Lecture #19: Engineered Disease Models
Tissue Engineering – Cancer Research
Microenvironmental Regulation of Tumorigenesis

Suppressive forces
- Tissue architecture
- Tissue-specific ECM
- Myoepithelial cells
- Tissue macrophage
- MMP inhibitors
- Normal metabolism
- Antioxidants
- Fibroblast

Promotional forces
- Loss of architecture
- Aberrant ECM (context matters!)
- Aberrant myoepithelial cells
- CAFs
- Inflammation
- Fibrosis
- Tumor associated macrophage

- Angiogenesis
- Cytokines
- MMPs/aberrant proteases
- ROS
- Growth factors
- Hormones
- Mutagens

Matrix Mechanics- Breast Cancer

A

Unconfined Compression

Elastic Modulus (Pa)

Normal | Premal | Tumor | Adjacent

B

Shear Rheology

Elastic Modulus (Pa)

Normal | Premal | Tumor | Adjacent

Levental et al., *Cell*, 139, 891, 2009
Glycation of Collagen Gels (w/ ribose)

Wei et al., *BBA-General*, 1820, 488, 2012
Glycation of Collagen Gels (w/ ribose)

Wei et al., BBA-General, 1820, 488, 2012
Roy et al., J Biomed Mater Res A, 93, 843, 2010
Matrix Mechanics - Breast Cancer

Levental et al., *Cell*, 139, 891, 2009
In-Class Exercise
Part 1
In-Class Exercise
Part 1

Majority of Mammary Carcinomas Arise from Terminal Duct Units

Mouse Model Breast Cancer

Control Mice

+ Oncogene

Boghaert et al., *PNAS*, 2012
In-Class Exercise

Part 1

Boghaert et al., PNAS, 2012
In-Class Exercise
Part 1
What will happen?

Add blebbistatin in the media...
Blocks nonmuscle myosin II activity
Blocks tumor cell invasion from ends

Is there a problem with this experiment?

What cells are being affected by blebbistatin?
In-Class Exercise
Part 1
What will happen?

Add dominant negative mutant E-cadherin to normal epithelial cells...

Blocks interaction with cytoskeleton, only in normal cells and not tumor cells

Blocks tumor cell invasion from ends
In-Class Exercise
Part 1
What will happen?

Add constitutively active mutant RhoA to normal epithelial cells...

Increases endogenous contractility, only in normal cells and not tumor cells

Tumor cells invade from all locations
Sickle Cell Disease

- Mutation in gene encoding β-globin protein
- Variant hemoglobin, HbS
- Polymerization of HbS into long chains upon deoxygenation
- Vaso-occlusive crisis events

- No reliable biomarker that predicts disease severity
Microfluidic Measurements

\[ C = \frac{1}{Z} = \frac{Q}{P_1 - P_2} \]

Conductance = inverse of resistance

Wood et al., *Sci Transl Med*, 2012
Microfluidic Measurements

http://stm.sciencemag.org/content/4/123/123ra26/suppl/DC1
In Vitro Biomarker

Wood et al., Sci Transl Med, 2012
Biomarkers: Receiver operator characteristic (ROC) curve

http://www.stattools.net/ROCs_Exp.php
In Vitro Biomarker

Wood et al., Sci Transl Med, 2012
In Vitro Biomarker

Wood et al., *Sci Transl Med*, 2012
In-Class Exercise
Part 2