physical ‘signals’ from outer matrix.
- Atherosclerosis and blood flow.



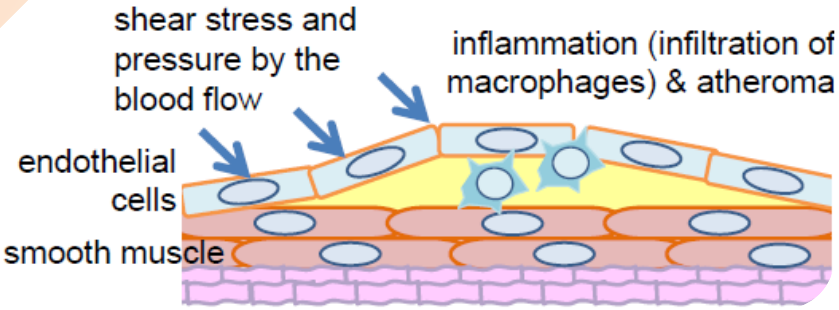
Physical stress on the cell may change…

Differentiation, Proliferation, Infiltration and Metastasis

Cancer cell invasion

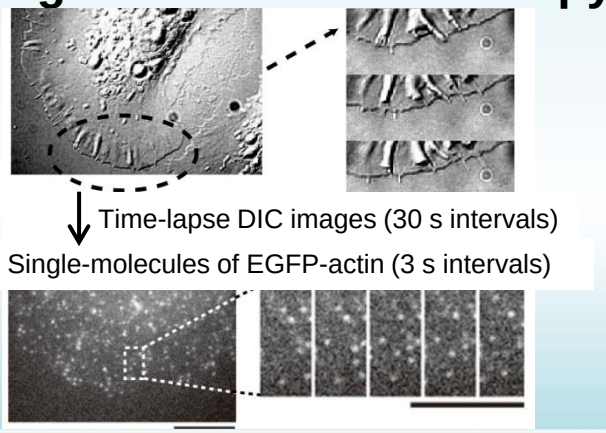
Atherosclerosis

This project aims at visualizing mechanosense reactions in the cell on the order of a second.

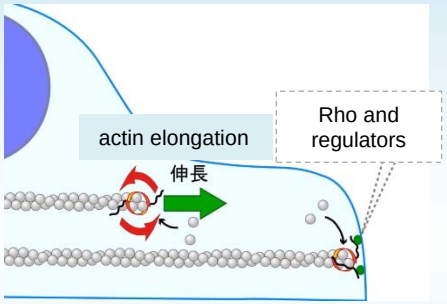


Actin Polymerizing Machineries, the Driving Force for Cell Morphogenesis, Respond to Physical Stress on the Cell.

Direct visualization of mechano-transduction by fluorescence single-molecule microscopy

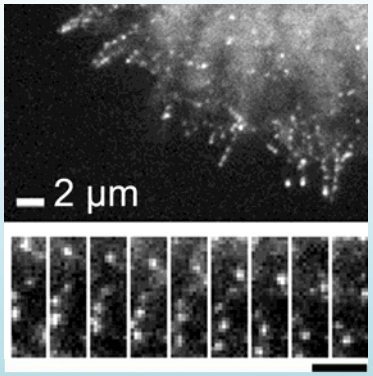


The formin family; the fast, processive polymerizer of actin.



rapidly polymerizes actin in response to physical stimuli.

twists the actin filament.



Live-cell single-molecule imaging

Direct viewing of actin assembly

High resolution imaging under physical perturbation

Real-time monitoring of drug effects

Capturing the specific molecular reactions in the mechanosense cell signaling

These are used to reveal spatiotemporal molecular actions.

This project aims to elucidate the fast-phase reactions in the mechanosense and also to apply the high-resolution imaging to rapid evaluation of drug therapies.