Biologic Subtypes of TNBC

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Topics

• Histopathology
• Molecular pathology
• Clinical relevance
A definition of “triple-negative” breast cancer

Immunohistochemistry
- ER and PR <1% nuclear with positive normal breast internal control
- HER2 "negative" is 0 or 1+ staining or 2+ staining with negative FISH

Histologic subtypes that are often TNBC
- Ductal, NOS
- Medullary-like
- Apocrine
- Adenoid cystic
- Squamous
- Metaplastic spindle cell
- Other

Ductal, NOS (25% TN of 70%)
- Large central scar or fibrotic focus
- High grade
- Geographic necrosis

Livasy et al. Modern Pathology 2006; 19: 264-271
Other common features of TN Ductal

High Ki67 (50-70%)  
p53 +  
Basal keratins (5, 14, 17)  
p63


Medullary-like (1%)

Pushing borders  
Syncytial sheets and abundant lymphocytes

Apocrine features

Androgen receptor
Metaplastic subtype of TNBC may have more common EGFR amplification

- 47 MBC analyzed by EGFR IHC and CISH
- 68% IHC +
- 23% amplified
- EGFR amplification in spindle and squamous metaplastic
- No activating mutations found
- Maybe important subtype for treatment, based on having this potential target?

Metaplastic spindle cell carcinoma?

No, Metastatic Melanoma!

Keratin AE1/AE3, MART-1
Recognition of ER -, basal CK+ tumors with poor outcome


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Gene expression profiling: rediscovery of “Basal-like” TN tumors and their poor prognosis

Sørlie et al. PNAS 2001; 98:10869-10874
“Claudin-low” subtype estimated to be 10% of TNBC in first publication


Gene expression pattern similar to normal fibroblasts

TCGA: 76 TNBC’s

- 65/76 (86%) TNBC were “basal-like”
- High frequency of p53 mutation
- Activation of PI3K pathway but not by PI3K mutation
- 20% had germline or somatic BRCA1 or 2 variant
- Only 8 claudin-low (~1% of BC’s overall)


DNA aberrations: high Allelic Imbalance

Telomeric AI

Interstitial AI
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Triple-negative breast cancer: basal markers CK5 and EGFR

- Analyzed 951 primary breast cancers into 5 subgroups based on ER, PR, HER2, CK5, EGFR
- After multivariate analysis of TNBC’s, the BRCa’s did not have worse prognosis than the CNBC’s
- Suggests that subsetting TNBC based on IHC of basal markers may not have prognostic relevance
- High concordance between TN and “basal-like” when ER and HER2 IHC is done well

"New" Subsets of Triple Negative Breast Cancer

Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies.

A clinically relevant gene signature in triple negative and basal-like breast cancer.
Subtypes of 386 TNBCs and targeted therapy selection

Greater number of chromosomes with telomeric allelic imbalance (NtAI) is associated with sensitivity to cisplatin

TNBC subsets based on metagene expression (394 discovery, 185 validation)


Key points

- Roughly three TNBC “subtypes” identified in multiple studies
  - **Basal** (BL1, BL2, Basal-like, Basal A)
    - Most common (~85% of TN), Ductal NOS
    - Sensitive to chemotherapy
    - Level of AI and BRCA1 mRNA may predict for cisplatin sensitivity
  - **Metaplastic** (ML, MSL, Claudin-low, Basal-B)
    - Rare (~1% of breast cancer)
    - EGFR amplifications? Sensitive to PI3K/mTOR inhibitors?
    - Enriched in breast cancer cell lines
  - **Luminal/AR+** (LAR, apocrine-like, AR+)
    - Rare (~1% of BC, 10% of TNBC)
    - May be the TN tumors with apocrine features and lower grade
    - Response to anti-androgens?
  - **Others**
    - Squamous, Adenoid cystic, and metastatic must be very rare

Key Points

- **Immune/Inflammatory “signature”**
  - Not identified in cell lines so likely not a tumor “subtype” but related to stromal immune cell infiltrates
  - Good prognosis in TNBC in multiple studies
  - Rody et al. suggests this is true across the TNBC subtypes
  - Quantitative histologic assessment of lymphocytic infiltrates and central fibrosis could be a prognostic measure
Thank You!