Biology of Ovarian Cancer
Lessons for Treatment

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Biology of Ovarian Cancer

• Key Processes in Human Biology
  • Cell Division
  • Apoptosis
  • Differentiation & Development
• Lessons for Treatment
  • Early Detection
  • Ovarian Cancer is Many Diseases
  • Ovarian Cancer Metastases
  • Recurrent Disease
  • Ovarian Cancer Diversity
• Advances for today and tomorrow
  • Molecular Targeting
  • BRCA and Ovarian Cancer
  • Immune Checkpoint Therapies
We begin as a single cell...
Apoptosis is Critical for Life
These cellular processes are tightly regulated.
DNA, Genes and Mutations
What is Cancer?

“Cancer is an expansionist disease; it invades through tissues, sets up colonies in hostile landscapes. Seeking ‘sanctuary’ in one organ and then immigrating to another. It lives desperately, inventively, fiercely, territorially, cannily, and defensively—at times, as if teaching us how to survive. To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are.”
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  - Early Detection
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Why has early detection of ovarian cancer been so challenging?

Challenge: Approximately 75% of patients with ovarian cancer are diagnosed with advanced disease.

Salani et al. Am J Obste & Gyn 204 (2011): 466-78

What is a screening test?

- A screening test is done to detect potential health disorders or diseases in people who do not have any symptoms of disease. The goal is early detection and lifestyle changes or surveillance, to reduce the risk of disease, or to detect it early enough to treat it most effectively. Screening tests are not considered diagnostic, but are used to identify a subset of the population who should have additional testing to determine the presence or absence of disease.
How specific is the test? The proportion of healthy patients without ovarian cancer, who will test negative for it.

- Ovarian cancer is uncommon (less than 40 new diagnoses per 100,000 per year in postmenopausal women)
- Therefore a screening test for ovarian cancer will need to achieve a minimum of 99.6% specificity
- A consequence of a positive screening test for ovarian cancer may be surgical intervention and the associated risks of surgery

How sensitive is the test? The proportion of patients with ovarian cancer who will test positive for it.

- Many markers can detect patients with advanced disease.
- The important measure is the duration of the marker-positive before a patient presents with symptoms of advanced ovarian cancer (preclinical identification)

Who to test? Selecting the target population

- Hereditary syndromes account for ~5-10% of ovarian cancers
- Over 90% of the remaining cancers occur in women aged of 50
Symptoms suggestive of ovarian cancer are non-specific. They include:
- Increased abdominal size/bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency), especially if these symptoms are new (<1 year) and frequent (>12 days/month).

A large randomized trial in more than 78,000 women in the United States recently found that screening with transvaginal ultrasonography and CA-125 did not decrease mortality from ovarian cancer.
- A larger, ongoing trial from the UK will give us more information about an alternative screening strategy using ultrasonography and CA-125 soon.

Lessons:
- Women and their care providers should be aware of and follow up on new and frequent symptoms that are suggestive of ovarian cancer
- New strategies for early detection are needed and actively being investigated
Ovarian Cancer is Many Diseases

- “Ovarian cancer” is a general term for distinct diseases that share an anatomic location
- Supported by Epidemiologic/Molecular/Genetic studies
- The unifying feature of ovarian cancers is frequent local/regional dissemination to ovary and abdominal/pelvic organs
- Lesson: Design Clinical Trials that focus on fewer patients but are more specific and include clinical, QoL & molecular analyses

Ovarian Cancer Metastases

- Happen by Direct Extension then Exfoliation, Lymphatic, Blood
- Seed the abdomen, carried by peritoneal fluid circulation
- Occur frequently and can be found at presentation
  - Omental/Peritoneal Carcinomatosis is common
- Have capacity to affect multiple vital organs in the abdomen and form malignant ascites
- Ascites may be caused by:
  - Dietary deficiency
  - Decreased fluid drainage
  - Increased fluid leaking from small vessels in abdomen
  - Increased vascularity induced by cancer
- Lesson: Highlights the importance of Systemic/Intraperitoneal Chemotherapy
What are the challenges with treating recurrent ovarian cancer?

- How to define recurrence?
  - Increase in CA-125
    - Elevations in CA125 are only seen in approximately 80% of patients
    - Typically happens 3-4 months before clinical presentation
  - Imaging evidence of disease
  - Clinical evidence of disease (A patient with symptoms, exam findings consistent with disease)

- Treatment sequencing and selection
  - 36 regimens on the current NCCN Guidelines for Recurrence

- Aligning therapy with patient needs

- Lesson: Treatment of recurrent disease is individualized to each patient.

Adapted from D. Armstrong The Oncologist 2002;7:20-28
Ovarian Cancer Diversity (Heterogeneity)

Lesson 1: Molecular Targeted Therapy
Lesson 2: Target the Supporting Cast (Tumor Microenvironment)

- Blood Vessel Formation/Angiogenesis: Vascular Growth Factor (VEG-F)
- Immune System: Therapeutic Vaccines, Immune Checkpoint Inhibitors
Molecularly Targeted Therapies

Development of cancer involves mutations that activate genes that are normally involved in:

- regulation of cell division and apoptosis,
- inactivation of genes involved in protection against DNA damage or driving apoptosis.

We can then use rational drug design targeting these signaling pathways.

- This approach moves away from the “one size fits all” approach to a more personalized strategy of treating patients with a specific drug only if their cancer bears particular molecular mutations that are target of that drug.
- Rapid advancement in diagnostics is revolutionizing our ability to customize therapies.
- Most of these approaches remain in the realm of clinical trials.
Problems in DNA Repair are a Common Theme in Cancer

- Inherited mutations in BRCA1 and BRCA2 genes represent 5-10% of Epithelial Ovarian Cancer
- BRCA gene products form part of the molecular machinery for one type of DNA Repair (HR)
- About 50% of all high-grade serous ovarian cancers show disruption of BRCA pathway
- Lesson: Disrupting other DNA repair pathways (such as the PARP pathway [BER]) increases chances that a lethal mutation occurs in a cancer cell
- PARP inhibitors are in clinical trials around the country

Featured in the November 21, 2006, issue of Biomedical Beat. Courtesy of Tom Ellenberger, Washington University School of Medicine in St. Louis.
Problems in DNA Repair are a Common Theme in Cancer

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Targeting immune checkpoints improves median survival but also may provide long-term durable responses, raising the tail of the survival curve.

Hope for Today and Tomorrow

- Spread the word about symptoms that should prompt evaluation for ovarian cancer
- Diverse Origin of Ovarian Cancer has lead to more focused clinical trials
  - Treating the subtypes of ovarian cancer
  - Clinical, QoL & molecular outcomes will help us to better understand the disease
- Mechanisms of Metastases highlight the importance of systemic treatment for the most ovarian cancers
- The BRCA DNA repair pathway in ovarian cancer
  - The rational use of PARP inhibitors in many ovarian cancer
- Genetic Heterogeneity in Ovarian Cancer suggests we continue to look to more stable and tailored targets
  - Blood Vessel Formation/Angiogenesis: Inhibitors of Vascular Growth Factor (VEG-F) such as Bevacizumab
  - Immune System: Immune Checkpoint Therapies/Therapeutic Vaccines
  - Rational Targeted Therapies determining which patients may potentially benefit from treatment.
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- Lessons for Treatment
  - Origins of Ovarian Cancer
    - Dr. Burdette–Univ of Illinois at Chicago
  - Ovarian Cancer Metastases
  - Fueling Ovarian Cancer Growth
    - Dr. Lengyel–Univ of Chicago
  - BRCA and Ovarian Cancer
    - How PARP Inhibitors work
  - Ovarian Cancer Heterogeneity
    - Targeting Chemotherapy–Northwestern
    - A new Early Detection Strategy
We begin as a single cell...
Apoptosis is Critical for Life
Understanding Ovarian Cancer using a Mouse Model

- We have a poor understanding of early events responsible for ovarian cancer
- Our lack of understanding delays detection and increases the chance of poor prognosis
- Some ovarian cancers are thought to originate from the single layer of cells that comprise the Ovarian Surface Epithelium (OSE)
- A 3D experimental model will help understand those early events
- 2013 Update: The hormones that control ovulation also activate signals in OSE similar to those signals in serous ovarian carcinoma

Three-Dimensional Ovarian Organ Culture as a Tool to Study Normal Ovarian Surface Epithelial Wound Repair

Kevin S. Jackson, Kari Inoue, David A. Davis, Tyvette S. Hilliard, and Joanna E. Burdette

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612

Endocrinology, August 2009, 150(8):3921–3926  endo.endojournals.org
Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth

Kristin M Nieman, Hilary A Kenny, Carla V Penicka, Andras Ladanyi, Rebecca Buell-Gutbrod, Marion R Zillhardt, Iris L Romero, Mark S Carey, Gordon B Mills, Gökhan S Hotamisligil, S Diane Yamada, Marcus E Peter, Katja Gwin & Ernst Lengyel
Rational Drug Targeting
PROCEED Trial, Endocyte

- **Target: Folate Receptor**
  - Folate is a vitamin required for cells to grow
  - Receptor is present at high levels in many ovarian cancer cells
  - Delivers chemotherapy at high doses to the “target” cells

- **Randomized Trial**
  - Platinum Resistant Ovarian Cancer
  - **Protocol:**
    - Imaging Study to determine whether or not a patient’s ovarian cancer expresses the targeted receptor molecule
    - Liposomal Doxorubicin possibly with Experimental Drug
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Currently, experimental
Researchers suspected that ovarian cancers shed a few cells that trickle down into the cervix and could be detected in a Pap smear
Using Next Generation DNA Sequencing Technology looked for common ovarian cancer mutations
Only correctly identified 40% of patients with known ovarian cancer
None of the normal samples tested were incorrectly diagnosed with

Evaluation of DNA from the Papanicolaou Test to Detect Ovarian and Endometrial Cancers