Biologic Basis of Breast Cancer Treatment

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History of Cancer Treatment
From George Sledge’s ASCO 2011 Presidential Address

- 19th century: Loco-regional era
- Late 1940s-50s: Developed non-specific systemic approaches
- Past decade: Targeted therapies exploded
- Just entering a 4th era: Genomics
Genomic Classification: Many Subtypes of Breast Cancer!

Genes and Cancer

Red dots: Genes “turned up” in cancer cells compared to normal cells

All cancers are caused by genetic changes

Individual genes

Individual tumors

Genomic Profiling “Heat Map”
Genomic Classification: Many Subtypes of Breast Cancer!

Subtypes vary with respect to:
- Likelihood of recurrence
- Sites of metastases
- Response to treatment
- Frequency of subtypes varies across populations – additional subtypes likely exist
Breast Cancer Biology: Not all Breast Cancers are the Same!!

Estrogen Receptor (ER) +
75% of Breast Cancer

HER-2 +
20-25% of Breast Cancer

Tumor ER and HER2 status are CRITICAL in selecting therapy in both early stage and metastatic breast cancer!
Estrogen Receptor Positive Breast Cancer is a Spectrum in Itself: Luminal A and Luminal B Subtypes
Breast Cancer:
Luminal A and B Subtypes

• Express ER, PR, and genes associated with ER activation

• Luminal A (40 percent of all breast cancers)
  – High expression of ER-related genes, low expression of HER2 cluster genes and proliferation-related genes
  – Best prognosis of all breast cancer subtypes

• Luminal B (20 percent)
  – Relatively lower (although still present) expression of ER-related genes, variable expression of HER2 cluster, higher expression of proliferation cluster
  – Worse prognosis than luminal A
Estrogen Receptor as a Target for Therapy

Aromatase inhibitors, ovarian suppression

SERMS, SERDS

Cell Growth and Division

Estrogen

Endocrine therapy is effective only in ER-positive breast cancer

ER/PR staining: CRITICAL IN SELECTING THERAPY!
Breast Cancer: HER-2 Subtype

- 10 to 15 percent of breast cancers
- High expression of HER-2 and proliferation gene clusters, low expression of luminal cluster
  - Typically ER/PR negative, HER-2 positive
  - This subtype comprises only about half of clinically HER-2-positive breast cancer (the rest is luminal B)
- Before HER2-targeted therapy, this subtype carried a poor prognosis.
  - Markedly affected by advances in HER2-directed therapy
HER2 as a Target for Therapy

- HER-2
- Anti-HER-2 Antibody
- Pertuzumab
- Trastuzumab (Herceptin)
- Lapatinib (Tykerb)
- Dual HER-1/HER-2 Tyrosine Kinase Inhibitor
- Ado-trastuzumab emtansine
- Antibody-Drug Conjugate
- T-DM1

HER2 therapy effective only in HER2-overexpressing breast cancer
HER2 staining: CRITICAL IN SELECTING THERAPY!
Breast Cancer: Basal Subtype

- 15 to 20 percent of breast cancers
- Low expression of luminal and HER2 gene clusters
  - Typically ER-, PR-, and HER-2-negative ("triple negative")
- High expression of proliferation cluster genes, virtually always high grade, widespread genomic instability
  - High expression of EGFR and unique basal cluster genes (basal epithelial cytokeratins 5, 14, and 17)
- Common in BRCA1 mutation carriers (over 80%)
- Overrepresented in premenopausal and African women
- Poor prognosis
- Sensitive to chemotherapy
- Associated with DNA repair defects - PARP1 commonly increased
6 subtypes of TNBC identified by gene expression array
Targeting the Cancer Environment

In Addition to Targeting the Cancer Cell, We Can Also Target the Cancer Environment

- Cancer cell
- Immune cell
- Blood vessels
- Fibroblast
- Osteoclast
Biologic Basis of Breast Cancer Treatment: Opportunities and Challenges in Targeting Cancer Therapy

• Identifying the target
  – patient and tumor selection

• Understanding the target
  – role in tumor
  – networks and interactions
  – role in normal tissues

• Monitoring the target
  – does an agent actually target the intended pathway and does it result in clinical benefit?
Merging the Targeted Therapy Era with the Genomic Era of Cancer Treatment: Targets and Drugs

- EGFR Inhibitors
- HER-2 Inhibitors
- IGF-R Inhibitors
- MUC-1 Antibodies
- Metastasis Inhibitors
- Anti-Angiogenesis
- Death Receptors
- Raf Inhibitors
- HIF Inhibitors
- MEK Inhibitors
- HSP90 Inhibitors
- MEK Inhibitors
- Proteosome Inhibitors
- Tubulin-interacting Agents
- mTOR Inhibitors
- Src Inhibitors
- Cell Cycle Inhibitors
- Farnesyl Transferase Inhibitors
- Aurora Kinase Inhibitors
- Mdm2 Inhibitors
- Pro-apoptotic Drugs
- Kinesins
- HDAC Inhibitors
Ongoing NCI MATCH (Molecular Analysis for Therapy Choice) Clinical Trial

Genomic Profiling of Tumor

↓

Actionable mutation detected

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Study Agent 1

Continue until progression

Progressive disease

Check for additional actionable mutations

Study Agent 2

• Eligibility:
  – Metastatic solid tumors and lymphomas that have progressed on ≥ 1 line of therapy
• Access to many drugs in development: currently > 40 drugs pledged
Biologic Basis of Breast Cancer Treatment: The Future

- Cancer care is set to change dramatically in the next 20 years
- Advances in technology and a deeper understanding of cancer biology will transform cancer care
- Continued investments in cancer research required to translate scientific breakthroughs into new treatments