HKU Scientists Develop A New Chemical Tool That Sheds Light On How Proteins Recognise And Interact With Each Other

By **India Education Diary ...** On **Apr 26, 2021**

A research group led by Professor Xiang David LI from the Research Division for Chemistry and the Department of Chemistry, The University of Hong Kong, has developed a novel chemical tool for elucidating protein interaction networks in cells. This tool not only facilitates the identification of a protein's interacting partners in the complex cellular context, but also simultaneously allows the 'visualisation' of these protein-protein interactions. The findings were recently published in the prestigious scientific journal Molecular Cell.

In the human body, proteins interact with each other to cooperatively regulate essentially every biological process ranging from gene expression and signal transduction, to immune response. As a result, dysregulated protein interactions often lead to human diseases, such as cancer and Alzheimer's disease. In modern biology, it is important to comprehensively understand protein interaction networks, which has implications in disease diagnosis and can facilitate the development of treatments.

To dissect complex protein networks, two questions need to be answered: the 'who' and 'how' of protein binding. The 'who' refers to the identification of a protein's interacting partners, whereas the 'how' refers to the specific 'binding regions' that mediate these interactions. Answering these questions is challenging, as protein interactions are often too unstable and too transient to detect. To tackle this issue, Professor Li's group has previously developed a series of tools to 'trap' the protein-to-protein interactions with a chemical bond. This is possible because these tools are equipped with a special light-activated 'camera' – diazirine group that capture every binding partner of a protein when exposed to UV light. The interactions can then be examined and interpreted. Unfortunately, the 'resolution' of this 'camera' was relatively low, meaning key information about how proteins interact with each other was lost. To this end, Professor Li's group has now devised a new tool (called ADdis-Cys) that has an upgraded 'camera' to improve the 'resolution'. An alkyne handle installed next to the diazirine makes it possible to 'zoom in' to clearly see the binding regions of the proteins. Coupled with state-of-the-art mass spectrometry , ADdis-Cys is the first tool that can simultaneously identify a protein's interacting partners and pinpoint their binding regions.

In the published paper, Professor Li's lab was able to comprehensively identify many protein interactions — some known and some newly discovered — that are important for the regulation of essential cellular processes such as DNA replication, gene transcription and DNA damage repair. Most importantly, Professor Li's lab was able to use ADdis-Cys to reveal the binding regions mediating these protein interactions. This tool could lead to the development of chemical modulators that regulate protein interactions for treating human diseases. As a research tool, ADdis-Cys will find far-reaching applications in many areas of study, particularly in disease diagnosis and therapy.

For more information about the paper "A tri-functional amino acid enables mapping of binding sites for posttranslational modification-mediated protein-protein interactions" published in Molecular Cell, please visit: https://www.cell.com/molecular-cell/fulltext/S1097-2765(21)00268-9

香港大学科学家研发出新化学工具，可有效解构蛋白辨识及互动机制

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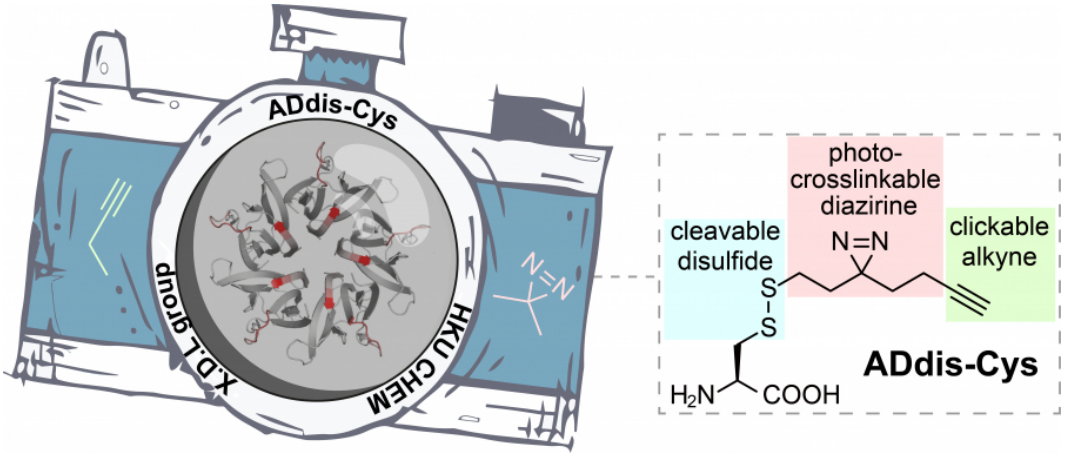
香港讯由香港大学化学研究部及化学系李祥教授率领的研究团队研发了一项新的化学分子工具，用以解析细胞内蛋白之间的互动。此工具不但能帮助从复杂的细胞环境中辨识与目标蛋白互动的其他蛋白，同时更容许这些互动被直接「观测」。研究结果最近于顶尖科学期刊《分子细胞》(Molecular Cell) 发表。

在人体内，包括基因表达、信息传递及免疫反应等所有生物过程都牵涉到各种蛋白之间的互相作用，因此蛋白互动失调经常会导致各种疾病，例如癌症及失智症等。对蛋白互动网络的全面及深入理解与疾病的诊断及治疗息息相关，因而成为现今生物学的一个重要课题。



为了剖析错综复杂的蛋白互动网络，有两个需要回答的问题：目标蛋白跟「谁」互动？这些蛋白「如何」互动？回答跟「谁」互动需要辨识目标蛋白的互动伙伴，而回答「如何」互动则须找出参与蛋白结合的区域。由于蛋白互动经常过为微弱或短暂，传统方法难以捕捉，回答上述两个问题是一项重大挑战。为了解决这些难题，李教授的团队先前研发了一系列的化学分子工具，成功以化学键的连接「捕捉」蛋白互动的状态。这些工具成功的关键在于它们带有特殊的光激活「摄影机」——二氮环丙烯基团（diazirine group）。这个化学基团在受紫外线照射时能捕捉目标蛋白的所有互动伙伴，而这些蛋白互动之后便可以再分别验证。但是此「摄影机」的「分辨率」不高，导致有关蛋白结合表面的关键信息的流失。为了弥补这项缺点，李教授的团队研发了新的化学分子工具：ADdis-Cys。这个化学分子工具具有升级版的「摄影机」，提高了其「分辨率」：他们在二氮环丙烯基团旁边安装了一个炔烃基团（alkyne group），使「摄影机」能清楚「聚焦」至蛋白结合的区域。若再辅以最先进的质谱分析，ADdis-Cys便成为了第一个能够同时辨识蛋白互动伙伴及找出蛋白结合区域的化学分子工具。

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在这次发表的文章中，李教授的团队利用ADdis-Cys能够全面辨识包括已知及新发现的蛋白互动，涉及调控DNA复制、基因转录及修复DNA损坏等各种基本细胞机制及过程。更为重要的是，李教授的团队利用ADdis-Cys找出了参与这些蛋白结合的蛋白区域。此项工具为今后设计化学调制器，针对性调节这些蛋白互动以治疗相关疾病奠定基础。ADdis-Cys作为一项研究工具，于多种研究领域及对疾病的诊断及治疗均能发挥重要的作用，影响深远。 **（《中国基建报》记者蒋毅笙 香港报道）**

关键字：蛋白 化学 香港大学 工具 基团