The Origins of Ovarian Cancer:

Clear Cell Carcinoma of the Ovary

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Disclosure

• Nothing to disclose
Study Objective

• Introduction
• Clinicopathological features
• Endometriosis as the origin
• Molecular analysis
• Summary
Subtypes of ovarian epithelial carcinoma

- high-grade serous
- mucinous
- endometrioid
- CCC
- low-grade
Clinical features

• ~5% of all ovarian CA in North America; higher incidence in Asia
• Highly aggressive; chemoresistance
• 50-70 y/o with enlarging abdominal mass
• 50%-70% with endometriosis
• 80% unilateral; ~50% stage I
• Paraneoplastic hypercalcemia & pelvic venous thromboses
• 2/3 are nulliparous
Histological features

Polyhedral cells with abundant clear and/or eosinophilic cytoplasm; hobnail cells; infrequent mitotic figures; admixtures of tubulocystic, papillary and solid patterns;
Cystic vs. adenofibromatous type
Better clinical outcome in CCC with cystic lesion and endometriosis
Hepatocyte nuclear factor-1β (HNF-1β)

- Enhance survival in CCC cells
- Glucose/glycogen metabolism

Oncogene 29:1741, 2010

Utility of hepatocyte nuclear factor-1β as a diagnostic marker in ovarian carcinomas with clear cells
Histopathological evidence
Epidemiologic evidence

13 ovarian cancer case-control studies; 13226 controls and 7911 OVCA patients’ Self-reported endometriosis and risk of OVCA

- **Clear cell**
  - OR = 3.05
  - (95% CI: 2.43-3.84)

- **Endometrioid**
  - OR = 2.04
  - (1.67-2.48)

- **Mucinous**
  - OR = 1.02
  - (0.69-1.50)

- **HG serous**
  - OR = 1.13
  - (0.97-1.32)
Transcriptome profile evidence

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Normal Ovary</th>
<th>Fallopian Tube</th>
<th>Colon</th>
<th>Endometrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>0.9623</td>
<td>0.7791</td>
<td>0.6775</td>
<td><strong>0.0002</strong></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>0.4915</td>
<td>0.5928</td>
<td>0.9748</td>
<td><strong>0.0172</strong></td>
</tr>
<tr>
<td>Serous</td>
<td><strong>0.0743</strong></td>
<td><strong>0.0042</strong></td>
<td>0.9993</td>
<td>0.8504</td>
</tr>
<tr>
<td>Mucinous</td>
<td>0.6905</td>
<td>0.4863</td>
<td>0.9993</td>
<td>0.9860</td>
</tr>
</tbody>
</table>

*rank-sum analysis*

**Human Cancer Biology**

Patterns of Gene Expression in Different Histotypes of Epithelial Ovarian Cancer Correlate with Those in Normal Fallopian Tube, Endometrium, and Colon

Rebecca T. Marquez, Keith A. Baggerly, Andrea P. Patterson, Jinsong Liu, Russell Broaddus, Michael Frumovitz, Edward N. Atkinson, David I. Smith, Lynn Hartmann, David Fishman, Andrew Berchuck, Regina Whitaker, David M. Gershenson, Gordon B. Mills, Robert C. Bast, Jr., and Karen H. Lu
Clear cell carcinoma or endometrioid carcinoma

- **PIK3CA** mutation
- **PTEN** LOH & mutation
- **ARID1A** mutation

- Sato, Cancer Res, 2000
- Yamamoto, J Pathol, 2011
- Ayhan, 2012;
- Yamamoto, Mod Pathol, 2012
Endometriosis-related ovarian neoplasms

- Clear cell carcinoma
- Endometrioid carcinoma
- Seromucinous borderline tumor
Summary of histogenesis

Ectopic endometrium

Retrograde menstruation

Hematopoietic stem cells

OSE metaplasia

EM/CC borderline tumor
The Fenton Reaction – Iron-induced multiplication of ROS

\[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^\cdot + \text{OH}^- \]

oxidative stress

accumulated DNA damage
Genomic Analysis in Gyn Cancer

Ovarian Cancer:
- High-grade serous carcinoma
- Low-grade serous carcinoma
- Clear cell carcinoma

Endometrial Cancer:
- Serous carcinoma
- Endometrioid carcinoma

Lower genital tract cancer
- Squamous carcinoma

Leiomyosarcoma
Mutational Analysis

Frequent Mutations of Chromatin Remodeling Gene ARID1A in Ovarian Clear Cell Carcinoma

Siân Jones,1 Tian-Li Wang,2 Ie-Ming Shih,3 Tsui-Lien Mao,4 Kentaro Nakayama,5 Richard Roden,3 Ruth Glas,6 Dennis Slamon,6 Luis A. Diaz Jr.,7 Bert Vogelstein,3 Kenneth W. Kinzler,1x Victor E. Velculescu,4* Nickolas Papadopoulos4*  

Average of 48 non-synonymous mutations/tumor

ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas

Genomic alterations in CCC
Mutation frequency of ARID1A in human cancer

Ovarian HGSC
Uterine serous CA
Ovarian EMC
Lung adenocarcinoma
Pancreatic CA
Prostate CA
Colorectal CA
Gastrointestinal CA
Uterine cervical CA
Lung SCC
Lymphoma
Medulloblastoma
Burkitt lymphoma
Bladder TCC
Liver CA (HBV)
Esophageal CA
Ovarian clear cell carcinoma
Uterine clear cell carcinoma

PLOS ONE 8:e55119, 2013
Diverse functions of ARID1A

DNA damage repair

Apoptosis

Cell cycle progression

Cancer metabolism

AKT signaling

PI3K signaling

Epithelial-mesenchymal transition (EMT)
History of chromosomal instability of ovarian CCC is similar to other Type I gyn cancers.

**ZNF217 & PPMID are the most common amplified genes in CCC**

Association of 17q21-q24 gain in ovarian clear cell adenocarcinomas with poor prognosis and identification of PPM1D and APPBP2 as likely amplification targets.

PPM1D is a potential therapeutic target in ovarian clear cell carcinomas.
Prognostic and Therapeutic Impact of the Chromosome 20q13.2 ZNF217 Locus Amplification in Ovarian Clear Cell Carcinoma

Mohammed Tanjimur Rahman, MBBS1; Kentaro Nakayama, MD, PhD1; Munmun Rahman, MBBS1; Naomi Nakayama, MD1; Masako Ishikawa, MD, PhD1; Atsuko Katagiri, MD1; Kouji Iida, BSc1; Satoru Nakayama, MD2; Yoshiro Otsuki, MD2; Ie-Ming Shih, MD, PhD3; and Kohji Miyazaki, MD, PhD1
Targeting PI3K in ovarian clear cell carcinoma

BKM120 in Cancers With PIK3CA Activating Mutations
This study is currently recruiting participants.
Verified April 2012 by Massachusetts General Hospital
ClinicalTrials.gov Identifier: NCT01501604

Am J Pathol 2009;174:1597
Sorafenib efficacy in ovarian clear cell carcinoma revealed by transcriptome profiling

Noriomi Matsumura, Masaki Mandai, Takako Okamoto, Ken Yamaguchi, Shogo Yamamura, Tomonori Oura, Tsukasa Baba, Junzo Hamanishi, Hyun S. Kang, Shigeyuki Matsui, Seiichi Mori, Susan K. Murphy and Ikuo Konishi
Unique histology, immuno-profiling (**HNF1β**)
& molecular genetic changes (**ARID1A, PIK3CA**)

Ovarian CCC is most likely arising from Endometrioma *(epidemiology, pathological & molecular)*

New studies suggest potential novel therapy for advanced CCC *(inhibitors for PI3K, mTOR, HNF1β, Sorafenib, etc)*