Companion PowerPoint slide set
Obesity-associated breast cancer risk: a role for epigenetics?

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Dr. Liza Makowski

Studies Basal-like Breast Cancer (BBC)

- Aggressive cancer
- No specific drug therapies
- Short survival time if it spreads beyond breast tissue (metastasis)
- More prevalent in young pre-menopausal women
- More prevalent in African Americans
- Obesity is a risk factor for all breast cancers
Obesity causes BBC tumors to form at a faster rate compared to lean mice.
Cross-section of mammary (milk) duct

http://www.womenshealth.gov/breast-cancer/what-is-breast-cancer/
Label epithelial cells, fat cells and fibroblasts on the diagram below:

Inside (lumen) of milk duct
Epithelial Cells of Milk Duct Inside (lumen) of milk duct

Fibroblasts
Adipocytes (Fat cells)

Stroma of mammary tissue

Epithelial Cells of Milk Duct

Inside (lumen) of milk duct

Immune cells are also present but are not shown in order to simplify schematic of the stroma.
microenvironment
Cancer & the microenvironment

The microenvironment (“soil”) surrounding a cell (“seed”) plays a role in tumor formation.

Liza Makowski: “How does obesity alter the microenvironment in breast cancer?”
Cell to cell communication

HGF-cMET paracrine signaling

Adapted from Melissa Troester/Patricia Casbas-Hernandez @ UNC
Cell to cell communication

HGF-cMET paracrine signaling

- Promotes cell division
- Promotes motility (leads to metastasis)
- Prevents cell death
- Promotes growth of blood vessels to supply tumor

Melissa Troester/Patricia Casbas-Hernandez @ UNC
Obesity increases levels of HGF mRNA and protein in normal mammary tissue.
**Ex vivo cell culture model**

<table>
<thead>
<tr>
<th>Lean Mice</th>
<th>Isolate Fibroblasts</th>
<th>Culture Fibroblasts</th>
<th>Measure</th>
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</thead>
<tbody>
<tr>
<td>Lean Mice</td>
<td><img src="image1" alt="Normal" /></td>
<td><img src="image2" alt="Normal" /></td>
<td>HGF Secretion</td>
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<tr>
<td>Lean Mice</td>
<td><img src="image3" alt="Cancer-associated" /></td>
<td><img src="image4" alt="Cancer-associated" /></td>
<td>HGF Secretion</td>
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</tbody>
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<tbody>
<tr>
<td>Obese Mice</td>
<td><img src="image5" alt="Normal" /></td>
<td><img src="image6" alt="Normal" /></td>
<td>HGF Secretion</td>
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<td>Obese Mice</td>
<td><img src="image7" alt="Cancer-associated" /></td>
<td><img src="image8" alt="Cancer-associated" /></td>
<td>HGF Secretion</td>
</tr>
</tbody>
</table>
HGF secretion in cultured cells

- BBC tumor cell line (epithelial cells)
- Normal fibroblasts (lean mice)
- Normal fibroblasts (obese mice)
- Cancer-associated fibroblasts (lean mice)
- Cancer-associated fibroblasts (obese mice)

HGF concentration (ng/ml) vs. Time (h)
Lean Mice

Obese Mice

Isolate Fibroblasts

Normal

Cancer-associated

Culture Fibroblasts

HGF Secretion
Analysis of c-Met protein levels in BBC tumor cell line

C.

- BBC Tumor cell line
- BBC Tumor cell line + CM
- BBC Tumor cell line + mHGF

Phospho-c-Met

c-Met

Control
“How does obesity alter the microenvironment in breast cancer?”

Microenvironment

Conclusion: growth factor signaling pathway (HGF/cMet) was upregulated with obesity.
EPIGENETIC MECHANISMS
are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

HEALTH ENDPOINTS
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

Histone modification
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.