Genetics in Breast Cancer

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Overview

• Evolution

• Advances in cancer genomics

• Implications for therapy
Historical View

Size

Nodal Spread

Metastasis
Modern Era

- NSABP B04 – Total mastectomy
- NSABP B06 – BCT

- All breast Ca has metastatic potential

- Shift to early Dx, treatment, breast conservation
Receptors as prognostic

- ER / PR negative = worse
- HER2-neu positive = worse
- Triple negative = worst
Receptors as predictors

• **ER / PR negative** = may better respond to adjuvant

• **HER2 positive** = may respond to TK inhibitor

• Shift in understanding
Receptors as predictors

• Triple negative
  – poor prognosis
  – aggressive behavior
  – highly proliferative

• Some advocate MRM for early stage
LRR in BCT vs MRM for TNBC

Receptors for therapy

• ER targeted therapy
• HER2 targeted therapy
• Don’t always respond as expected
Genomic Subtypes of Breast Ca

- Luminal A $\rightarrow$ ER$^+$/PR$^+$/HER2$^-$
- Luminal B $\rightarrow$ ER$^+$/PR$^+$/HER2$^-$
- Basal-like $\rightarrow$ TNBC
- HER2E $\rightarrow$ HER2$^+$
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

We analysed primary breast cancers by genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays. Our ability to integrate information into previously defined gene expression subtypes and demonstrated the existence of four main histological subtypes of breast cancer with distinct molecular profiles. Of specific note, we identified a novel subtype associated with novel gene mutations including the enrichment of PIK3CA and MAP3K1 with the luminal A subtype. We identified two novel protein–protein regulatory pathways dominated in each molecular subtype including a HER2/phosphorylated...
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Basal-like</th>
<th>HER2E</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/HER2- (%)</td>
<td>87</td>
<td>82</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>HER2+ (%)</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>TNBCs (%)</td>
<td>2</td>
<td>1</td>
<td>80</td>
<td>9</td>
</tr>
<tr>
<td>TP53 pathway</td>
<td>TP53 mut (12%);</td>
<td>TP53 mut (32%);</td>
<td>TP53 mut (84%);</td>
<td>TP53 mut (75%);</td>
</tr>
<tr>
<td></td>
<td>gain of MDM2 (14%)</td>
<td>gain of MDM2 (31%)</td>
<td>gain of MDM2 (14%)</td>
<td>gain of MDM2 (30%)</td>
</tr>
<tr>
<td></td>
<td>PIK3CA mut (49%);</td>
<td>PIK3CA mut (32%);</td>
<td>PIK3CA mut (7%);</td>
<td>PIK3CA mut (42%);</td>
</tr>
<tr>
<td></td>
<td>PTEN mut/loss (13%);</td>
<td>PTEN mut/loss (24%);</td>
<td>PTEN mut/loss (35%);</td>
<td>PTEN mut/loss (19%);</td>
</tr>
<tr>
<td></td>
<td>INPP4B loss (9%)</td>
<td>INPP4B loss (16%)</td>
<td>INPP4B loss (30%)</td>
<td>INPP4B loss (30%)</td>
</tr>
<tr>
<td>PIK3CA/PTEN pathway</td>
<td>Cyclin D1 amp (29%); CDK4 gain (14%); low expression of CDKN2C; high expression of RB1</td>
<td>Cyclin D1 amp (58%); CDK4 gain (25%)</td>
<td>RB1 mut/loss (20%); cyclin E1 amp (9%); high expression of CDKN2A; low expression of RB1</td>
<td>HER2 amplicon signature; high proliferation</td>
</tr>
<tr>
<td>mRNA expression</td>
<td>High ER cluster; low proliferation</td>
<td><strong>Lower ER cluster</strong>; high proliferation</td>
<td>Basal signature; high proliferation</td>
<td>HER2 amplicon signature; high proliferation</td>
</tr>
<tr>
<td>Copy number</td>
<td>Most diploid; many with quiet genomes; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (24%)</td>
<td>Most aneuploid; many with focal amp; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (51%); 8p11.23 amp (28%)</td>
<td><strong>Most aneuploid; high genomic instability</strong>: 1q, 10p gain; 8p, 5q loss; MYC focal gain (40%)</td>
<td><strong>Most aneuploid; high genomic instability</strong>: 1q, 8q gain; 8p loss; 17q12 focal ERRB2 amp (71%); TP53 (75%); PIK3CA (42%); PIK3R1 (8%)</td>
</tr>
<tr>
<td>DNA mutations</td>
<td>PIK3CA (49%); TP53 (12%); GATA3 (14%); MAP3K1 (14%)</td>
<td>TP53 (32%); PIK3CA (32%); MAP3K1 (5%)</td>
<td>TP53 (84%); PIK3CA (7%)</td>
<td>TP53 (75%); PIK3CA (42%); PIK3R1 (8%)</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>-</td>
<td>Hypermethylated phenotype for subset</td>
<td>Hypomethylated</td>
<td>-</td>
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<tr>
<td>Protein expression</td>
<td>High oestrogen signalling; high MYB; RPPA reactive subtypes</td>
<td><strong>Less oestrogen signalling</strong>; high FOXM1 and MYC; RPPA reactive subtypes</td>
<td>High expression of DNA repair proteins, PTEN and INPP4B loss signature (pAKT)</td>
<td>High protein and phosphoprotein expression of EGFR and HER2</td>
</tr>
</tbody>
</table>
Implications

• Personalized genotype based therapies

• Broadened use of RTX

• Broadened use of adjuvant therapies

• Obsolescence of TNM staging
Mechanism of RTX

Ionization

Direct

Indirect

H$_2$O $\rightarrow$ Free Radicals

DNA Strand damage
Mechanism of RTX

• Single strand DNA damage inheritable
  – leads to cell dysfunction
  – reduced mitoses
  – aberrant life cycle

• RTX tissue damage starts immediately but can continue for YEARS
Summary

• Understanding of breast Ca is rapidly evolving

• Therapies will continue to evolve rapidly

• We will radiate more people
References


*Selected Readings in General Surgery*. Breast Cancer.