A Pan-Cancer Proteomic Perspective on The Cancer Genome Atlas

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UT MD Anderson Cancer Center
Analyzed 3,467 samples across 11 tumor types:
- BLCA, BRCA, COAD, READ, GBM, HNSC, KIRC, LUAD, LUSC, OVCA, UCEC

181 proteins
- 128 total proteins
- 1 cleaved
- 1 acetylated
- 51 phosphorylated forms

Data produced in 6 Reverse-Phase Protein Array (RPPA) batches
- Developed Replicates Based Normalization (RBN) method to reduce batch effects
Gene:protein matched (cis) comparisons

mRNA:protein Spearman correlation global mean = 0.3

CNV:protein mean fold change
- Amplifications = 1.05, Deletions = 0.95

Mutation:protein mean fold change
- Elevating mutations = 1.2, Suppressing mutations = 0.9

Other comparisons (all vs. all)

miRNA:protein mean Spearman correlation = ±0.07
Protein:protein mean Spearman correlation = ±0.15
## Focus: ERBB2 CNV vs. mRNA vs. protein

<table>
<thead>
<tr>
<th>Disease</th>
<th>CNV ERBB2 (%)</th>
<th>mRNA ERBB2 (%)</th>
<th>Protein HER2 (%)</th>
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Women’s cancers: OV, UCEC, BRCA (except basal, HER2+)

http://bioinformatics.mdanderson.org/main/TCGA/Pancan11/RPPA
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<th>Tumor lineage</th>
<th>BLCA</th>
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<th>BRCA-HER2</th>
<th>BRCA-LuminalA/B</th>
<th>BRCA-Reactive</th>
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Some outcome differences

BRCA reactive group markers: Caveolin, Collagen, MHY11, Rictor

Endo-like BLCA  Squamous-like KIRC  BRCA
Women’s cancers: ER-alpha, AR
Luminal breast: AR, BCL2, FASN, ACC1, and pACC
OV: CMYC (new MYC therapies under development)
All except women’s cancers and bladder: pSRC
HNSC: pSRC, a downstream target of EGFR (sensitive to EGFR therapy?)
UCEC, BLCA, BRCA, COAD/READ: HER2
KIRC: HER3
GBM: pEGFR with NOTCH1 and HER3 activation (combination therapy?)
Unsupervised clustering shows 7 clusters

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Next Gen Clustered Heat Maps (NG-CHM)
• Tumors cross clusters
• Sanity check: Her2 amplified cases cluster together
Reactive cluster (V)
Some outcome differences – Reactives

Reactive group

BRCA

COAD

KIRC

LUSC

OVCA

BLCA
Some outcome differences – AKT pathway

Cluster VII - AKT pathway suppressed

Cluster IV - AKT pathway activated
Take-home findings

Cross platform comparisons
- Mutations have greater mean fold changes than CNV
- mRNA:protein correlations can vary widely by disease
- HER2 protein levels not predicted well by CNV or mRNA in certain diseases (e.g. CRC, LUAD, BLCA)

Several novel markers identified

Outcome differences seen across clusters, possibly driven by pathway differences

Pathways effects are not equal by disease
- Certain pathway activations may have good or bad prognosis depending on disease

Protein:protein correlations vary by disease

**Poster #1**

MD Anderson  
*Gordon B. Mills*  
Patrick Kwok Shing Ng  
Henrica M.J. Werner  
Maria Shahmoradgoli  
Fan Zhang  
Zhenlin Ju  
Wenbin Liu  
Ji-Yeon Yang  
Kosuke Yoshihara  
Jun Li  
Shiyun Ling

Elena G. Seviour  
Prahlad T. Ram  
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Lauren A. Byers  
Funda Meric-Bernstam  
Bradley M. Broom  
Roeland G.W. Verhaak  
Han Liang  
Yiling Lu  
John N. Weinstein

The Netherlands Cancer Institute  
Steven M. Hill  
Frank Dondelinger  
Nicolas Städler  
Sach Mukherjee

UT Southwestern Medical Center  
John D. Minna