Proteoglycans in Breast Cancer

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Outline

- Why should we care about context (microenvironment)?
- Why should we care about proteoglycans like versican?
- How can we use 3D tissue culture assays to help understand disease?
- Where is this research currently?
Cancer is a disease of mutation

But ...

Why don’t we get more cancer? A proposed role of the microenvironment in restraining cancer progression

Mina J Bissell & William C Hines

Cancer is a disease of mutation

But ...

Phenotype is dominant over genotype

Why don’t we get more cancer? A proposed role of the microenvironment in restraining cancer progression

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Connective Tissue = ECM (extracellular matrix)

Dynamic Reciprocity

Context

Pre-invasive

Invasive

Suppressive forces

- Tissue architecture
- Tissue-specific ECM
- Myoepithelial cells
- 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

Versican
Versican in development

- Knockout is embryonic lethal
- Involved in:
  - Migration and proliferation
  - Tissue visco-elasticity
  - Anti-adhesive
  - Leukocyte homing
  - Binding to cell surface receptors

Yamamura, H. et al., 1997, Dev. Biol. 186:58
Versican in mammary gland development

Versican in dormancy

Versican in breast cancer


Kharashvili, G. et al., 2011, J. Clin. Pathol. 64:977
Versican isoforms

Bandtlow, C.E. and Zimmermann, D.R. 2000, Physiol. Rev. 80:1267
Versican cleavage
3D cell culture

Lee, G.Y. et al., 2007, Nature Methods 4:359
3D cell culture

Cross section of a TDLU (an acinus)

An acinus-like structure in 3D culture

A preinvasive to invasive model

Rizki, A. et al., 2008, Cancer Res. 68:1378
A preinvasive to invasive model

Lee, G.Y. et al., 2007, Nature Methods 4:359
"Reversion"

Phenotype is dominant over genotype

Hypothesis

Versican expression and turnover are central events in the transition from pre-invasive to invasive phenotype in breast cancer cells.
What have we done?

- Is versican expressed by breast epithelial cells?
- Is versican found in human breast tissue?
- Isoform expression in breast epithelial cells?
- Versican knockdown in T4-2 cells
- Does versican contribute to epithelial cell invasion?
Normal human breast versican expression (RNA seq)

Courtesy of Dr. Curt Hines
Do S1 or T4-2 cells make versican?

Lower levels of versican expression but still detectable
Normal breast - N239
Normal breast - N239
D23698T (DCIS w/ minimal invasion)
Versican isoform expression in S1 & T4-2 cells

Figure 10. Relative mRNA expression of versican in S1, T4-2 and HFL-1 cells. HFL-1 (n=1 for total and all isoforms); S1 (n=2 for total and all isoforms); T4-2 (n=2 for all isoforms and n=1 for total versican). Columns show mean value and error bars represent SD.
Versican V1-DPEAAE secretion increases in T4-2 cells.
Lentiviral knockdown

VCAN1 (C-terminal) = All isoforms
VCAN2 (signal) = All isoforms
VCAN3 (GAG-beta) = V0 & V1
Versican knockdown inhibits T4-2 invasion

No V0 or V1
No DPEAAE signalling
What’s next

- Do T4-2 knockdowns behave differently in 3D cell culture (morphology)
- Influence of T4-2 versican knockdown on communication with other cells
Thanks!

- **Katie Timms**
- Mina Bissell
- Curt Hines
- Sun-Young Lee
- Kate Thi
- Northern Medical Program
- You!
D23698T (DCIS w/ minimal invasion)

CD49f
Versican

Versican
DPEAAE

Versican
DPEAAE + peptide
Rizki, A. et al., 2008, Cancer Res. 68:1378