PIK3CA mutation-gene signature associated with down-regulation of PI3K/AKT/mTOR signaling & good prognosis in ER+ breast cancer

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Background

- PI3K pathway aberrations are common in breast cancer
- PIK3CA mutations occur in around 25% of breast cancers (esp. ER+ and HER+)
- Breast cancers with PIK3CA mutations are thought to represent a population sensitive to PI3K/mTOR pathway inhibition

Aims

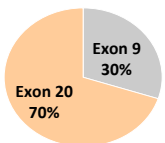
- To investigate the molecular changes induced by a PIK3CA mutation using gene expression profiling
- To understand the clinical relevance of a PIK3CA mutation in breast cancer, particularly in ER+BC molecular subtypes

Methods

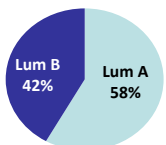
- PIK3CA mutations sequenced from 173 ER+BC with associated gene expression data (training set)
- 2 independent validation sets were used to assess ability of PIK3CA-GS to predict mutation status (total 210)
- 323 ER+BC samples treated with tamoxifen monotherapy with array data (TAM dataset)
- 717 ER+ BC that had not received systemic Rx (UNT)
- Protein evaluation using immunohistochemistry and reverse-phase protein lysate arrays (RPPA) at the MD Anderson Cancer centre

Results

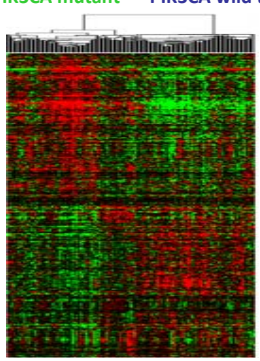
Total of 46 PIK3CA mutations found (26%)



No association with either Luminal subtype

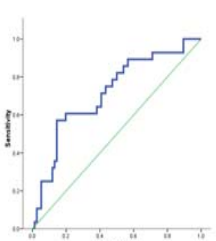


PIK3CA mutant PIK3CA wild type

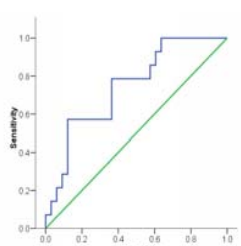


- PIK3CA mutations are associated with a distinct gene expression profile.
- 361 probe sets were identified using a two sample t-test. (p=0.02)
- The signature could predict PIK3CA mutation status in 2 independent datasets

1. Dataset Saal et al, PNAS 2007 n=105; AUC=0.73; p=0.02

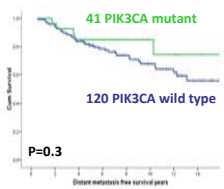


2.. Dataset Liedtke et al, BCR 2008 (MDACC) n=129; AUC=0.75; p=0.001

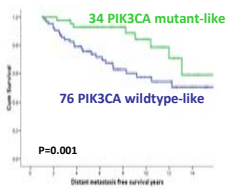


Clinical outcome

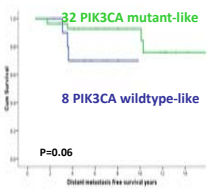
PIK3CA- GS was a stronger predictor of clinical outcome in ER+ BC that mutation status by sequencing;
Multivariate HR: 0.5 (0.3-0.9); p=0.001, n=323, TAM dataset & untreated BC (n=717) HR 0.7 (0.6-0.9); p=0.03



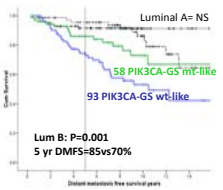
All BC seq PIK3CA mutations



PIK3CA wt (seq) by PIK3CA-GS



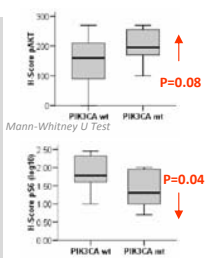
PIK3CA mt (seq) by PIK3CA-GS



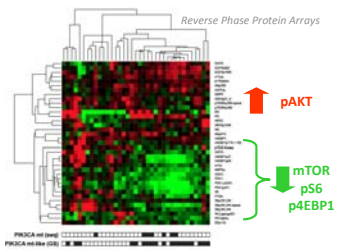
Luminal A, B by PIK3CA-GS

Effects of PIK3CA mutations on PI3K pathway

- PIK3CA mts was associated with activation of AKT but down-regulation of mTOR signaling suggesting strong negative regulation.
- This was seen in two datasets with two different methods of protein evaluation
- Known negative regulators of the pathway were seen – IRS2, PP2A and PML



TAM dataset- IHC



Independent dataset Liedtke et al, MDACC

CONCLUSIONS

- PIK3CA mutations in human breast cancer induce a distinct gene expression profile.
- Surprisingly in ER+BC, PIK3CA mutations are associated with a gene signature of activation of the pathway but ultimately down-regulation of the PI3K/AKT/mTOR pathway suggesting powerful negative regulation
- PIK3CA-GS associated with a better outcome in ER+ BC and also in the Luminal B subgroup