Cell-based Screening Identifies Gene Expression Signature Correlated with Sensitivity to PI3KmTOR Dual Inhibitor BEZ235

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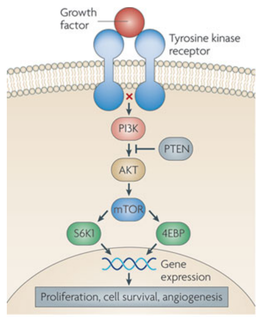
Introduction

The PI3K-Akt-mTOR signaling cascade is one of the most well known pro-proliferation and pro-survival pathways involved in tumor growth and progression. Activation of tyrosine kinase receptors recruits p85 subunit of PI3K to cell membrane; activates p110 kinase unit that phosphorylates and activates serine/ therionine kinases Akt. mTOR is one of the major downstream kinase of Akt. mTOR activation leads gene and protein expression profile modulation, which is most cases leads to tumor cell proliferation, survival as well as activation of tumor angiogenesis.



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Abstract

The PI3KmTOR pathway is one of the major signaling cascades that promote tumor growth and cell survival. Multiple inhibitors targeting this important axis are currently under clinical investigation for cancer treatment and some are under preclinical development. Here we examined the anti-proliferation activity of BEZ235, a PI3K and mTOR dual inhibitor, in 243 human cancer cell lines of different caner types. We identified 35 lines that are sensitive to the inhibitor with IC50 values less than 0,04uM and 57 insensitive lines with IC50 values more than 0.4uM. We compared gene expression of the two groups by Affymetrix U219 arrays. With a p-value cutoff set at 0.00001, we identified 14 genes that are differentially expressed. These genes include epithelial membrane glycoprotein EPCAM and serine threonine kinase 31 (STK31). Furthermore, the mutation status of tubulin tyrosine ligase TTL is significantly correlated with sensitivity to BEZ235. These results suggested a potential genomic signature that could be predictive of response to BEZ235 and provided information that may help selecting patients that are likely to receive clinical benefit.

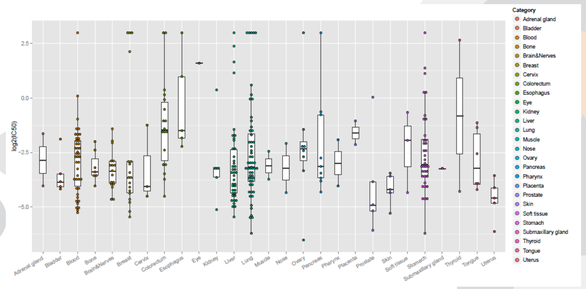
Method

We performed cell viability assay to determined IC50s of BEZ235 in 247 cell lines of various cancer types. Based on IC50 values, we divided the cell lines to 3 groups: a sensitive group, an insensitive group, and an uncertain group. For the sensitive group, IC50 values are less than 0.04, and for insensitive group, IC50 values are greater than 0.4. Other cell lines were classified into the uncertain group. Accordingly, we got 35 sensitive and 52 insensitive cell lines. Only cell lines with genomic data were used in subsequent analysis.

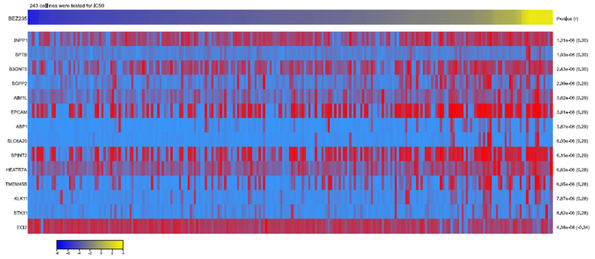
The correlation between gene expression and IC50 was evaluated by Pearson correlation analysis; the correlation between gene mutation status and IC50 was analyzed by t-test. We then performed gene expression and pathway enrichment analysis using GSEA software.

Results

Cell panel screen for BEZ235 in 247 cell lines of various cancer types:



The expression of 14 genes are significantly different in sensitive and insensitive groups.



Results

The GSEA analysis found 9 gene sets which enriched in the sensitive cell lines (nominal p-value <0.01). These gene sets include

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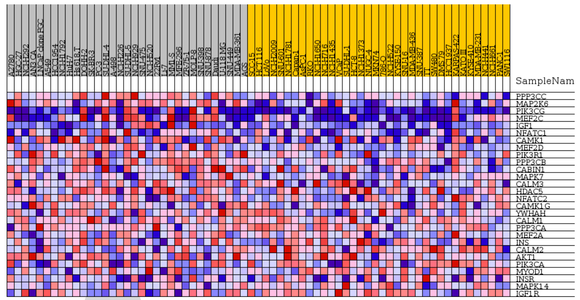

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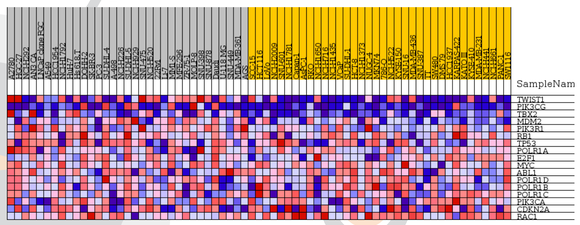
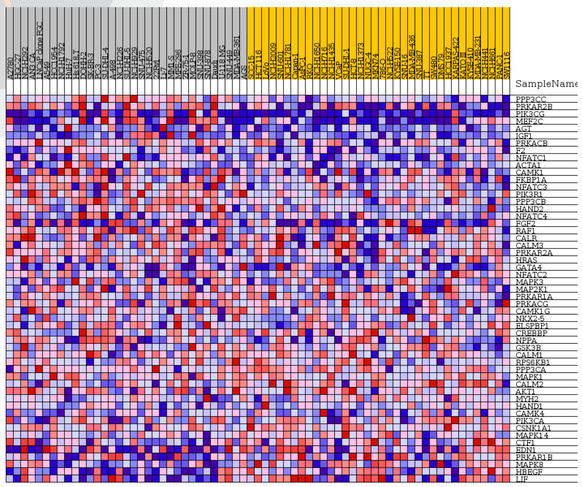
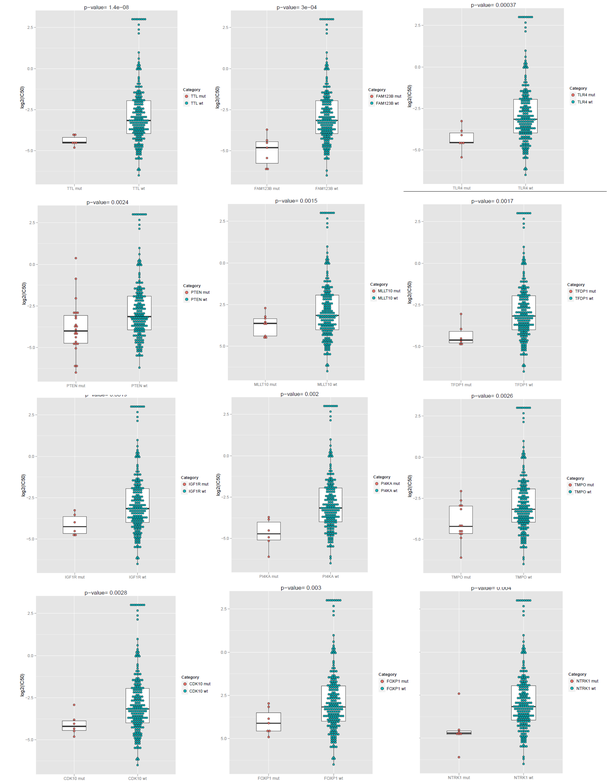


BIOCARTA_NFAT_PATHWAY



Results

Bioinformatic analysis reveals 14 genes (12 illustrated) whose mutation status strongly correlate with sensitivity to BEZ235



Conclusions

- Using a large panel of cancer cell lines, we have identified 14 genes whose expression levels significantly correlate with BEZ235 sensitivity.
- Mutation status of 14 cancer-associated genes strongly correlates with BEZ235 sensitivity.
- The results proposed genetic signatures that predict sensitivity to BEZ235. Further investigation on these gene will provide valuable information for clinical trials as well as personalized medicine.