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Innovative computational approach yields novel cancer targets

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Researchers at Weill Cornell Medicine have used artificial intelligence to identify drug targets based on mapping regulatory networks in patient tumors. The study, published in *Cell Systems*, experimentally identified and validated four drug candidates for neuroendocrine, liver and renal cancers, which have a dismal prognosis with current therapeutic options.

This research offers a much-needed new way to identify novel drug

targets for many cancers. Though targeted therapy for some cancers has improved survival rates, treatment resistance and resulting disease progression are constant challenges. In addition, many cancer types have no known specific drug targets.

Senior author Dr. Ekta Khurana, associate professor of physiology and biophysics and WorldQuant Foundation Research Scholar, led the effort that mapped gene regulatory networks for tumor samples from 371 patients which included 22 cancer types, using a new computational approach. Gene regulatory networks—models that describe the complex relationships between genes in a cell—are often altered in cancer.

Building accurate gene regulatory networks is not an easy task. The researchers incorporated data from the tumor cells into messenger RNA, which is translated to proteins and chromatin accessibility, and can help reveal how DNA packaging and other factors affect gene expression.

The researchers developed an innovative computational approach, named Cancer Regulatory Networks and Susceptibilities (CaRNetS), to discover key proteins that can be drug targets for cancer therapy within the gene regulatory networks. They identified known targets, such as BRAF in skin, CTNNB1 (B-Catenin) in colon and ERBB2 (Her2) in lung cancers.

"With these known positive cases as reference points, we sought to validate the top candidates in cancers with limited effective targeted therapies," said the authors.

Then the researchers used their approach to find the key transcription factors and their interacting proteins, which may be vulnerable points that can be targeted to stop or slow tumor growth. Transcription factors are proteins that bind to specific DNA sequences and regulate the expression of genes, turning their production on and off.

Using CaRNets on patient tumor samples, the researchers were able to cluster patients into 22 groups—nine corresponded to only one cancer type and 13 contained patients from multiple cancer types. Importantly, the approach revealed drug targets for all 22 clusters. The researchers validated four of these protein candidates in cells. They found that inhibiting the proteins they identified significantly affected growth in cell lines representing renal, liver, and neuroendocrine cancer types as compared to controls.

The researchers envision that with the ease of measuring chromatin accessibility from patient tissue on a large scale, their computational approach will be widely used to find novel treatment options for more cancer types and subtypes.

Dr. Khurana is also a member of the Sandra and Edward Meyer Cancer Center where she co-leads the Genetics and Epigenetics program. First authors on the paper are Dr. Andre Forbes and Dr. Duo Xu, who worked in the Khurana lab at the time of this research.

More information: Andre Neil Forbes et al, Discovery of therapeutic targets in cancer using chromatin accessibility and transcriptomic data, *Cell Systems* (2024). DOI: 10.1016/j.cels.2024.08.004

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