Molecular Mechanism of Distant Metastasis and Clinical Implication

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คณะแพทยศาสตร์ศิริราชพยาบาล
Avastin, Erbitux, Gleevec, Herceptin…
The new wonder drugs might make you think we’re finally beating this dreaded scourge

We’re not
“Failure to control establishment of secondary colonies was the major contributor to failure… Winning the war against cancer would require increasing resources devoted to studying metastasis”
What is the Importance of Distant Metastasis?
Metastasis is the Cause of 90% of Deaths from Breast Cancer
Distant Recurrences are Associated with the Highest Risk of Death

* Hazard ratio (and $P$ value) relative to patients with no recurrence.

Molecular Mechanism of Distant Metastasis
The "Halstedian" Theory

“Breast cancer begins as a strictly **LOCAL** disease and that tumor cells spread over time in a contiguous manner away from the primary site through lymphatics.

Distant metastases are the result of direct extensions of local involvement.”

*Halsted WS. Ann Surg 1907; 46: 1-19*
Breast cancer is a **SYSTEMIC** disease and can be divided into two distinct groups: tumors that have the ability to metastasize and those that lack this ability.

If distant metastases were destined to develop, such metastases had already occurred at the time of diagnosis of the breast tumor. 

*Fisher B. Cancer 1977; 40: Suppl 1: 574-87*
Breast cancer is a heterogeneous disease... with a spectrum extending from a disease that remains local throughout its course to one that is systemic when first detectable.

Failure to achieve initial local control will allow some tumors to disseminate later to distant sites.

Hellman S. J Clin Oncol 1994; 12: 2229-34
Models of the Metastatic Cascade

Nat Rev Cancer 2004; 4: 448-56
Potential Routes of Distant Metastasis

Ann NY Acad Sci 2008; 1131: 225-34
Molecular Mechanism of Lymph Node Metastasis
Lymph Node Metastasis

- Extent of lymph node metastasis is a major determinant for staging, prognosis and therapeutic decisions in most solid tumors.

- During the initial stages of the metastasis, there is a strong predilection for spread to regional lymph nodes.
Molecular Biology of Lymphatic System
Mechanism of Lymph Node Metastasis

Traditional View

Tumor cells are passively taken up by lymphatic vessels along with interstitial fluid and are facilitated by higher permeability of lymphatic vessels and absence of basement membrane barrier.
Mechanism of Lymph Node Metastasis

Current View

1. Suppression of anti-tumor immunoresponses
2. Induction of lymphangiogenesis
3. Preparing metastatic niche
Suppressed Immunoresponses in SLN against Tumor Metastasis

- “The first lymphoid organ to respond to tumor antigenic stimulation”
- Cancer cells produce immunomodulators that lead to immunosuppression and reduction of the density and maturity of dendritic cells and T-cells in SLN
- Primary tumors enable suppression of the immune functions and facilitate development of SLN metastasis
Lymphangiogenesis in Tumor & SLN

- Tumor lymphangiogenesis significantly predicted the presence of SLN metastases.
- Lymphangiogenic growth factors secreted from a primary tumor induce lymphangiogenesis in SLN before metastasizing to these tissues.
  - “Tumor-reactive lymphadenopathy”
- Lymphangiogenesis in metastasis-containing SLN facilitates further metastatic spread.
Lymphangiogenic Factors
VEGF-A and VEGF-C Predict Nodal Metastasis


<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
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<tr>
<td>Mode of invasion (Mi)</td>
<td></td>
<td></td>
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<tr>
<td>MI1–2 vs. MI3–4</td>
<td>13.7</td>
<td>3.6–52.4</td>
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<tr>
<td>VEGF-A isoforms 121</td>
<td></td>
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<tr>
<td>Low vs. high</td>
<td>35.2</td>
<td>7.5–164.8</td>
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<td>VEGF-A isoforms 165</td>
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<tr>
<td>Low vs. high</td>
<td>20.1</td>
<td>4.9–81.3</td>
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<tr>
<td>VEGF-A isoforms 189</td>
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<tr>
<td>Low vs. high</td>
<td>12.6</td>
<td>3.4–46.0</td>
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<tr>
<td>VEGF-A isoforms 206</td>
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<tr>
<td>Low vs. high</td>
<td>8.31</td>
<td>2.4–28.3</td>
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<tr>
<td>VEGF-C</td>
<td></td>
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<tr>
<td>Low vs. high</td>
<td>33.1</td>
<td>7.4–148.4</td>
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The Importance of Lymphangiogenesis in Breast Cancer

- Intra- and peri-tumoral lymphatic vessels are important for promoting lymphatic metastasis

- Increased levels of VEGF-C promote tumor and SLN lymphangiogenesis, regional nodal spread and distant metastasis

- VEGF-A induces tumor and SLN lymphangiogenesis and promotes lymphatic metastasis

VEGF-C Increases Metastasis by Increasing Delivery of Cancer Cells to Lymph Nodes

Cancer Res 2006; 66: 8065-75
Lymphangiogenesis in Sentinel Lymph Node

Primary tumour

Lymphangiogenesis
(VEGFC and D; VEGFR2 and 3)

Metastatic tumour cells

Sentinel lymph node

Pre-existing lymphatics

Lancet Oncol 2002; 3: 44–52
Chemokines and Lymphatic Metastasis

- Small secreted proteins that regulate the chemotactic response
- SLN produce and release specific chemokines that attract cancer cells bearing specific corresponding receptors in primary sites
- CXCR4 and CXCR7 were highly expressed in breast cancer, and their ligand CXCL12/SDF-1 was expressed in bone marrow, lung, and LN where breast cancer cells preferentially metastasize

Nature 2001; 410: 50–6
Seed and Soil Hypothesis

“When a plant goes to seed, its seeds are carried in all directions; but they can only grow if they fall on congenial soil.”

Stephen Paget, 1889
Primingle the ‘Soil’ for Cancer Metastasis: The Pre-metastatic Niche
Molecular Mechanisms of SLN Metastasis

- Cytokines
- Growth factors
- Chemokines

Lymphangiogenesis

- Lymphatic vessel density
- Lymphatic destruction
- Extracellular matrix
- Interstitial fluid pressure

Lymphatic valve dysfunction
- Lymphatic dilatation

Tumor cell density
- Lymph node status

Tumor type/location

Lymph node metastasis

*Cancer Metastasis Rev 2006; 25:677–94*
Lymphangiogenesis in Breast Cancer:
Clinical Implication
Clinical Implication

- **Prognostic markers**
  - Monitoring the abundance of lymphatics in or adjacent to a primary tumor or SLN
  - Analyzing expression of lymphangiogenic growth factors and their cognate receptors

- **Therapeutic implications**
  - Targeting VEGFR-3 and/or VEGFR-2 pathway, chemokine receptors CXCL12-CXCR4 signaling (antibodies, small molecule kinase inhibitors)
Targeting Lymphangiogenic Pathway

Targeting Lymphangiogenesis to Prevent Tumor Metastasis

Timeline of treatment

**Preoperative treatment**
- Antilymphangiogenesis and chemotherapy
- Surgery

**Aim**
- Restrict metastasis during treatment designed to facilitate surgery

**Relevant cancers**
- Breast cancer (L,C,D)
- Gastric cancer (L,D)
- Colorectal cancer (L,C,D)

**Postoperative treatment**
- Antilymphangiogenesis and chemotherapy
- Surgery

**Aim**
- Restrict metastasis after surgery in patients with high risk of relapse

**Relevant cancers**
- Breast cancer (L,C,D)
- Melanoma (L,C)

**Advanced disease**
- Antilymphangiogenesis and chemotherapy
- No surgery

**Aim**
- Restrict progression of disease in nonresectible cancer

**Relevant cancers**
- Breast cancer (L,C,D)
- Melanoma (L,C)
- Colorectal cancer (L,C,D)
Sunitinib: Mechanism of Action

- Inhibition of cancer progression & metastasis
  - ↑ VEGF
  - ↑ PDGF

Sunitinib targets VEGFR and PDGFR in different cell types:
- Lymphatic Endothelial Cell
  - Lymphatic permeability
  - Cell survival, proliferation, migration
- Pericyte/Fibroblast/Vascular Smooth Muscle
  - Lymphatic formation, maturation

Inhibition of cancer progression & metastasis

# Multi-kinase Inhibitors

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<thead>
<tr>
<th>Sunitinib (sun)</th>
<th>Sorafenib (sor)</th>
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<tr>
<td><strong>Phase II monotherapy trial in MBC (n=64)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Phase II second-line monotherapy trial in MBC (n=54)</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>PR = 14%, SD &gt;6 months = 5%</td>
<td>PR = 1.9%, SD &gt;6 months = 11%</td>
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**Eight ongoing phase II trials**
- Two neoadjuvant:
  - Monotherapy, sun + weekly paclitaxel → AC
- Three MBC first-line:
  - Monotherapy, sun + Avastin + paclitaxel, Sun + Herceptin
- Three MBC second-/third-line:
  - Monotherapy x 2, Sun versus standard of care in triple-negative breast cancer

**Four ongoing phase III trials in MBC**
- Sun + paclitaxel versus Avastin + paclitaxel, sun + docetaxel versus docetaxel, sun versus Xeloda, sun + Xeloda versus Xeloda

**Seven ongoing phase II trials**
- Four first-line MBC
  - Sor + endocrine therapy versus endocrine therapy
  - Sor + paclitaxel versus paclitaxel
  - Sor + nab-paclitaxel
- Three second-/third-line MBC
  - Monotherapy x 2
  - Sor + gemcitabine versus gemcitabine

**No ongoing phase III trials**

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<sup>1</sup>Miller KD, et al. Oral presentation at ASCO 2007 (Abstract 563)

<sup>2</sup>Bianchi GV, et al. Poster presentation at ASCO 2007 (Abstract 164)
Conclusion

- Metastatic spread is the most lethal aspect of cancer and often occurs via lymphatic vasculature.

- The immune suppression in SLN by tumor cells results in failure of prevention or eradication of tumor metastasis.

- Lymphangiogenic growth factors promote formation of tumor lymphatics and metastatic spread of tumor cells to lymph nodes.
‘Chemokine-chemokine receptor network’ plays an important role in lymphatic metastasis

Lymph node lymphangiogenesis may contribute to further metastatic tumor spread beyond the SLN

Efficient anti-lymphangiogenic therapies are needed
Thank you for your attention