How Cancer Cells Go Awry: The role of mechanobiology in cancer research

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Outline

• What is mechanobiology?
• How does cancer progress?
• What is metastasis and how does it occur?
• What are the unanswered questions at the intersection of cancer and mechanobiology that need to be addressed?
• How can mechanobiology translate into the clinic?
**Mechanobiology**

Tissue and Cellular Mechanical Properties
- Deformability/stiffness
- Cytoplasmic Viscosity

Imposed Forces: Mechatransduction
- compression, stretch, shear, etc.

Cell-Generated Forces:
- traction stresses at the cell-ECM interface
- cell-cell tension
Mechanobiology is multi-scale

Molecules/Proteins
 Sub-cellular Structures/organelles
 Cells
 Tissues
 Human Body

nanometers 1 micron 10 micron mm-cm meters

Cell mechanics is not new...
But it has been reinvented in the post DNA-discovery era.

http://www.uoguelph.ca/zoolgy/devobio/210labs/epithelial1.html
Metastasis
Cancer (TNM) Staging

- **T:** Tumor size
- **N:** Lymph node involvement
- **M:** Spread to other organs
Metastasis Progression

The complexity of the tumor microenvironment


Intratumor heterogeneity

The complexity of the tumor microenvironment
Multi-scale, interdisciplinary approaches to studying cancer
What are the genes that cause and contribute to cancer?

How do those genes lead to cancer?

What are the molecular biomarkers of cancer?

- *Prognostic*: Likelihood of developing cancer
- *Diagnostic*: Type and stage of cancer, recommendation on treatment
- *Predictive*: Likelihood of recurrence

Wu, L and X. Qu, Chem. Soc. Rev., 2015, 44, 2963
An engineering view of cancer progression

- Increased pressures
- Altered vessel permeability
- Barriers to drug delivery
- Increased tissue stiffness
- Oxygen tension

- Altered tissue structure
- Chemical gradients
- Cell movement and forces
- Drivers of individual versus collective migration

An engineering view of cancer progression

- Adhesion in flow
- Cell squeezing
- CTC capture and analysis
- Drug targeting

- Cell Squeezing
- Shear stress survival

Better platforms to mimic cancer progression

Cell migration in metastasis

How is 3D cell migration initiated and directed?
Stochastic or deterministic?
Cell-intrinsic or cell-extrinsic?
Metastatic cell migration
Recreating the tumor microenvironment

- *In vivo* stromal extracellular matrix (ECM) is heterogeneous in composition, density, and organization
- Dynamic, bi-directional cell-matrix interactions underlie cell migration

![In vitro ECM](image1.png) ≠ ![In vivo stromal ECM](image2.png) → ![Rationally-designed in vitro ECM](image3.png)

Extracellular matrix alignment predicts patient survival

Extracellular matrix alignment *in vivo* and *in vitro*

*In vivo* mammary stroma

MDA-MB-231  Stromal ECM

MDA-MB-231/Lifeact-GFP
Collagen

5 µm

100 µm
Migration in tracks

Carey, et al. AJP-cell, 2015
Recreation of tracks

1. Create silicon master and cast PDMS Stamp
2. Invert PDMS Stamp over Neutralized Liquid Collagen & Polymerize
3. Seed Cells at Low Density onto Channels & Allow to Settle
4. Wash Away Excess Cells
5. Cap with Collagen Lid

Kraning-Rush et al, Integrative Biology, 2013
Cell-Sized Channels Mimic Cell-Generated Microtracks

Cell-created Microtrack

Micropatterned Track

Kraning-Rush et al. Integrative Biology, 2013
Cell migration in tracks vs 3D

Rahman et al, 2016, Molecular Biology of the Cell
Angiogenesis in Cancer

Given that:

1. Tumors are stiffer
2. Tumor vasculature is abnormal

Does altered matrix stiffness contribute to abnormal vascular structure?

Angiogenic network formation

Matrigel


Collagen

Davis et al.: The Anat Rec 268:252-75:2002

Matrix stiffness alters angiogenesis

Scale is 200 µm

• Mechanics can drive disease progression.
• Engineering has the ability to recreate systems that mimic the chemical, mechanical and architectural features of the tumor microenvironment, overcoming limitations in simple systems and animal models.
Future Directions

• Can mechanics and mechanobiology be a therapeutic target?
• How do current cancer treatments affect cell and tissue mechanics?
• What are the relative roles in genetic mutations and mechanics in driving cancer progression?