
Article

# Uncovering Key Interactions Between Cancer-Driving Proteins

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Research conducted as part of the Cancer Cell Map Initiative (CCMI), has revealed interactions between cancer-driving proteins, that were unknown, until now. Findings were published in three separate papers in *Science*.

The CCMI aims to transform the field of cancer drug discovery by uncovering the molecular networks underlying the disease. It is hoped that insights from the initiative will advance basic research and clinical decision-making through the development of computational cancer cell models. The CCMI comprises investigators from UC San Diego and the University of California, San Francisco (UCSF) with

expertise in various areas.

The team was able to consolidate the data generated from each study, allowing them to create a single map of protein pathways underlying cancer pathophysiology. Integrating the information into a single resource provides a clearer picture of how the pathways influence one another, helping researchers to identify interactions that drive cancer growth and metastasis and expose elements that have the potential to be therapeutically modulated.

“Science moves so much more quickly when scientists from different disciplines work together. This is evident in these papers and was seen during the pandemic. In order to accomplish this more effectively across science, the reward system needs to change where groups and collaboration are rewarded more than individuals. The systems need to reward younger scientists more effectively, especially in a way that encourages them to collaborate,” explains Professor Nevan J. Krogan from the Department of Cellular and Molecular Pharmacology at UCSF, corresponding author of the *Science* papers.

## A better interpretation of the genome

In 2003, The Human Genome Project was declared complete. This international scientific effort marked a revolutionary turning point in the genomics field. Since then, further technological advances in DNA sequencing have enabled researchers to better interrogate the genome, and as a result, it has been possible to identify specific genetic alterations that disrupt the normal functioning of cells, some of which cause cancer.

While understanding the underlying genetic mutations responsible for initiating and driving tumor progression is important, looking beyond the nucleus, is equally valuable. Especially as the majority of cancer drugs act on protein targets.

“We often think of genomes as biological blueprints. But the blueprints of a car do not, themselves, tell you how a car will handle or perform in a crash test. Genomes relate even less straightforwardly to the cells or organisms they describe,” says Marcus R. Kelly, a postdoctoral fellow at the University of California San Diego and joint first author of the Zheng/Kelly study.

Kelly explains that their paper organizes mutations into protein systems sharing common cellular functions, but he adds that mutations in the same system are likely not even on the same chromosome as each other.

## Identifying druggable targets

In recent years, there has been concern that many cancer drugs are directed towards the wrong molecular targets and that this may be to blame for the low clinical success rate in oncology. In 2019, Wong, et al. reported that the failure rate for cancer drug development was almost 97%. Without a comprehensive understanding of the protein–protein interactions involved in cancer, it’s possible to misidentify therapeutic targets, and original targets may be nonessential for cancer cell survival.

“When we look for druggable targets, we are mostly trying to find specific molecules that control functions that cancer cells depend on more than healthy cells do,” says Kelly. To understand these unique functions, a variety of experimental techniques are required.

Kelly elaborates, “Affinity purification coupled with mass spectrometry (AP–MS), for example, tells us which proteins bind one another, which is strong evidence that they perform related functions in the cell." He adds,

"This is why AP–MS experiments are the focus of the Swaney and Kim papers, and why they contribute so significantly to the Zheng/Kelly paper. Rather than looking 'beyond' the genome, these other experiments help us interpret the genome more clearly."

"The Zheng/Kelly study uses the high-quality protein–protein interaction data focused on breast and head/neck cancers along with other datasets to derive a hierarchical model of the cancer cell," explains Krogan.

Zheng et al. took the data from the Swaney et al. and Kim et al. papers and combined it with existing public data on protein–protein interactions to generate a map of protein pathways that they used to expose hard-to-detect mutations that may play a role in metastasis. The studies provide a resource that will be helpful in interpreting cancer genomic data.

The key findings from the Kim et al. and Swaney et al. papers are described in more detail below.

## A protein network map of head and neck cancer

Danielle Swaney, assistant professor of cellular molecular pharmacology at UCSF and colleagues studied protein–protein interactions for genes commonly mutated in head and neck squamous cell carcinoma (HNSCC). Their aim was to determine what impact they have on the molecular machinery within the cell and the various signaling pathways in which they function. The protein coding gene *PIK3CA* – the most commonly mutated oncogene in HNSCC (~ 20%) – provides instructions for making the alpha catalytic subunit of phosphoinositide 3-kinase (PI3K). Swaney explains that they observed mutation-enriched interactions between the human epidermal growth factor receptor 3 (HER3) and PIK3CA. This is important because changes in the way they interact could affect response to HER3-targeted therapeutics.

"We find that this interaction depends [specifically] on which mutation *PIK3CA* has. One mutation can cause low binding to HER3, another mutation can result in high binding. This is important because HER3 is a drug target. We find that when a tumor has a *PIK3CA* mutation associated with high binding to HER3, you can use a HER3 inhibitor to stop tumor growth," says Swaney. This knowledge could help to determine the sensitivity of *PIK3CA*-mutant tumors to HER3 inhibitors.

## Probing protein interactions in breast cancer

Kim et al. aimed to assess the specific molecular alterations that occur in breast cancer beyond those commonly associated with the disease, the goal being to improve treatment efficacy and safety through targeted therapy. The researchers found two proteins (UBE2N and spinophilin) that interacted with the tumor suppressor gene *BRCA1*, as well as two proteins that regulate PIK3CA.

According to the study's first author Min Kyu Kim, assistant professor of cellular molecular pharmacology, UCSF, while UBE2N is known to be involved in DNA double-strand break repair by homologous recombination, its relevance as a predictive biomarker for response to PARP inhibitors (e.g., carboplatin) and other DNA-damaging drugs hadn't previously been explored. He elaborates on their findings: "We found that patients with pathologic complete response (basically tumors are eradicated) to PARPi/carboplatin treatment tend to have low mRNA expression of UBE2N in their tumors. So, this result suggests that cancer patients with low expression of UBE2N (but with normal levels of other DNA repair proteins, such as BRCA1) in their tumor could be considered to be treated with PARPi/carboplatin, as *BRCA1/2*-mutated cancer patients."

The team was also able to show that spinophilin could regulate the phosphorylation status of many DNA repair proteins (including BRCA1) by removing phospho-marks (dephosphorylation). “This dephosphorylation is an important step to turn on and off the cellular response to DNA damage. Spinophilin is often found amplified in breast cancer patients (8% in TCGA study), so our study also shed light on the pathogenic mechanism of spinophilin-altered cancer patients,” says Kim.

Talking of the novel PIK3CA-interacting proteins (BPIFA1 and SCGB2A1) Kim says, “Knockdown of these proteins in cells led to up-regulation of PIK3CA-AKT signaling, which is strongly associated with tumorigenesis and cancer cell proliferation. Furthermore, in an *in vitro* assay, these proteins were shown to preferentially inhibit wild-type PIK3CA kinase activity.” Based on this, Kim says that the team believes BPIFA1 and SCGB2A1 are negative regulators of the PIK3CA-AKT pathway.

“Given their specificity for wild-type PIK3CA, they might have a therapeutic potential towards PIK3CA-amplified tumors,” he adds.

Krogen emphasizes the significance of the protein–protein interactions identified in the Swaney and Kim papers, “[They] were the single most informative data type for the identification of protein systems, and many protein systems simply would not have been identified without that data.”

He notes that while the Swaney and Kim papers were primarily focused on identifying systems mutated in head and neck and breast cancer, they also helped to identify systems mutated in other cancers as well.

## Looking beyond cancer

The Zheng study notes that the multiscale map of protein assembly strategies could be generalized to other diseases that are affected by rare genetic alterations. Kelly elaborates, “The CCMI has two sister programs, the Psychiatric Cell Map Initiative, and the Host-Pathogen Map Initiative. Both neurodegenerative diseases and susceptibility to particular pathogens have heritable components, but few truly determinative genes are known in either case. It seems likely that, like cancer, these diseases are best understood in terms of dysregulated protein systems."

He concludes, "Organizing many rare mutations into a map will help us understand the underlying principles of patient response.”

**References**

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*Marcus R. Kelly, Min Kyu Kim, Nevan Krogan, and Danielle Swaney were speaking to Laura Elizabeth Lansdowne, Managing Editor for Technology Networks.*