Metastasis

1. The metastatic cascade

3. Pathologic features of metastasis

4. Therapeutic ramifications

Sir James Paget (1814-1899)
British Surgeon/Pathologist
Paget’s disease of bone
Paget’s disease of the nipple (intraductal Ca breast spreading to skin of nipple)

Stephen Paget, MD (1855-1926)
METASTASIS: “Seed and Soil”
Paget S. The distribution of secondary growths in cancer of the breast.
Lancet 1889; 1: 571-573.
"the best work in pathology of cancer is done by those who...are studying the nature of the seed..."
"the observations of the properties of the soil may also be useful."

Carcinoma of breast

Which malignant cells will metastasize?

1. Subclone theory
   -a specific clone has the prop's for metastasis

2. Cancer stem cell theory
   -only the stem cells have the prop's for metastasis

3. Genetic signature theory
   -many malignant cells at different stages have the signature genes allowing metastasis

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2. Intravasation & vasc. dissemination
3. Extravasation, colonization & growth

Stage 1: Invasion of B.M. and ECM

Stage 2: Intravasation & vasc. dissemination

EMT: epithelial-mesenchymal transition

4. Locomotion of tumor cells

HOSTILE ENVIRONMENT:
Most tumor cells do not survive

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- Angiogenesis
- EMT
- Chemokine express.
- Adhesion molecules
- Down-regulate “metastasis suppressor proteins”

Alveolar space

Example: METASTASIS TO LUNG

Vascular Sprouting

Angiopoietins 1 & 2
- TGF-α, β
- PDGF
- FGF
- EGF
- Angiogenin

A, B, D, E:
- Angiogenesis
- Endothelial mitosis

Anti-angiogenic factors
- Thrombospondin-1
- p53 expression → VEGF expression
- Proteases (from tumor cells or proteolytic cleavage)
  - Plasminogen → Angiostatin
  - Collagen → Endostatin
  - Transthyretin → Vasculostatin

Carcinoma of breast
Chemokine receptors on tumor Cells: ...ligands in metastatic sites

N Engl J Med
2001; 345: 833-835

Breast Carcinoma (invasive)

Breast Carcinoma (intraductal and invasive)

Ductal carcinoma
In situ (DCIS)
Intraductal and invasive Carcinoma

Lymph node

Lymphatic

capsule

subcapsular sinus
**General Modes of Metastasis**

- Carcinoma
- Lymphatics
- Regional lymph nodes
- Sarcoma
- Veins
- Lungs
- Bone

**Common Sites of Metastasis**

- **Colorectal**
- **Breast**
- **Renal cell Ca**
- **Hepatocellular Ca**

**Common Sites of Metastasis**

- **Lung**
- **Liver**

- **Colorectal**
- **Pancreas**
- **Other GI: carcinoid, bile ducts**
  - **Lung**
  - **Breast**

**Unique Sites of Metastasis**

- **Virchow’s node** (supraclavicular node)
- **gastric Ca** (signet ring Ca)
- **Krukenberg tumor** (bilateral ovarian mets)
Lung Carcinoma metastasis to Adrenal

Source: University of Alberta, Dep’t of Laboratory Medicine & Pathology

Therapeutic Implications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mech. of action</th>
<th>Neoplasm(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>against VEGF</td>
<td>colorectal</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multi-kinase inhibitor of VEGFR, PDGFR</td>
<td>renal cell; GIST</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multi-kinase inhibitor: VEGFR, PDGFR, C-kit, Raf</td>
<td>renal cell</td>
</tr>
<tr>
<td></td>
<td>Anti-chemokine receptors</td>
<td></td>
</tr>
</tbody>
</table>

Anti-angiogenic agents

Epithelium

Blood vessels: cap./venule/lymphatic

Brain

Lungs

Bone

Liver

Distant sites