S2-06
Extracellular matrix stiffness modulates tissue inflammation to promote breast tumor aggression

Dr. Acerbi: Nothing to disclose.
Dr. Hwang: Nothing to disclose.
Dr. Munson: Nothing to disclose.
Dr. Waisuk: Nothing to disclose.
Dr. Au: Nothing to disclose.
Dr. Zheng: Nothing to disclose.
Dr. Yu: Nothing to disclose.
Dr. Mouw: Nothing to disclose.
Dr. Lohkai: Nothing to disclose.
Dr. Swartz: Nothing to disclose.
Dr. Shi: Nothing to disclose.
Dr. Liphardt: Nothing to disclose.

Dr. Ruffell: Nothing to disclose.
Dr. Lund: Nothing to disclose.
Dr. Coussen: Nothing to disclose.
Dr. Yunn-Yi: Nothing to disclose.
Dr. Weaver: Nothing to disclose.
Exploring the relationship between breast cancer progression and aggression, extracellular matrix stiffness and tissue inflammation


Stromal-epithelial interaction is necessary for breast cancer progression

Egeblad et al., Developmental Cell 2010
Lopez et al., J Integ Biol 2011
Lu et al., J Cell Biol 2012

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Her2/Neu transgenic model of tumor progression

Tumor progression is accompanied by collagen deposition, linearization

Levental et al., Cell, 2009
Lopez et al., J Integr Biol 2011
Her2/Neu transgenic model of tumor progression

Tumor progression is accompanied by collagen deposition, linearization and ECM stiffening

Levental et al., Cell, 2009
Lopez et al., J Integr Biol 2011

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ECM stiffening promotes tumor aggressio

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ECM stiffening promotes
tumor aggression

Levental et al., Cell, 2009

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ECM stiffening promotes
tumor aggression

Levental et al., Cell, 2009

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Preventing ECM stiffness inhibits metastasis

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Pickup et al., Cancer Res 2013
Mouw, Yui and Yu et al., in preparation

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What is the relevance of ECM stiffness to human breast cancer?

Human paraffin, frozen and fresh tissue samples

Paraffin → Histological analysis
Snap Frozen → Biophysical analysis
Fresh → Immune analysis

UCSF
Valerie Weaver
Yunn-Yi Chen
Breast Oncology Program
Breast cancer advocates

Duke University
Shelley Hwang
Kristen Brannock

OHSU
Lisa M Coussens
Brian Ruffell
Anna Waiwak

EPL
Melody Swartz
Jenny Munson
Amanda Lund

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Human breast cancer is accompanied by collagen deposition, collagen fibers linearization and ECM stiffness.
Human breast cancer is accompanied by collagen deposition, collagen fibers linearization and ECM stiffness

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Human breast cancer is accompanied by collagen linearization, crosslinking and ECM stiffness

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Tumor aggression is accompanied by increased inflammation

Ruffell et al., PNAS 2011
DeNardo et al., Cancer Discovery, 2011
Qulan and Pollard, Cell, 2010

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Tumor aggression is accompanied by increased inflammation

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<thead>
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<th>ER+/PR+ cancer</th>
<th>TRIPLE NEGATIVE cancer</th>
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<tr>
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<td>CD206</td>
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Brian Ruffell
Lisa M Caussain Lab

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Tumor aggression is accompanied by increased inflammation

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Do tumor associated macrophages drive aggression by stiffening the ECM?

Does ECM stiffness drive aggression by inducing tumor associated macrophages?

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Do tumor associated macrophages drive aggression by stiffening the ECM?

Early macrophage depletion reduces ECM deposition

... and reduces metastasis
DeNardo et al., Cancer Discovery 2011
DeNardo and Coussens, unpublished
Does ECM stiffness drive aggression by inducing tumor associated macrophages?

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Does ECM stiffness drive aggression by inducing tumor associated macrophages?

...in a softer ECM:

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Does ECM stiffness drive aggression by inducing tumor associated macrophages?

...in a softer ECM:

↓ Regulators of ‘pro-tumor' phenotype

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Tumor associated macrophages can influence ECM stiffening

ECM stiffness creates a permissive environment maybe ‘tuning’ the chemokines and cytokines that regulate the immune response
Summary

- Tumor associated macrophages can influence ECM stiffening
- ECM stiffness creates a permissive environment maybe ‘tuning’ the chemokines and cytokines that regulate the immune response

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Kristen Brannock
Lisa M Coussens
Brian Ruffell
Anna Waiusk

Women who donated their breast tissue for research

breast cancer advocates
Susan Samson, Hannah Connolly, Linda Vincent

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