Understanding the Biology of Breast Cancer: A Pathologist’s Perspective

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GOALS

- Current understanding of the biology of breast cancer and its relevance to treating and preventing the disease
- Pathology’s role in personalized medicine
- What I learned going through treatment
WHAT IS BREAST CANCER?

Understanding the Biology of Breast Cancer is Key to Prevention and Treatment!!!
BREAST CANCER IS NOT ONE DISEASE!
BREAST CANCER UNDER THE MICROSCOPE

- Histologic type
- Grade
- Size
- Lymph node status

Predict Behavior
WHAT DRIVES THE CANCER?
THERAPEUTIC TARGETS

- What proteins does it express in abnormal levels?
- Categorizes biology
  - Hormone + vs +
  - HER2 + vs -
  - Fast vs slow proliferators
- Determines Therapy Targets!

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<th>Hormone Receptors:</th>
<th>Her2</th>
<th>Ki-67</th>
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<td>ER and PR</td>
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CLINICALLY RELEVANT SUBTYPES OF BREAST CANCER

- **ER+**
- **HER2+**
- **HER2-**
- **ER-**

**Hormone Therapy**

**“Triple Negative”**

**Targeted Therapy**
Based on similarity of gene expression profiles

4 Distinct Subtypes:
- Luminal A (ER+)
- Luminal B (ER+)
- Her2+
- Basal-like

Perou, Nature 406, 747-752 (17 August 2000)
Outcomes by gene expression based subtype

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

- Copy number aberrations and gene expression
- 10 breast cancer subtypes associated with outcome differences

Curtis 2012 doi:10.1038/nature10983
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

do:10.1038/nature11412

There is more diversity within each subtype!

- 50% of driver mutations are present in < 10% of breast cancers (TCGA)
- Many mutations are unique!
- If we want to personalize therapy with more targeted drugs --- have to get very specific!
Mutations are more common across cancer types

Blurring lines between current cancer categories?

Will molecular profiles tell us how to treat (and IF to treat?)

BREAST CANCER IS NOT ONE DISEASE

Invasive Ductal Carcinoma, NOS

Special types

ER +    ER -

HER2+   HER2-
WE WILL FIND A “CURE” FOR BREAST CANCER
WE WILL FIND NEW “CURES” FOR BREAST CANCER
CAN WE PREVENT BREAST CANCER?

How does it develop?
What are the risk factors?
Who and how to screen?
Breast cancer precursors revisited: molecular features and progression pathways

Maria A Lopez-Garcia,1,2 Felipe C Geyer,1 Magali Lacroix-Triki,1,5 Caterina Marchio,6 & Jorge S Reis-Filho1

Histopathology 2010, 57, 171–192. DOI: 10.1111/j.1365-2559.2010.03568.x
DCIS IS NOT ONE DISEASE

Luminal (ER positive)

HER2

Basal (Triple Negative)
Progression from ductal carcinoma \textit{in situ} to invasive breast cancer: Revisited

Catherine F. Cowell\textsuperscript{a,1}, Britta Weigelt\textsuperscript{a,*,1}, Rita A. Sakr\textsuperscript{b}, Charlotte K.Y. Ng\textsuperscript{a}, James Hicks\textsuperscript{c}, Tari A. King\textsuperscript{b}, Jorge S. Reis-Filho\textsuperscript{a,*}

Dependent on multiple factors: Stroma, basement membrane, ability to invade
BREAST CANCER BIOLOGY: WHAT WE KNOW

Slow accumulation of many minor mutations

"Bad" mutation(s) as initiating event

Low grade Hormone-Driven Precursors

Hormone Positive Invasive Cancers

Luminal A (slow growing)

Luminal B (faster growing)

Hormone Negative High Grade Invasive Cancers

HER2 (fast growing)

Basal/"Triple Negative" (fast growing)

Anti-Hormone Therapies

Anti-HER2 Therapy

Chemotherapy
More targeted treatments
Better prevention strategies

Screen all ➔ Better defined risk groups

- Risk signature 1 ➔ Screening/management protocol 1
- Risk signature 2 ➔ Screening/management protocol 2
- Risk signature 3 ➔ Screening/management protocol 3
- Risk signature 4 ➔ Screening/management protocol 4
PATHOLOGIST AS KEY TO PERSONALIZED MEDICINE

Translation and integration of biologic information

Treatment Team

Patient Factors

Individualized Treatment Decisions
HOW DO I KNOW THE PATHOLOGY IS ACCURATE?

Ask your doctor if:

- Are they familiar with the pathologist?
- Do they specialize in breast pathology?
- Are there aspects of the diagnosis that are borderline?

Most common disagreements:

- Atypical ductal hyperplasia – DCIS spectrum
- Papillary lesions
- Invasive cancers:
  - Grade
  - HER2 IHC interpretation
  - ER and PR status

Second opinion from a specialist
MEDICINE HAS ALWAYS BEEN PERSONAL
Diagnosed at age 33 with Stage 3 pregnancy associated breast cancer
YOU NEVER EXPECT TO GET WHAT YOU DIAGNOSE
Passage from “Bad Day at the Office”
DIAGNOSIS:

INVASIVE DUCTAL CARCINOMA

- 8 CM
- GRADE 3
- ER/PR NEGATIVE
- HER2 POSITIVE
- POSITIVE LN BX

Survival rate: 40%
EMOTIONAL IMPACT OF DIAGNOSIS

- FEAR
- Panic – need to do something now
- Defective
- What did I do wrong?
Addressing Fears

The longer it takes to be seen the more they magnify....
Hope Helps Heal
A patient is not a statistic
- Establishing a clinical team
- Coordination of treatment
- Second opinions
My treatment plan:

- Chemotherapy first (AC+TH)
- Surgery (bilateral mastectomies)
- Radiation
- 1 year of antibody therapy Herceptin
- Participation in clinical trials

Adriamycin “The Red Devil”
CLINICAL ACTION PLAN

- A team approach to the patient
- Personalized medicine matters
- Embracing therapy
HOW TO SURVIVE

- Connection to resources
- Connection to patients
HEALING TAKES MANY FORMS

- Healing you not just treating the disease
- Everyone’s list is unique
- Development of a personal action plan
CONFRONTING THE DISEASE

- Powerful to be able to look directly at my enemy
- Acknowledging that cells make mistakes (let go of guilt)
- Offer to other patients

Passage from “Staring Down the Beast”
LOW POINTS
TRIUMPHS
Breast Cancer has a diverse biology:
- Understanding the unique drivers of each cancer is key to developing the most successful treatment and prevention strategies
  “Cures” not “Cure”
- Pathology determines therapy options
- Personalized medicine is creating new success stories!