Biophysical strategies for graded and dynamic actuation of cellular signaling

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NSF Workshop on Biologically Enabled Wireless Networks
Arlington, VA
July 19-20, 2011
Cells are **actuators** that can convert physical inputs into biochemical outputs.

Discher et al., Science (2005)  
Wang et al., Nature (2005)  
Shu Chien, Roger Tsien, Michael Berns  
Shu Chien, Roger Tsien, Michael Berns  
Wang et al., Nature (2005)  
~15 min
Strategies to actuate cell behavior with biophysical inputs

- Nanomagnetic activation of receptor-mediated signaling
  
  MAGNETIC INPUT $\rightarrow$ BIOCHEMICAL OUTPUT

- Laser nanosurgery to probe and control cell shape and mechanics
  
  OPTICAL INPUT $\rightarrow$ MECHANICAL OUTPUT
Nanomagnetic activation of receptor-mediated signaling

MAGNETIC INPUT $\rightarrow$ BIOCHEMICAL OUTPUT
Receptor clustering as a critical event in signal transduction

Binding and clustering are often coupled.

Can we introduce control by uncoupling these processes?

CORE CONCEPT: Can we use magnetic forces to control clustering and hence signal transduction?

- Load FceRI receptors with anti-DNP IgE
- Treat cells with magnetic nanoparticles coated with DNP
- Cluster particles using magnetic needle

http://microbiology2009.wikispaces.com/Histamines--What+They+Do+%26+What+Anti-Histamines+Do+to+Stop+Them

http://www.med.osaka-u.ac.jp/pub/molonc/www/eng/achievements/03.html
IgE-based signaling depends on ligand valency

**SOLUBLE receptor agonist**

**NANOPARTICLE-BOUND receptor agonist**

Mannix,* Kumar* et al., Nature Nanotech (2008)
Magnet activation induces nanoparticle aggregation and signal activation

Mannix,* Kumar* et al., Nature Nanotech (2008)
Dynamic magnetic inputs produce dynamic biochemical outputs

Mannix,* Kumar* et al., Nature Nanotech (2008)
Laser nanosurgery to probe and control cell shape and mechanics

OPTICAL INPUT → MECHANICAL OUTPUT
Stress fibers, nonmuscle myosin II, and tensional homeostasis

Goffin et al., J Cell Biol (2006)


Castella et al., J Cell Sci (2010)
The femtosecond laser nanoscissor

Inspired by: M. Berns (UCSD), K. Konig (Jena), C. Reider (SUNY)

Photoablation of a living stress fiber

Inspired by Michael Berns, Conly Rieder, Karsten König, many others

30 sec

Kumar et al., Biophys J (2006)
Location, location, location:
Different myosin activators control different stress fibers

ROCK: Central SFs
MLCK: Peripheral SFs

Totsukawa et al., JCB (2000)
Katoh et al., AJP Cell Physiol (2001)
Katoh and Ookawara, Genes to Cells (2007)
Do central and peripheral stress fibers differ in their viscoelastic retraction properties and contributions to cell shape?
Central SF Ablation

Peripheral SF Ablation

<table>
<thead>
<tr>
<th>FIBER TYPE</th>
<th>“ELASTICITY”</th>
<th>“PRESTRAIN”</th>
<th>SHAPE STABILITY CONTRIBUTION</th>
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<tr>
<td>Peripheral</td>
<td>Low</td>
<td>High</td>
<td>High</td>
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<tr>
<td>Central</td>
<td>High</td>
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Severing a central fiber in the absence of peripheral fibers leads to cell retraction.

SUMMARY

• Receptor-mediated signaling can be controlled in a dynamic and molecularly-specific fashion using magnetic inputs

• Femtosecond laser nanosurgery can be used to investigate cellular mechanics at the sub-micron scale and to manipulate cell shape

FUTURE CHALLENGES

• How do we obtain biochemically specific outputs from nonspecific physical inputs?

• Can we build orthogonality into these systems?

• How can we incorporate these concepts into devices? [Multiplexing, throughput, automation, ... ]
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NSF CMMI 072742
NSF CMMI 1055965 (CAREER)
NIH 1U54CA143836-01 (PSOC)
NIH 1DP2OD004213 (New Innovator Award)
Beckman Young Investigator Award
ARO W911NF-09-1-0507 (PECASE)