Cell Biology of Cancer Progression

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### Metastatic Tumors

<table>
<thead>
<tr>
<th>Primary (solid) tumor</th>
<th>Secondary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Brain cancer</td>
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</tbody>
</table>

What are the likely steps required for a cancer cell to colonize a distant organ or tissue?
Detach from surrounding cells

Penetrate the basement membrane

Invade the local tissue

Migrate to distant sites

Colonize the new location
Delamination

Migration

Invasion

Differentiation
Cancer vs development

Cells in the tumor acquire mutations that initiate the ‘metastasis’ program.

The cell detaches from neighboring cells and invades through the local tissue (ECM).

The metastatic cell seeks a new site to form a new tumor.

Cells in the embryo receive signals that initiate EMT (epithelial-mesenchyme transitions).

Cells detach from neighbors and invade into the local tissues.

Cells home in on an embryonic destination and differentiate into the proper tissue type.
Cell-cell and cell-substrate adhesion

Non-adherent solitary cell (simple unicellular organisms)
- e.g. inactive blood cells

Cell-cell adhesion (cadherin-based)
- e.g. T-cell B-cell synapse

Cell-substrate adhesion (integrin-based)
- e.g. fibroblast

Cell-substrate and cell-cell adhesion (complex tissue of a multicellular organism)
- e.g. neurons, epithelia, cardiomyocytes
The molecular basis of cell-cell (homotypic) adhesion

Farquhar & Palade, 1963

ACTIN

α

β

catenins

Cadherin

Ca^{++}

Ca^{++}
Breaking Cell-Cell Contacts

Slug, Snail

ACTIN

src

Cadherin

Cadherin

Cadherin

Cadherin
Focal adhesions

What might integrins stick to?
Actin
Integrin

Focal adhesions
1. Cell protrudes the leading edge.
2. New focal adhesions are assembled, anchoring the membrane to the ECM.
3. Focal adhesions at the rear are disassembled.
4. Traction forces from focal adhesions and stress fibers pull the cell forward.
Actin at the leading edge
Detach from surrounding cells

Penetrate the basement membrane

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Colonize the new location

EMT
Routes of Invasion: VLI

Primary Tumor → Vasculature/Lymphatic system → Secondary Site
How tumors recruit new blood vessels

Normal oxygen levels (normoxic): HIF transcription factors are rapidly hydroxylated, ubiquitylated, and then degraded in the proteasome.

Low oxygen levels (hypoxic): HIF transcription factors cannot be hydroxylated, so they accumulate and begin transcription of genes.

Drugs can be designed so that they only become active in low oxygen conditions!
Max tumor diameter:
vascularized: no limit
not vascularized: 2mm

But how do invasive cancer cells find the blood/lymphatic vessels?
Routes of Invasion: VLI

Primary Tumor

VEGF, cytokines

Immune cells

Vasculature/Lymphatic system

Secondary Site
But, primary tumors accumulate blood vessels at a rapid rate while metastatic tumors remain largely unvascularized (and therefore small). Following surgical resection of the primary tumor, small metastatic tumors become rapidly vascularized and begin to expand in size. What might be going on? How might you find out?
The invasion-angiogenesis connection

Primary tumor

VEGF

Blood vessels

VEGF

Secondary tumor

Elastin (ECM) fragments
Routes of Invasion: PNI

Primary Tumor → Nerve networks (ouch!) → Secondary Site

NGF, ?
migration

???
migration