

Lung cancer cells have differential signaling responses to KRAS inhibitor treatment

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Genetic alterations of the KRAS gene are some of the most common mutations in lung cancer patients, but unfortunately these patients have few effective treatment options. Drugs that target the G12C mutation in KRAS have shown some activity in lung cancer; however, alternative signaling pathways are often activated that bypass the KRAS inhibitor, resulting in drug resistance. In a new article published in *Clinical Cancer Research*, Moffitt Cancer Center researchers show that various subtypes of lung cancer cells activate different signaling pathways in response to KRASG12C inhibitor treatment. These results may help identify potential combination therapy approaches and guide treatment decisions for lung cancer patients in the future.

The G12C mutation of KRAS occurs in approximately 16% of lung adenocarcinomas. Several drugs that target this specific mutation are in clinical development and have shown activity in some lung cancer patients, but these drugs are less effective in certain patients. As a result, combination treatment with other targeted agents may be necessary to see a benefit, but it is not

clear which combination treatment strategies would work best.

"Given the diverse responses observed in both preclinical models and human patients, it is critical to understand how [cells](#) escape from targeted inhibition, which pathways contribute to resistance and how to predict pathway utilization for escape to enable precision medicine in the form of combination therapy," said Eric Haura, M.D., associate center director of Clinical Science at Moffitt.

The researcher team performed a series of preclinical studies using a technique called mass spectrometry to determine how cells respond to KRASG12C inhibitor treatment and to characterize their different responses. They treated a panel of KRASG12C mutant [lung cancer](#) cell lines with the KRASG12C inhibitor and discovered that each cell line displayed varied sensitivity to the drug, which was associated with different protein signaling patterns after treatment.

They characterized the panel of cell lines into either an epithelial or mesenchymal cell type. Epithelial cells are specialized cells that line organs and vessels and have strong cell connections between them, while mesenchymal cells are less specialized, associated with connective tissues, and are typically more motile. Epithelial and mesenchymal cells are known to express particular proteins and act in certain ways; however, they can change protein expression patterns and become similar to the alternative cell type under certain conditions.

The researchers discovered that the cell line that was sensitive to the KRAS inhibitor and displayed epithelial characteristics activated the HER2 and HER3 signaling pathways after KRAS inhibitor treatment, and cotreatment with a drug that targets these proteins resulted in greater cell death than either agent alone. They also demonstrated that

activation of the downstream proteins SHP1, SOS1 and IRS1 contributed to responses after KRASG12C inhibitor treatment in this cell line.

After assessing signaling responses of the KRAS inhibitor resistant and moderately sensitive [lung cancer](#) cell lines, which have mesenchymal characteristics, they found that activation of the FGFR1 and AXL signaling pathways mediates resistance to KRAS inhibitor treatment in these cell lines, respectively, and that co-treatment with an FGFR or AXL inhibitor sensitized the cells to KRAS inhibition.

These data support the idea that the ideal therapy for [lung cancer patients](#) cannot be a one-size-fits-all approach. The researchers hope their results and experimental approach can be used to develop targeted cotreatment approaches for patients.

"Our data highlight the importance of phosphoproteomics-based approach to identify tumor specific adaptive rewiring, which can be utilized to aid personalized patient care in KRASG12C mutants," said Haura.

More information: Eric B Haura et al, Cell-type Specific Adaptive Signaling Responses to KRASG12C inhibition, *Clinical Cancer Research* (2021). DOI: [10.1158/1078-0432.CCR-20-3872](https://doi.org/10.1158/1078-0432.CCR-20-3872)

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