Discovery and characterization of driver MAPK and PI3K pathway mutations in tumors and association with drug response in cell lines

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Abstract: In this study, we assessed drug sensitivity to PI3K and MAPK pathway inhibitors in single and cell line screening panels including CCLE, Sanger cell line panel, GlaxoSmithKline (GSK), and Cancer Genome Atlas (TCGA). We identified mutations by deep sequencing and performed targeted exome sequencing to confirm the findings and validate our discovery. The data was integrated from TCGA, Broad, and Broad whole exome analysis.

Results: Gain of Function and Loss of Function mutations in MAPK pathway genes were most observed in uterine (78%), breast cancer (36%), cervical squamous cell carcinoma (28%), prostate adenocarcinoma (17%), and colon adenocarcinoma (17%). In contrast, PI3K pathway genes were observed in uterine (78%), breast cancer (36%), cervical squamous cell carcinoma (28%), and skin cutaneous melanoma (28%). The MAPK and PI3K pathways are frequently altered in human cancer and are targeted by dozens of agents in clinical trials. The efficacy of these therapies, alone or in combination, is increasing, we sought to characterize the association of pathway mutation status with clinical outcomes.

Methods: Patient samples subjected to whole exome analysis. Gain of Function and Loss of Function mutations in MAPK pathway genes were most observed. Mapkinase and phosphatidylinositol 3-kinase (PI3K) pathways were frequently altered in human cancers. Pathway gene mutations were assessed for association with drug sensitivity to MAPK and PI3K pathway inhibitors in cell line screening panels. The efficacy of these therapies, alone or in combination, is increasing, we sought to characterize the association of pathway mutation status with clinical outcomes.

Conclusions: Pathway gene mutations were recurrent missense mutations. The most responsive cell lines to MAPK pathway inhibitors were consistent with our previous observations. 

Relevant tables and figures are included to illustrate the findings. 

Figure 1. Patient samples subjected to whole exome analysis.

Figure 2. Compounds Bioscience mutation classification schemes.

Figure 3. Permutation analyses of Tumor and MAPK pathway mutations.

Figure 4. MAPK and PI3K pathway gene classifications.

Figure 5. Coexistence and mutual exclusivity of MAPK and PI3K pathway mutations in 17 cancer types.

Figure 6. Essential cancer patients with reversionary MAPK and PI3K pathway mutations exhibit decreased overall survival.

Table 1. MAPK pathway mutations associated with sensitivity to MAPK pathway inhibitors in vitro.

Table 2. PI3K pathway mutations associated with sensitivity to PI3K pathway inhibitors in vitro.