Multiplication on, multiplication off: Targeting an enzymatic switch to develop oncology drugs

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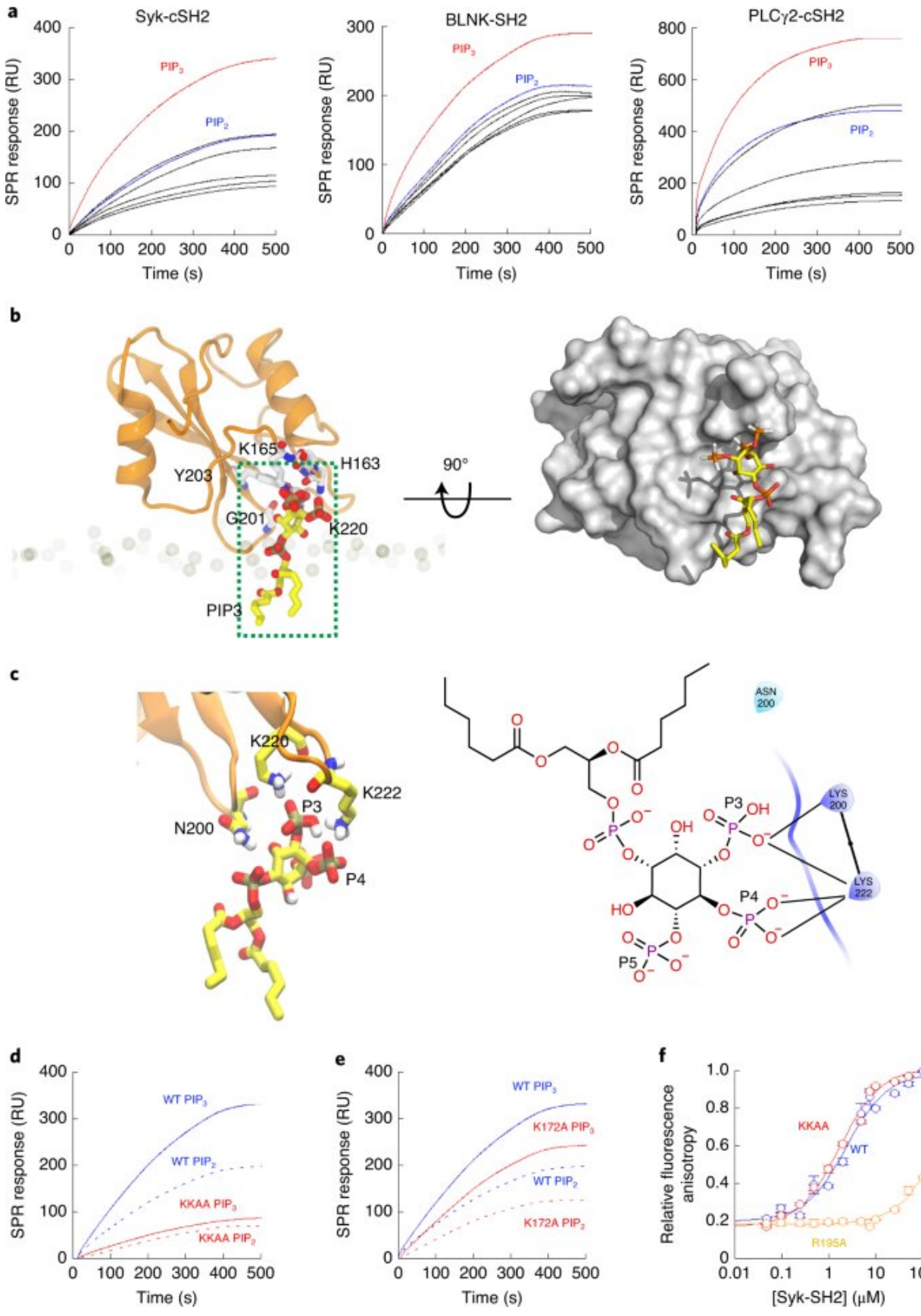
a
Syk-cSH2
BLNK-SH2
PLCγ2-cSH2
SPR response (RU)
Time (s)
PIP3
PIP2
b
K165
H163
Y203
G201
K220
PIP3
90°
c
K220
K222
P3
N200
P4
ASN 200
LYS 200
LYS 222
P5
d
WT PIP3
WT PIP2
KKAA PIP3
KKAA PIP2
e
WT PIP3
K172A PIP3
WT PIP2
K172A PIP2
f
Relative fluorescence anisotropy
KKAA
WT
R195A
[Syk-SH2] (μM)

The membrane-binding mechanisms of SH2 domains. Credit: *Nature Chemical Biology* (2022). DOI: 10.1038/s41589-022-01150-z

Researchers from the University of Illinois Urbana-Champaign and the University of Illinois Chicago have demonstrated a powerful new approach to small molecule drug development.

Published in *Nature Chemical Biology*, their study highlights lipid-protein interaction as a new avenue for drug development and demonstrates its functionality by designing small molecule-based inhibitors to target acute myeloid leukemia.

AML, a cancer of the blood and bone marrow, has traditionally been treated with chemotherapy. In recent years, a new treatment avenue has emerged which targets tyrosine kinases, enzymes that function as "on" or "off" switches in many cellular processes, including cancer-related multiplication. The small-molecule inhibitors designed by the researchers bind to these enzymes and reduce their activity, making AML-infected cells less resistant to treatment.

"Targeting lipid-protein interaction sites in protein is advantageous because it is less prone to resistance-causing mutations," said study co-author Emad Tajkhorshid, who is a researcher at the Beckman Institute for Advanced Science and Technology as well as the Endowed Professor of Biochemistry and Director of the National Institutes of Health Center for Macromolecular Modeling and Bioinformatics at UIUC.

The researchers study membrane proteins, which gather on the surface of a cell's biological membrane. Biological membranes are made up of multi-component lipids and are responsible for controlling the function

of many cellular proteins—mainly membrane proteins.

But most drugs on the market designed for specific oncology targets suffer from a major problem, according to Shashank Pant, an author on the paper and a graduate researcher at UIUC at the time of its publication. Over time, certain residues within these proteins begin to mutate. When that happens, the drugs designed to target the initial protein might not work anymore.

However, these mutations occur only in certain areas of the protein. Each protein is comprised of a chain of peptides broken up into several regions, or domains. The researchers realized if they could inhibit those domains that interact specifically with the biological membrane, the proteins would no longer work, and their activities would be suppressed.

"We wanted to give a different perspective to drug research," Pant said.

The researchers first had to understand how spleen tyrosine kinase proteins, or Syk proteins, interact with the biological membrane. In this early stage, they realized that Syk proteins contain SH2 domain molecules, which are responsible for interaction with the biological membrane in a lipid-dependent manner.

They found that blocking SH2-lipid interaction was an efficient approach to targeting SH2-domain-containing proteins. This approach suppressed reported acquired resistance to Syk inhibitors.

While the research group initially believed that the specific domain interacting with the lipid in Syk would bind to a well-defined region of the protein (known as a canonical binding site), they were surprised to discover multiple non-canonical binding sites as well.

"We targeted multiple membrane binding sites using the small molecules

with the help of our collaborators at the University of Illinois Chicago," Pant said. "It was exciting to see that targeting lipid-binding sites resulted in inhibition, and that the protein was no longer active."

This development is just the beginning.

"I think this is just the start of designing compounds to specifically target lipid-protein interactions," Pant said. "The most impactful thing I see in the future is leveraging this technology to design better drugs and help patients."

The success of this research was made possible through the power of collaboration.

"We are a computational lab working on biomedically relevant proteins, but we are limited in scope," Pant said. "We were able to collaborate with the lab of Professor [Wonhwa] Cho at University of Illinois Chicago who could see and verify in realistic systems that these inhibitors are important, and that we can specifically target lipid-protein interactions."

The collaborative benefits of the study design were multi-faceted.

"The study also highlights the power of combining computational and experimental methods in well-designed studies targeting specific problems," Tajkhorshid said.

More information: Indira Singaram et al, Targeting lipid–protein interaction to treat Syk-mediated acute myeloid leukemia, *Nature Chemical Biology* (2022). DOI: 10.1038/s41589-022-01150-z

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