Cell of origin: Stem cells

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Mouse model for epithelial ovarian cancer (EOC) associated with TRP53 and RB1 deficiency

- Has common molecular mechanisms with human EOC
- Phenotypically similar to human high-grade serous ovarian adenocarcinomas
- Shows features of neoplastic progression similar to those in human EOC, such as intraperitoneal spreading, formation of ascites and metastasis to the contralateral ovary, the lung, and the liver
- Allows modeling in adult immunocompetent mice

Flesken-Nikitin et al., *Cancer Res.* 63: 3459-3463, 2003
TP53 mutations and deregulation of RB pathway are common alterations in high-grade serous ovarian carcinoma

TP53 mutations: 96%
RB pathway alterations: 67%
316 cases

Cancer Genome Atlas Research Network.

TP53 mutations: 90%
RB pathway alterations: 66%
http://www.cbioportal.org/ Current
Potential tissues of ovarian carcinoma origin

- Ovarian surface epithelium
- Fimbrial epithelium of the uterine (Fallopian) tube
- Stem cells?
- High-grade serous adenocarcinoma
Stem cells and cancer

Stem cell niche

Stem cells
Transit-amplifying cells
Mature cells

Cancer
Cancer
Cancer
No cancer
No cancer

Initiating genetic or epigenetic alteration
Cancer propagating cells (CPC)
Non-CPC
Normal cells of a cell lineage
Mouse transplantation experiments

# How do we identify stem cells?

<table>
<thead>
<tr>
<th>Assay</th>
<th>Pitfalls</th>
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<tbody>
<tr>
<td>Immunodetection (e.g., CD44, CD49&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>Insufficiently specific</td>
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<tr>
<td>Functional properties, such as enzymatic activity (e.g., ALDH) or compound efflux (e.g., side population)</td>
<td>Insufficiently specific</td>
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<tr>
<td>Label retention (e.g., BrdU, H2B-GFP)</td>
<td>Not all stem cells are slowly cycling (e.g., Lgr5+ intestinal stem cells)</td>
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<td>Formation of monoclonal spheres/organoids for consecutive rounds of dissociation and regeneration (e.g. prostaspheres)</td>
<td>Cell culture assays are not sufficient for the unambiguous identification of stem cells</td>
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<tr>
<td>Formation of a complete tissue after single cell transplantations in several consecutive rounds of dissociation and regeneration (e.g., mammary stem cells)</td>
<td>Under physiological conditions stem cells may have more restricted potential (e.g., prostate epithelium stem cells)</td>
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<tr>
<td>Cell lineage (fate) tracing (e.g., intestinal cells)</td>
<td>Identification of stem cell-specific promoters is a major challenge</td>
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Stem cells of the ovarian surface epithelium

- BrdU and H2B-GFP label retaining cells (LRCs) in the OSE
- LRCs are able to divide during OSE regeneration
- H2B-GFP LRCs have enhanced growth in adherent colony formation assays
- Side population enriches for H2B-GFP LRCs in the OSE
- IHC H2B-GFP LRCs: Positive for CK8, β-catenin, vimentin, E-cadherin, collagen IV, GATA-4, P13K. Negative for EpCam, α-smooth muscle actin, c-kit, CD90, CD45, CD31

Not addressed
- clonogenic properties
- OSE sphere formation
- self-renewal
- specific markers
- anatomical location
- stem cell niche
- connection between stem cell compartment and cancer

Hilum cells contribute to the OSE regeneration

Stem Cell Niche in the hilum
LGR5+
ALDH1+
LEF1+
CK6B+
CD133+

TA and differentiated OSE

Mesothelium
Hilum cells deficient for TRP53 and RB1 are highly tumorigenic and metastatic
Future challenges

• Human equivalent?

• Single cell pool or several, perhaps some reserve, pools, similarly to other tissues, such as intestinal, prostate, and epidermal epithelia?

• What are the mechanisms rendering stem cells more susceptible to the malignant transformation as compared to more differentiated cells?
Transitional zones and cancer

- Corneal Limbus
  - conjunctiva
  - cornea

- Cervix Uteri
  - Squamo-columnar Junction
  - Dysplasia
  - Barrett’s metaplasia
  - Cancer

- Gastric Squamo-columnar Junction
  - E-S Jct
  - S
  - E
Serous tubal intraepithelial carcinoma (STIC) was present in 73 of 141 (52%) cases in which the fimbriae were present and in 62 of 100 (62%) cases in which the tubal-peritoneal junction (TPJ) was present. When fimbriae and TPJ were absent, STIC was found in 8 of 61 (13%) cases (P<0.0001).
Stem cells of the tubal epithelium?

Mouse
• Patterson and Pru. Long-term label retaining cells localize to distinct regions within the female reproductive epithelium. *Cell Cycle* 2013; 12:2888-98; PMID:24018418

Human
• Paik at el. Stem-like epithelial cells are concentrated in the distal end of the fallopian tube: a site for injury and serous cancer initiation. *Stem Cells* 2012; 30:2487-97; PMID:22911892

To be addressed:
• Not all stem cells are label retaining cells
• Lineage tracing has not been done
• Association with the tubal-peritoneal junction remains uncertain
• Susceptibility of putative stem cells for malignant transformation has not been tested
Current status

• The hilum region of the mouse ovary, the transitional/junction area between the ovarian surface epithelium (OSE) and other cell types contains a cancer-prone stem cell niche of the OSE.

• This finding suggests that the susceptibility of other transitional zones, such as squamo-columnar junctions of the cervix and anus, to malignant transformation may be explained by presence of previously unknown stem cell niches.

• It is likely, that, in addition to the OSE stem cell niche, there is a stem cell niche for the tubal epithelium, which is located in the distal region of the uterine tube. Its propensity for malignant transformation remains to be determined.
Challenges

• Stem cell biology of the reproductive tract remains largely in its primordial stage, significantly lagging behind the research of other organs and systems.

• Role of stem cells in ovarian cancer remains insufficiently elucidated.

• Modeling of ovarian cancer needs to take into account not only the tissue of origin but also the differentiation stage of target cells.

• Novel approaches for studies of normal human OSE and TE cell lineages in vivo are required.