Genomic Characterization of Invasive Lobular Breast Carcinoma

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TCGA Breast Cancer AWG
Invasive Breast Carcinoma

Invasive Ductal Carcinoma (IDC) 50-80%

Mixed IDC.ILC 4-5%

Invasive Lobular Carcinoma (ILC) 10-15%

Ductal

Lobular

The Cancer Genome Atlas
Pathology centrally re-reviewed (Andy Beck, Harvard)
Identification of differentially expressed genes

Ductal Lobular

2 Class SAM FDR=0

N=663 genes

Immune signaling (multiple)
MAPK signaling
MYC targets (multiple)
E-cadherin stabilization

ATM network

CDH1

Mike Gatza, UNC
Development of Integrated MAF

DNA Exome sequencing

UNCeqR (mRNAseq / DNAseq) → Integrated MAF

ABRA (CDH1, TP53, GATA3, PTEN, RB1)

Matt Wilkerson (UNC), Lisle Mose (UNC)
Giovanni Ciriello (MSKCC), Cyriac Kandoth (MSKCC)
Mike McLellan (Wash U)
Comparison of significant alterations: IDC vs. ILC

Giovanni Ciriello, MSKCC
Identifying IDC LumA and ILC LumA-specific alterations

Giovanni Ciriello, MSKCC

![Graph showing protein expression and alterations in IDC LumA and ILC LumA cancers.]

Key:
- **Red**: High amplification
- **Blue**: Deletion
- **Green**: Mutation
- **Gray**: (Not Significant)

* p ~ 0.05

**Markers**:
- **GATA3 (p=0.0002)**
- **PIK3CA**
- **CDH1**

**Genes of Interest**:
- 8q24 (MYC)
- 16p13 (GRIN2A)
- MAP3K1
- MAP2K4
- 8q11
- 11p13
- 8p23
- CTCF
- FOXA1
- TBX3
- 10q23 (PTEN)
- 17p11
PARADIGM analysis identifies IDC and ILC-associated signaling pathways

Blue: ILC DOWN  Red: ILC UP

IDC  ILC
mRNA

IDC  ILC
Protein

Low                                High
mRNA Expression

Low                                High
Protein Expression

CDH1
MYC
XBP1

p53/DNA Damage Response
Immune Related

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Development of mRNA-based ILC classes

ConsensusClusterPlus to ID 3 ILC classes
TCGA ILC LumA (n=106)

Identified samples with positive sil. width
TCGA ILC LumA (n=89)

ClaNC developed centroid predictor
TCGA ILC LumA (n=89)

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2 Class SAM identifies differentially expressed genes in ILC classes

988 genes (FDR=0)

Class 1 C2 C3

N= 722 genes
- EGFR
- MET
- GLI1
- FGF17
- WNT6
- AREG
- KIT
- KRT 14, 17, 32, 81
- KRK 1, 6-8
- CLDN 8, 10, 11, 19
- PTCH2
- TP63
- VIT
- ID4

N= 268 genes
- Immune-related genes: >100
- LCK
- IFNG

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ILC class mRNA / miRNA expression patterns correspond with IDC and Adjacent Normal

988 genes (FDR=0)

P<0.0001

Mike Gatza, UNC

Reanne Bowlby, BC Cancer Agency
ILC Class1 corresponds with RPPA Reactive Subtype

ILC Class (n=127) | Class1 | Class2 | Class3
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P<0.0001

RPPA Subtype (n=70)

Reactive | Non-reactive | Missing data

RPPA

Annexin1
Caveolin1
Collagen IV
Myh11
RMB15

Protein Expression

Low | High

Mike Gatza, UNC
Gordon Mills, MDACC
ILC Class1 tumors exhibit altered PDGFR/STAT3 and FoxM1 signaling

Christina Yau, Buck Institute
Mike Gatza, UNC
ILC class 2 defined by high immune signaling and proliferation

TCGA ILC (n=127)

P=1.39e-10

Proliferation Score (PAM50)
PARADIGM analysis identifies IFNG and FOXM1 as key pathways in ILC class 2 tumors.

Christina Yau, Buck Institute
Summary

- Developed unique integrated MAF utilizing both DNA exome and mRNA sequencing

- ILC vs. IDC
  - FOXA1, CDH1 mutations associated with ILC
  - GATA3 mutation associated with IDC
  - Altered signaling: CDH1, Myc, p53/DNA damage, immune signaling
  - Identified differentially expressed miRNA and methylation

- ILC classes
  - Class 1 associated with Reactive subtype
  - Class 2 immune component and highly proliferative