New screening method identifies inhibitors of cancer cell metabolism

November 18 2019

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A new screening system developed by scientists at the UCLA Jonsson Comprehensive Cancer Center leverages redundancy in an important component of a cell—nucleotide metabolism—to help identify new drugs that specifically and potently block processes that are essential for cancer cell growth.

There are many small molecule kinase inhibitors, such as Gleevec, that have been developed to target cancers and other diseases. However, scientists still don't fully understand the full effects of these drugs. Current screening methods do not capture the effects these inhibitors may have on other components of cells, such as biochemical metabolic networks. Using their understanding of metabolism, the team designed a new high-throughput screening system that allows for identification of selective inhibitors of metabolic pathways.

Working with the Molecular Screening Shared Resource at UCLA, the team performed a large scale analyses of 430 kinase inhibitors that have annotated targets within cellular signaling pathways and many of which are currently being used in the clinic. Unexpectedly, multiple inhibitors were found to block nucleotide metabolism and their targets were revealed using mechanistic studies.

This new metabolism-focused screening approach can be a powerful tool in getting new insight into how existing drugs impact metabolic networks and could potentially provide a new understanding into how these drugs are working in the clinic. In addition to characterization of existing compounds that are already being used for treating cancers and other diseases, this screening method could one day also be applied to identify new small molecule modulators of currently un-targeted metabolic pathways—not only nucleotide metabolism—which can help lead to new drug discoveries.

The study is published online in *Cell Chemical Biology*.

More information: Evan R. Abt et al, Metabolic Modifier Screen Reveals Secondary Targets of Protein Kinase Inhibitors within Nucleotide Metabolism, *Cell Chemical Biology* (2019). DOI: 10.1016/j.chembiol.2019.10.012

Provided by University of California, Los Angeles