Differential pathway activation associated with domain-specific PIK3CA mutations

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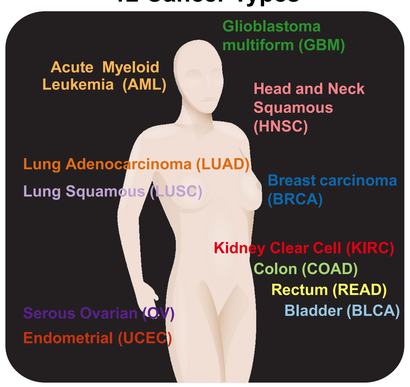
Abstract #4165

Introduction

A recent study of the mutation landscape of >3000 cancers across 12 major cancer types from the Cancer Genome Atlas (TCGA) program revealed PIK3CA as the second most commonly mutated gene, occurring at >10% frequency in 8 types of cancer. Limited preclinical evidence suggested that mutations affecting PIK3CA catalytic vs. non-catalytic domains can produce different phenotypic consequences in model systems; however, whether domain-specific PIK3CA mutations results in distinct pathway consequences across multiple cancer types remain unclear. Thus, we used the PARADIGM algorithm, which integrates gene expression and copy number data into a superimposed pathway structure, to infer the activities of ~13K pathway features and compared the signaling consequences associated with different domain-specific PIK3CA mutations within the TCGA Pan-Cancer dataset.

Dataset Characteristics

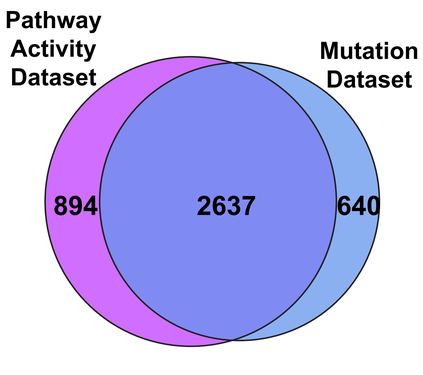


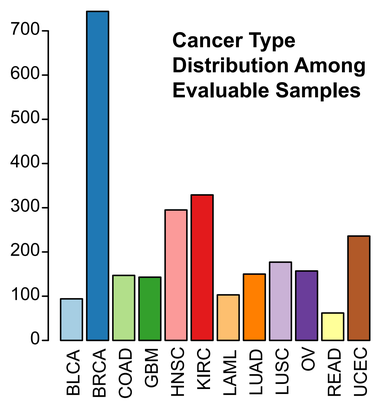
The TCGA Pan-Cancer 12 Dataset comprises :

12 Cancer Types

3531 samples with PARADIGM inferred pathway activity data

3277 samples with exon sequencing data



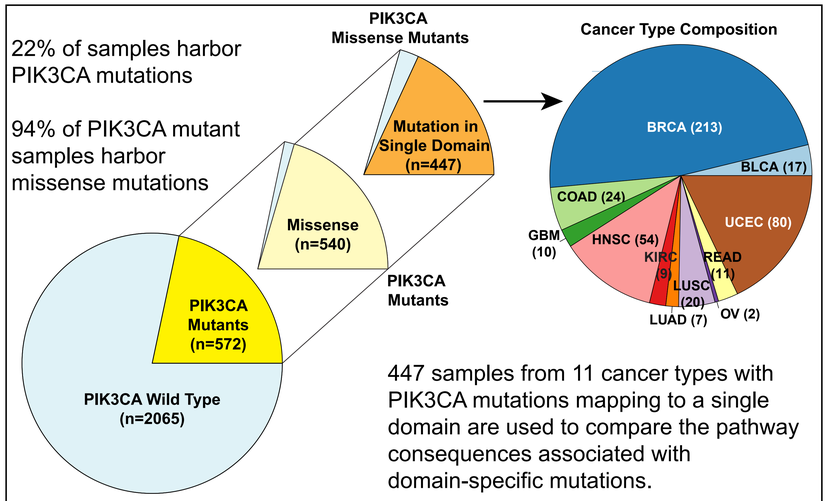


2637 samples with inferred pathway activity and mutation data are available for our evaluation.

PIK3CA Domain-Specific Mutations

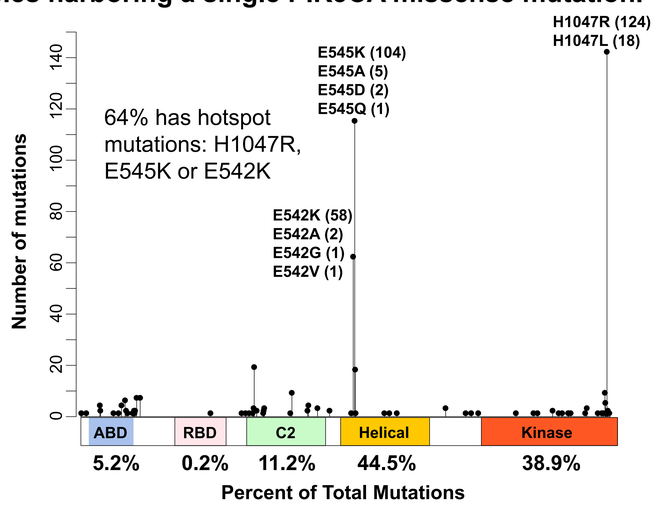
22% of samples harbor PIK3CA mutations

94% of PIK3CA mutant samples harbor missense mutations

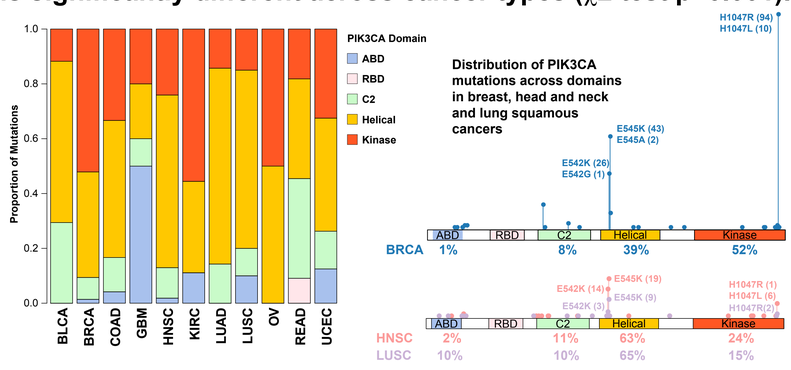


447 samples from 11 cancer types with PIK3CA mutations mapping to a single domain are used to compare the pathway consequences associated with domain-specific mutations.

I) Helical and kinase domain mutations account for 83% of samples harboring a single PIK3CA missense mutation.



II) The distribution of PIK3CA mutations among the domains is significantly different across cancer types (χ2 test p<0.001).

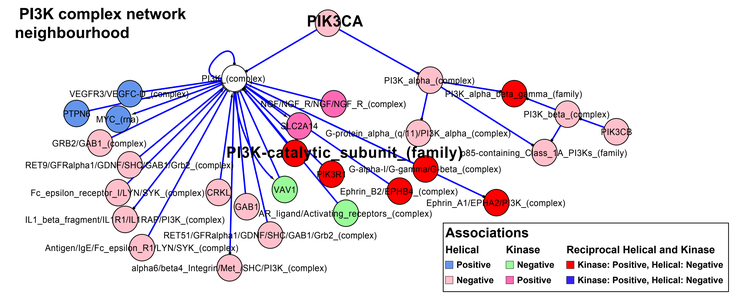


Differential Pathway Activation

Method

Features associated with kinase domain mutations (vs. all others) were identified using logistic regression adjusting for cancer type (Wald test p<0.05). Enriched pathways among significant features were assessed (FDR corrected EASE score < 0.05). Features and enriched pathways associated with helical domain mutations are similarly identified. Interconnected features with significant domain-specific associations were visualized using Cytoscape.

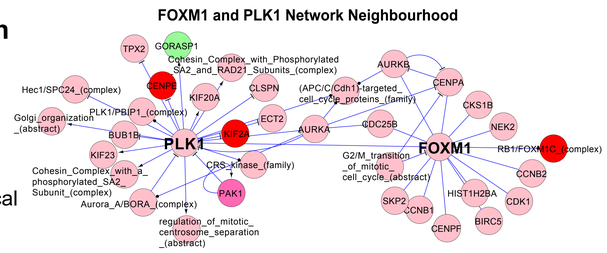
III) PI3K Catalytic Activity



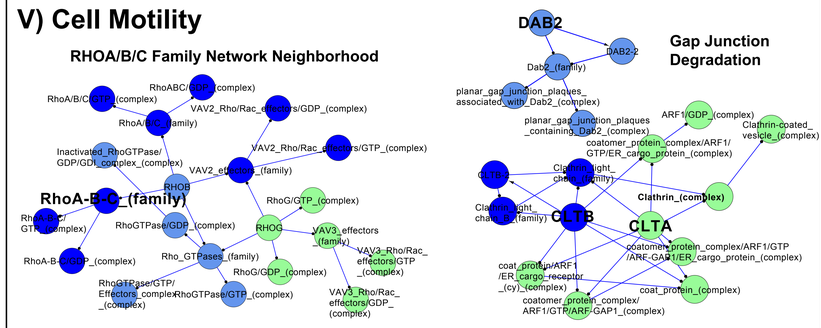
As expected, the inferred activity of the PI3K catalytic subunit is positvely associated with mutations in the kinase domain. Conversely, this activity, along with other PI3K complexes, shows negative association with helical domain mutations.

IV) Proliferation

Inferred activation of cell cycle related pathways (e.g. FOXM1, PLK1) appears negatively associated with helical domain mutations.



V) Cell Motility



In contrast, pathways relating to cell motility (e.g. degradation of gap junctions) are enriched among features positively associated with helical domain mutations. As well, inferred activity of RHO GTPases, known to regulate cancer cell motility, also show positive association with helical domain mutations.

Conclusion

In this study, we demonstrate that somatic mutations are distributed differently across the PIKCA domains among the TCGA Pan-Cancer 12 cancer types; and that helical and kinase domain mutations associate with distinct patterns of pathway activation. Altogether, our findings suggest that breast and kidney cancers may favor kinase domain mutations in order to enhance PI3K catalytic activity and drive proliferative processes. In contrast, lung cancers and head-and-neck squamous cancers appear to favor helical domain mutations to preferentially enhance malignant cell motility.