Breast Cancer Stem cells:  
Implications for Prevention and Therapy
Recent decrease in UK and USA breast cancer mortality at ages 50-69 years

Breast Cancer Development

Normal → Pre-neoplastic → Neoplastic → Metastatic

Genetics Risk Assessment → Prevention → Detection → Therapy

Local → Systemic
CANCER STEM CELL HYPOTHESIS

• Cancers Arise From Tissue Stem Or Progenitor Cells
• Cancers Are “Driven” By Cells With Stem Cell Properties
Characteristics of Stem Cells

• Self Renewal

• Multi-Lineage Differentiation
Common characteristics of normal stem cells and tumor stem cells

- Ability to self-renew
- Ability to differentiate
- Long lived/immortal
- Resistance to damaging agents
- Anchorage independent survival and ability to migrate

Carcinogenesis

- Uncontrolled proliferation
- Tumorigenicity
- Tumor heterogeneity
- Aberrant organogenesis
- Higher risk of accumulating mutations
- Often defects in DNA repair mechanisms, resulting in mutator phenotype and radioresistance
- Genomic instability
- Increased transporter activity and toxic agent exclusion
- Chemoresistance
- Metastasis

Normal stem cell functionality

- High proliferation potential, tightly controlled
- Organogenesis
- Adult tissue maintenance and repair
- Regeneration of an organ/tissue upon transplantation
- Generation of all types of differentiated cells in a tissue
- Organogenesis
- More exposed to damaging agents, higher risk of accumulating mutations, corroborated by
  - Active DNA repair mechanisms
- Increased transporter activity and toxic agent exclusion
- Homing
Pathways Involved in Stem Cell Self Renewal and Cancer

- Notch
- Hedgehog
- Bmi-1
- Wnt
Hedgehog Target Gli-2 Promotes Ductal Hyperplasia
CANCER STEM CELL HYPOTHESIS

• Cancers Arise From Tissue Stem Or Progenitor Cells
• Cancers Are “Driven” By Cells With Stem Cell Properties
Cancer cells are heterogeneous, but most cells can proliferate extensively and form new tumors.

Cancer cells are heterogeneous, and only rare cancer stem cells have the ability to proliferate extensively and form new tumors.
The Isolation of Human Cancer Stem Cells

dissociate

stain with antibodies

Flow-cytometry

CSC
## Tumorigenicity of Cancer Cell Subsets

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Tumor 1 was derived from a metastatic pleural effusion and Tumor 2 was derived from a primary breast tumor.
Tumor Formation by Human Breast Cancer Cells in Mouse Model

CD44+;B38.1+ CD24+

CD44+;B38.1+ CD24-
Both Non-Tumorigenic Cancer Cells and Cancer Stem Cells have a Malignant Appearance, but Only Stem Cells Give Rise to New Tumors
Breast Cancer Stem Cells give rise to Phenotypically Diverse Tumors after Transplantation
Hedgehog Activation & Bmi-1 Expression in Cancer Stem Cells

**PTCH1**

- **Total cells**
- **Non-tumorigenic cells**
- **Tumorigenic cells**

* p < 0.05

**Gli1**

- **Total cells**
- **Non-tumorigenic cells**
- **Tumorigenic cells**

* p < 0.05

**Gli2**

- **Total cells**
- **Non-tumorigenic cells**
- **Tumorigenic cells**

* p < 0.05

**hBmi-1**

- **Total cells**
- **Non-tumorigenic cells**
- **Tumorigenic cells**

* p < 0.05
Mammary stem cell self-renewal pathways

Normal

Hedgehog signaling pathway

Shh, Ihh, Dhh

Notch signaling pathway

DSL

Cyclopamine

Gli1

Gli2

Bmi-1

Deregulation

Self-renewal

Normal Stem cell

Normal Stem cell

Differentiation

Differentiated cells

Tumor

Tumorigenic Stem cell

↑PTCH1

↑Ihh

↑Bmi-1

Self-renewal

Differentiation

Non-tumorigenic cells

Figure 10
BMI-1 “Stem-Cell” Signature and Patient Survival
Glinsky et al. JCI 115:1503, 2005
Implications of TSC - Profiling/ Diagnosis/ Prevention

- Cell of origin may determine molecular profile
- Molecular profiling may miss important TSC genes
- Significance of TSC in metastasis
- Identification of TSC in situ may have diagnostic/prognostic value
- Elimination of mutated stem/progenitor cells important prevention strategy
Normal Development

- Stem cell ER-
- Progenitor cell
- Myoepithelial progenitor
- Ductal luminal progenitors
- Myoepithelial cell
- ER+ Ductal epithelial cell
- ER- Alveolar cell

Differentiation

Paracrine signals

Carcinogenesis

- Cancer stem cell ER-
- Basal
- Aberrant limited differentiation
- ER-

- Luminal B
- ER-
- Self-renewal
- ER- Differentiation

- Luminal A
- ER+
- Self-renewal
- ER+ Differentiation

- Cancer stem cell ER+
- ER+

- Cancer stem cell ER-
Cancer Stem Cells: Implications For Metastasis

1° Tumor

CSC = Cancer Stem Cell
TDC = Terminally Differentiated Cell

CSC with FULL malignant potential
Metastases in months to few years
Subsequently to other sites

CSC with PARTIAL malignant potential
Dormancy followed by Metastases after many years:
Secondary Oncogenic “Hits” and/or Changes in Microenvironment

No Metastases
The Implications of Human Cancer Stem Cells (CSCs) for Treatment

Drugs that kill cancer stem cells

CSCs regenerate tumor

Tumor regresses

Drugs that kill cancer cells but not CSCs

Tumor recurs

Tumor degenerates, patient is cured

Tumor looses its ability to generate new cells
Implications of TSC Therapeutics

- Tumor regression inadequate endpoint
  - Preclinical models
  - Phase II clinical trials
- TSC may be resistant to therapy (apoptosis)
- Effective therapies should target TSC while sparing normal cells
- Genes in TSC self-renewal pathway may provide new therapeutic targets
Evidence for “Stem Cells” in Human Cancer

- Breast Cancer
- Leukemia
- Multiple Myeloma
- Brain Cancer
- Lung Cancer
- Prostate Cancer
- Melanoma