Cancer invasion and metastasis

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Cancer is an extremely inefficient process

- 1000 mutations per cell per day
- 70 kg person = 700000000000000 cells
  (700000000000000000000000000000000)
- 75 years = 30000 days
  (210000000000000000000000000000000)
- 1:5 people gets cancer
  (1000000000000000000000000000000000) $10^{21}$
Overview

- What is cancer metastasis?
- Molecular mechanisms of metastasis
- Signalling pathways involved in metastasis
Cancer metastasis

Cancer defines as a population of cells that have lost their normal controls of growth and differentiation and are proliferating without check.

Metastasis is the process by which a tumor cell leaves the primary tumor, travels to a distant site via the circulatory system, and establishes a secondary tumor.
Pre-cellular theory of invasion and metastasis: recognition of malignant tumors and localized versus metastatic disease

**Hippocrates (460–375 B.C.)**

**Galen (131–201 A.D.)**

**Pre-1700:** The Greek physician Hippocrates coined “carcinoma” from *karkinos*, the word for crab.

**LeDran 1757:** Noted that malignant tumors begin as localized disease, then spread to regional lymph nodes and then enter the circulation to subsequently appear in the lung.

**Bichat 1801:** Tumors contain both parenchyma and stroma.

**Recamier 1829:** Used the term “Metastases”
The organ pattern of metastasis is characteristic of the tumor type and tissue of origin. 50-70% of the metastatic pattern can be predicted by the venous drainage blood flow. The remaining 30-50 % may be caused by specific molecular homing mechanisms.

Potential molecular mechanisms:

a) Preferential adhesion in the vessels of the target organ
b) Selective extravasation
c) Organ attractants
d) Organ specific survival and growth
Determining factors

- genetic disorder
- growth factors from environment
- detachment of neighboring cells
- digestion of the extracellular matrix
- cytoskeleton rearrangement
- adhesion molecule expression
- adhesion sites
- chemotaxis
- loss of contact inhibition
Other factors

- Tumor size
- Tumor stage
- Dedifferentiation
- EMT
## Preferential metastatic sites

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>Common distant site (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast' adenocarcinoma</td>
<td>Bone, brain, adrenal</td>
</tr>
<tr>
<td>Prostate adenocarcinoma</td>
<td>Bone</td>
</tr>
<tr>
<td>Lung small cell carcinoma</td>
<td>Bone, brain, liver</td>
</tr>
<tr>
<td>Skin cutaneous melanoma</td>
<td>Brain, liver, Bowel</td>
</tr>
<tr>
<td>Thyroid adenocarcinoma</td>
<td>Bone</td>
</tr>
<tr>
<td>Kidney clear cell carcinoma</td>
<td>Bone, liver, thyroid</td>
</tr>
<tr>
<td>Testis carcinoma</td>
<td>Liver</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>Brain</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Liver, adrenal</td>
</tr>
</tbody>
</table>
Stages of metastasis

- **Invasion**: primary tumour cells enter circulation
- **Circulation** to the secondary site of tumour growth
- **Colonisation**: formation of secondary tumour
Tumor invasion

1. Translocation of cells across extracellular matrix barriers
2. Lysis of matrix protein by specific proteinases
3. Cell migration
Matrix metalloproteinases (MMP)

• 16 members, subdivided into 4 groups, based on their structural characteristics and substrate specificities
• Soluble and secreted groups; collagenase, gelatinase and stromelysins
• Membrane type (MT-MMP) group are anchored in the plasma membrane
• A zinc ion in the active centre of the protease is required for their catalytic activities.
Regulation of MMP

- MMP is controlled by an increased expression on a transcriptional level.
- MMPs are calcium-dependent proteases, which are synthesized as inactive proenzymes and are activated by the cleavage of a propeptide.
- MMP activity is regulated by specific inhibitors, the tissue inhibitors of MMP (TIMPs). Binding TIMP to MMP is in a 1:1 stoichiometry.
- MMP2 and MMP9, which cleave type IV collagen the major constituent of basement membrane, are believed to be of special importance.
Serine proteases

- Serine protease involved in ECM degradation are plasmin, plasminogen activators and cathepsin G.
- Plasmin is believed to be the most important serine protease, firstly because its ability to degrade several matrix components like gelatin, fibronectin or laminin, and secondly by the possible activation of numerous proforms of MMPs by propeptide cleavage.
- Plasmin is synthesized in its inactive proform, plasminogen, which can be converted to plasmin by plasminogen activator.
Plasminogen activator

- Two main types: urokinase (uPA) and tissue (tPA).
- uPA is bound to the surface of tumor cells by means of a specific receptor (uPAR).
- There are specific inhibitors (PAI-1 and PAI-2) for the PA.
Cell adhesion and metastasis
Cell attachment

1. Integrin: cell-matrix adhesion

2. E-cadherin/catenin adhesion complex: cell-cell adhesion
1) Integrin

- Heterodimeric transmembrane receptors consists of alpha and beta subunits
- Function to provide interactions between cells and macromolecules in the ECM (beta-2 integrins)
- Integrin can affect the transcription of MMP genes
Integrin signaling

Diagram showing the signaling pathways involving integrins and their interactions with various proteins such as DOCK-180, CRK, CAS, GRB2, FAK, SRC, SHC, PKC, RAS, RAF, PI3-K, RAC, PAK, CDC42, MLCK, ERK, MEK, and their roles in cytoskeletal alterations, contraction, gene transcription, and integrin modulation leading to cell invasion and migration.
2) E-cadherin and catenin complex

- Most important cell-cell adhesion molecules in epithelial cells
- Reduced expression of E-cadherin and catenin increases the invasiveness of tumor cells
E-cadherin - catenin

- Involved in cellular complexes (epithelia)
- In adherence junctions
- Catenin part of Wnt-signaling as a downstream target (cellular organisation and polarity) in development
Metastasis and de-differentiation

- EMT – mesenchymal phenotype
  Vimentin, CD44, Nodal
- Embryonic phenotype
- Tumor stem cells
- Tumor cell plasticity - vasculogenic mimicry
Tumor cell plasticity

- Aggressive tumor cells dedifferentiate
- Development of more ‘stem cell’ phenotype
- Endothelial cell-like phenotype
- Tube formation
- ‘Vasculogenic’ structures
- Contribution to blood circulation
CD31/34 vs Ki-67 staining