Targeting breast cancer stem cells

SWOG 2014

Max Wicha M.D.
Cancer Stem Cell Hypothesis

Cancers Arise from Cells with Dysregulated Self-Renewal

Cancers Are “Driven” By Cells With Stem Cell Properties
Stem cells and breast carcinogenesis

Quiescent pool of stem cell

Early Progenitor

Stem cell

Late Progenitor

Cancer stem cell

Luminal cells

Myoepithelial cells

Alveolar cells
Implications of CSC Therapeutics

- Tumor regression inadequate endpoint
  - Preclinical models
  - Phase II clinical trials
  - Extrapolation to adjuvant settings
- CSC may be resistant to therapy
- Effective therapies should target CSC while sparing normal stem cells (eg. Gut, bm)
- CTC’s may be useful in monitoring response
Breast Cancer Stem Cell Markers

- CD44 +/
- CD24 -
- Aldehyde Dehydrogenase
Expression of CSC Markers in TNBC

Invasive Edge | Tumor Interior

CD44
CD24
ALDH1

S. Liu
EMT/MET gene expression in CD44+CD24- vs ALDH+ CSCs

<table>
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<tr>
<th>Probeset ID</th>
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Plasticity between CSC states

![Graph showing the plasticity between CSC states.](image)
Regulation of breast CSC states

MET-CSC
- ALDH
- E-Cadherin
- Vimentin
- Proliferative
- Tumor Growth
- Trastuzumab (Anti-Her2)
- Cell Death
- miR200, miR205, miR93, Xist, lncRNA-ATB

EMT-CSC
- CD44+/CD24-
- E-Cadherin-
- Vimentin+
- Quiescent
- Metastasis
- Drug Resistance
- Relapse
- BMP
- Tocilizumab (Anti-IL-6R)
- Repertaxin (Anti-CXCR1)
- Cell Death

Wnt, Hh, Notch
PI3K/AKT/mTor
STAT3, NF-kB
let7, miR-30, miR-34
miR-181, miR-100, miR-221
miR-155, Hotair, H19
MALAT1, treRNA, linc-ROR
lnc-RNA-ATB
Breast cancer stem cell states

- CD44+/24-
- ALDH+

EMT

MET
Recapitulation of Tumors Via CSC Metastasis

Breast Tumor

Micrometastasis

Macrometastasis

Vasculature

Aldefluor +

CD44+/CD24-

Invasive Edge of Tumor

Necrotic Zone

Distal Healthy Organ

Distal Colonized Organ

Time

EMT  MET
Breast Cancer Stem Cells are Metastatic

MDAMB 453
ALDH -  Total  ALDH+

MDAMB 231
Total  ALDH -  ALDH+

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Cancer Stem Cells: Implications For Metastasis

CSC = Cancer Stem Cell
TDC = Terminally Differentiated Cell

1º Tumor

CSC with FULL malignant potential

Metastases in months to few years
Subsequently to other sites

Dormancy followed by Metastases after many years:

Secondary Oncogenic “Hits” and/or Changes in Microenvironment

No Metastases
Targeting Self-Renewal Pathways in CSC’S

Breast Tumor

Mesenchymal Cells

Cyclopamine

Anti-DLL4

DSL

γ-secretase

GSI

Targeting Self-Renewal Pathways in CSC’S

Cancer stem cell

GLI

Bmi-1

TCF

HES

HER2

STAT3

JAK3

IL-8

IL-6

IL-6R

gp130

Repertaxin

Perifosine

Trastuzumab

Monoclonal Abs

Mesenchymal Cells

Breast Tumor

Cyclopamine

Anti-DLL4

DSL

γ-secretase

GSI

Cancer stem cell

GLI

Bmi-1

TCF

HES

HER2

STAT3

JAK3

IL-8

IL-6

IL-6R

gp130

Repertaxin

Perifosine

Trastuzumab

Monoclonal Abs

Mesenchymal Cells
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CLINICAL TRIAL WITH GSI (MK-0752)

A

Pretreatment biopsy

GSI days 1–3

Docetaxel 80 mg/m² day 8

Repeat biopsy after cycles 1 and 3

Continue sequential GSI/docetaxel combination until disease progression or cycle 6

Tissue biopsy at EOT

B

Tumor Size (mm)

0 50 100 150 200

Baseline Post-cycle 1 Post-cycle 2 Post-cycle 3 Post-cycle 4 Post-cycle 5 EOT

C

CD4+/CD24 (%)  0 10 20 30 40

Baseline Post-cycle 1 Post-cycle 3 Surgery

D

ALDH1 Subpopulation (%)  0 2 4 6 8 10

Baseline Post-cycle 1 Post-cycle 3 Surgery

E

MSFE (%)  0.0 0.5 1.0 1.5 2.0

Baseline Post-cycle 1 Post-cycle 3 Post-cycle 4 Post-cycle 5

30 patients

Schott, et al.,
Clinical Cancer Research, 2013
Isolation of circulating CSCs

A microfluidic high throughput label and label free isolation strategy for the sensitive isolation of CTCs and CSCs

Sunitha Nagrahth
High Throughput Inertial Microfluidics
Buffer, 2000 µL/min

DAPI (WBC)

FITC (CTC)
C1 System

Single Cell

http://www.fluidigm.com
Heatmap of expression of 96 genes in MC1 MCF7 and SUM 159 ALDH+ cells
Single cell gene expression analysis of T47D BC cell line in **Adherent Culture Condition** versus **Sphere derived Cells**
Pt 98  TNBC CTCs have EMT (CD44+/CD24-/ALDH-/Vim+) characteristics
Pt 95 LUMINAL CTCs have (ALDH+/EpCAM+/CDH1+/Vim-) characteristics
Generation of tumor cellular heterogeneity
Collaborators:

Christophe Ginestier
Emma Charafe-Jauffret
Dan Hayes
Kathie Day
Duxin Sun
Sunitha Nagrath
Dean Brenner

Euisik Yoon
Sunitha Nagrath
Ebrahim Azizi

Sunitha Nagrath
Ebrahim Azizi
Euisik Yoon
Plenary I
Translational Medicine

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