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:
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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<tbody>
<tr>
<td></td>
<td>Normal</td>
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<td>HGF Secretion</td>
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<td>Cancer-associated</td>
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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)**

**Graph:**
- **Y-axis:** HGF concentration (ng/ml)
- **X-axis:** Time (h)
- **Legend:**
  - Solid black circle
  - Open square
  - Open circle
  - Grey square
  - Grey open circle

**Key Points:**
- The graph shows the secretion of HGF over time in different cell types.
- BBC tumor cells exhibit a significant increase in HGF secretion from 6 hours onwards.
- Normal fibroblasts (both lean and obese mice) show a moderate increase.
- Cancer-associated fibroblasts (both lean and obese mice) have a low and consistent secretion throughout the time points.
Lean Mice

Obese Mice

Isolate Fibroblasts

Culture Fibroblasts

HGF Secretion

Normal

Cancer-associated

Isolate Fibroblasts

Culture Fibroblasts

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

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<table>
<thead>
<tr>
<th></th>
<th>BBC Tumor cell line</th>
<th>BBC Tumor cell line + CM</th>
<th>BBC Tumor cell line + mHGF</th>
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<tbody>
<tr>
<td>Phospho-c-Met</td>
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“How does obesity alter the microenvironment in breast cancer?”

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

CHROMATIN

CHROMOSOME

METHYL GROUP

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

DNA accessible, gene active

DNA inaccessible, gene inactive

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.