Local and systemic roles of estrogen in breast cancer formation and progression

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Unique Characteristics of AYA Cancers
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Breast Cancer is a Heterogeneous Disease

Basal type:
- ER/PR/Her2 negative
- Express basal epithelial cytokeratins (CK5/6/14/17)
- Often overexpress EGFR and have p53 mutations
- Associated with BRCA-1 mutations/low BRCA-1 expression
- Likely to be high grade and poorly differentiated

HER2 type:
- Her2 positive
- Overexpress genes in the Her2 amplicon on chromosome 17q21
- Hormone receptor negative or low
- Higher frequency of p53 mutations
- More likely to be high grade

Luminal type:
- Most common, usually low grade
- Hormone receptor (ER/PR) positive
- Express luminal cytokeratins (CK8/18)
- Luminal A has higher expression of ER-related genes and lower proliferative genes vs Luminal B

Basal-Like  Her2+  Normal Breast-Like  Lum. C  Lum. B  Luminal Subtype A

Sorlie et al. 2001, PNAS
Incidence of ER- negative breast cancers is more prevalent in younger women.

Legend:
- Blue = ER+/PR+,  
- Green = ER+/PR-,  
- Yellow = ER-/PR+,  
- Purple = ER-/PR-

Curtsey of Graham A. Colditz
ER negative breast cancers are sensitive to circulating estrogens

ER+ Breast Cancers

ER-Breast Cancers

nulliparous

age at birth=35

age at births =20,23,26,29

menopause

Increased local estrogen

Decrease in systemic estrogen

Curtsey of Graham A. Colditz
Estrogen accelerates tumor growth in ER-negative tumor models

Gupta et al, Cancer Res, 2007

**HMLER-low**

- **0.18 mg**
- **0.72 mg**

**PC3**

**SUM1315**
Estrogen promotes increased cellular recruitment and angiogenesis in the absence of tumor growth.
Increased stromal contribution and metastasis following estrogen-treatment

+17bEstradiol

Placebo

HMLE-Her2

HMLE-Her2

PC3

DU4475

DU4475
Tumor associated stroma following estrogen treatment is composed of LYVE1+, CD45+ and \( \alpha \text{SMA} \) cells.

GFP: Tumor Cells
Texas-Red: IHC
Where does stromal recruitment come from??


Can estrogen promote increased systemic angiogenesis through BM-cell recruitment?
Tumor-associated stroma is bone marrow derived- but not EPCs or MSCs

High-ras tumor
GFP BM cells
AMCA- IHC

Bone marrow derived cells in tumors are interspersed within stroma and heterogeneous cell types.

- BMDCs
- Tumor Cells
- SMA

Images show immunofluorescence staining of BMDCs, SMA, LYVE1, CD45, and DAPI.
Are bone-marrow derived cells from post-partum or estrogen-treated mice causal in the formation of tumors??

Harvested Bone Marrow

Bone Marrow Cells + 250,000 HMLER Cells

Co-mix and inject into untreated nulliparous mouse

Placebo- vs. 17β Estradiol-treated
Estrogen treated bone marrow is sufficient to promote and phenocopy tumor formation.
Portable two-color *in vivo* flow cytometer for real-time detection of fluorescently-labeled circulating cells

Boutrus et al., Journal of Biomedical Optics. 122, 2007
Estrogen mobilizes CD45+/CD31+/low cells into the circulation not CD34+ cells.
Estrogen-sensitive CD45+/CD31+/low cells are not Sca1+ EPCs

Placebo

Estrogen

EPC
Estrogen mobilization of CD45+/CD31+/low cells is ERα-dependent.

**WT**

+ placebo

+ 17b estradiol

**ERαKO**
Working model of estrogen and stroma contributions in breast cancer growth

- Estrogen
- ERα

- Monocyte/macrophage
  - Gr1+/CD11b+
  - CXCR4+/Col+

- EPC/CD31+

- VEGF
- MMP9
- IL-1
- TGFβ

- Myofibroblast
  - (LYVE1)

- Tumor Growth/Expansion
  - TGFβ
  - HGF

- Angiogenesis

CD45+/CD31+/low
ERα
CD45+/CD31+/low
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