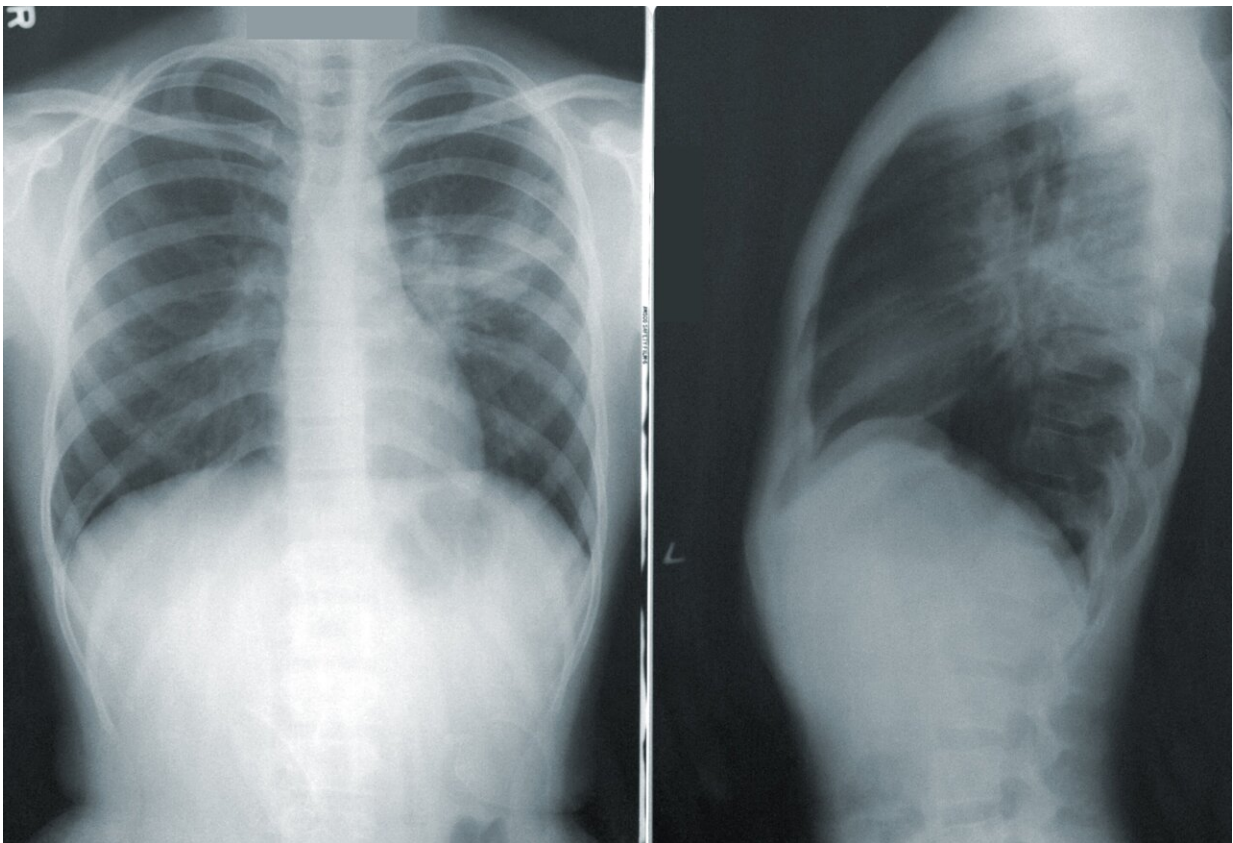


Researchers pinpoint nongenetic mechanisms in lung cancer resistance to one commonly used therapy

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In a recent study led by Ravi Salgia, M.D., Ph.D., the Arthur & Rosalie

Kaplan Chair in Medical Oncology, a team of researchers from City of Hope, one of the largest cancer research and treatment organizations in the United States, and other institutions found that nongenetic mechanisms are important in lung cancer patients who develop a resistance to one cancer therapy. Their [findings were published](#) in the October 13 issue of the journal *Science Advances*.

The team's study explored resistance to the anti-cancer medication sotorasib in patients with [non-small cell lung cancer](#) (NSCLC). Sotorasib inhibits a specific mutation of a protein, KRAS G12C, that causes unchecked cell growth.

The researchers' findings suggest that, initially, most tumor cells are sensitive to sotorasib. But some cells can become tolerant to [therapeutic treatment](#) without resorting to [genetic mutations](#) or alterations by manipulating the KRAS-sotorasib interaction network. Furthermore, they found that if sotorasib treatment is withheld, the [tumor cells](#) revert to becoming sensitive again, implying that the phenomenon is reversible and thus is driven by nongenetic mechanisms.

However, if treatment persists for a long time, genetic mutations can potentially occur that lead to permanent resistance to medication.

In addition, Salgia et al. discovered that medication resistance in NSCLC cells that already have genetic mutations that allows them to resist the effects of the medication can be addressed if sotorasib is used in combination with an anti-[cancer therapy](#) called carfilzomib that's currently Food and Drug Administration-approved for other types of cancers. The carfilzomib acts synergistically with sotorasib and again involves a nongenetic mechanism.

KRAS is mutated in many cancer types, including in approximately 30% of NSCLC patients. Small molecule inhibitors that specifically target the

mutated KRAS protein (G12C) like sotorasib are approved beyond first-line settings and are often initially effective. However, the response eventually declines, signaling that the tumors have developed medication resistance. This resistance can be innate, meaning mutations that ward off the toxic treatment effects exist prior to medication exposure, or it can be acquired, meaning the mutation is induced by the therapy. In either case, it has long been believed that the underlying mechanism of mutation is genetic in nature. However, it is now increasingly recognized, in part due to work by Salgia and his team, that genetic mechanisms may not be the only drivers of therapeutic resistance.

The results of this study not only highlight a nexus between genetic and nongenetic mechanisms at play in cancer tumor treatment resistance, but they also provide a potential therapeutic opportunity to address resistance in NSCLC patients. More importantly, the results are unique because the idea that the flexibility of the KRAS molecule may impact treatment response was not appreciated previously. For example, resistance to the KRAS G12C inhibitor sotorasib does not necessarily translate to resistance to a different KRAS inhibitor called adagrasib. This discovery suggests that changes induced by sotorasib may not impede KRAS interaction with [alternative treatments](#). Finally, the findings by Salgia et al. highlight potential alternative treatment strategies, such as the combination of carfilzomib and sotorasib, for managing challenging and refractory NSCLC KRAS G12C tumors. This means that figuring out what kind of resistance a patient has is key to personalizing their [treatment](#). Based on these exciting preclinical results, the research team is working on initiating a clinical trial at City of Hope.

More information: Atish Mohanty et al, Acquired resistance to KRAS G12C small-molecule inhibitors via genetic/nongenetic mechanisms in lung cancer, *Science Advances* (2023). [DOI: 10.1126/sciadv.ade3816](https://doi.org/10.1126/sciadv.ade3816)

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