Cancer Wars
The Metastasis Strikes Back
Amir H. Faraji
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1. “Messages Gone Awry” - Tyrosine Kinases
2. “Loss of Regulation” - The Cell Cycle & p53
3. “Cancer Supply Lines” - Angiogenesis
4. “Radical Changes” - Role of Mitochondria & ROS
1. Summary
Tyrosine Kinases

Activation of Downstream Pathways

Receptor Tyrosine Kinase
Constitutively Active Receptor Tyrosine Kinase

Fusion of Tyrosine Kinases to Partner Proteins with Oligomerization

Overexpression of Receptor Tyrosine Kinase or Ligand

The Cell Cycle

- G1 Phase
- S Phase
- G2 Phase
- M Phase

Images of different cell cycle phases:
- Interphase
- Prophase
- Premetaphase
- Metaphase
- Anaphase
- Telophase
Cyclin D-CDK4 Complex

Growth Signal

Cyclin D
CDK4

Cyclin D-CDK4 Complex

Activation of genes via phosphorylation and deactivation of Rb

Other proteins necessary for DNA Synthesis (S Phase Specific)

Cyclin E
CDK2

Cyclin E-CDK2 Complex

p53
p21

G1/S Checkpoint

Cyclin A

Cyclin A-CDK2 Complex

G2/M Checkpoint
Li-Fraumeni Syndrome

Classical Tumors:
- Breast Cancer
- Osteosarcoma
- Soft Tissue Sarcoma
- Adrenocortical Carcinoma
- Leukemia
- Astrocytoma
- Meningioma

Other Associated Tumors:
- Gastric Cancer
- Pharyngeal Cancer
- Choroid Plexus Carcinoma
- Pancreatic Cancer
- Melanoma
- Germ Cell Tumors
- Wilm’s Tumor
- Colorectal Cancer
- Ovarian Cancer
- Thyroid Cancer
- Endometrial Cancer
- Prostate Cancer
- Cervical Cancer

Growing tumor isolates interior cells from blood supply

† HIF-1α, HIF-2α

† VEGF

† Angiogenesis
Hypoxic Cells Have Three Options:

1. Apoptosis
2. Neoangiogenesis
3. Metastasis
Lewis Lung Carcinoma Cell Lines

**P29**: Low Metastatic Potential

**A11**: High Metastatic Potential

ETC DEFECTS

<table>
<thead>
<tr>
<th>Lewis Lung Carcinoma</th>
<th>Fibrosarcoma</th>
<th>Colon Cancer</th>
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</thead>
<tbody>
<tr>
<td>Low Metastatic Potential</td>
<td>P29</td>
<td>B82</td>
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<tr>
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<td>A11</td>
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Defects in NADH Dehydrogenase

ETC DEFECTS

Lewis Lung Carcinoma Cell Lines

**P29**: Low Metastatic Potential & Normal ETC Function

**A11**: High Metastatic Potential & Decreased ETC Function

Defects in NADH Dehydrogenase

**Conclusion 1**

ETC mutation accelerates growth of transformed cell lines, but does not control the development of tumorigenicity and metastasis in nontransformed cells.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Description</th>
<th>Result</th>
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<tbody>
<tr>
<td>B82mtB82</td>
<td>Low Metastatic Fibrosarcoma</td>
<td></td>
</tr>
<tr>
<td>B82mtA11</td>
<td>Cybrid w/ High Metastatic LLC</td>
<td><strong>Accelerated Growth</strong></td>
</tr>
<tr>
<td>NIHmtNIH</td>
<td>Nontransformed NIH3T3 Cells</td>
<td><strong>No Growth</strong></td>
</tr>
<tr>
<td>NIHmtA11</td>
<td>Cybrid w/ High Metastatic LLC</td>
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</tr>
<tr>
<td>NIHmtB82M</td>
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<td><strong>No Growth</strong></td>
</tr>
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**Conclusion 2**

ETC mutation is co-transferred with an up-regulation of MCL-1, HIF-1 α, and VEGF.


P29mtP29 & A11mtP29 Cybrids – Low Metastatic Potential

- mtDNA w/o Mutation
  - Normal Complex I Activity
    - ROS
      - HIF-1α
        - MCL-1
  - Hypoxia
    - Proteasome Digestion
      - HIF-1α Stabilization
        - VEGF
          - Hypoxia-Induced Neoangiogenesis
            - Hypoxia-Induced Apoptosis
  - Low Metastatic Potential

P29mtA11 & A11mtA11 Cybrids – High Metastatic Potential

- mtDNA w/ Mutation
- Reduced Complex I Activity
  - ROS
  - HIF-1α
  - MCL-1

- Hypoxia
  - Proteasome Digestion
    - HIF-1α Stabilization

- Hypoxia-Induced Neoangiogenesis
  - VEGF

- Hypoxia-Induced Apoptosis

N-Acetylcysteine (NAC)

http://marionvandewiel.blogspot.com/2008/04/i-recently-joined-new-forum-toonweekly.html
1. Tyrosine kinases are a target for cancer therapies, as they provide the "first hit" allowing transformation to a cancer phenotype; they are dysregulated in a variety of cancers.

2. Mutations in p53 provide the "second hit" allowing transformation to a cancer phenotype; uncontrolled cell cycling leads to tumor growth.

3. As a tumor grows, interior cells are isolated from blood vessels, nutrients, and oxygen; hypoxia is a prognostic factor for metastasis.

4. Metastasis is regulated by ROS-mediated reversible up-regulation of nuclear genes, such as MCL-1, HIF-1α, and VEGF, especially under hypoxic conditions.

5. ROS Scavengers may be therapeutically effective in suppressing metastasis – i.e.: mitochondrial-targeted hemigramicidin?
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