New Strategy for Targeted Degradation of Proteins

Targeted protein degradation (TPD) technologies, including the traditional proteolysis targeting chimeras (PROTACs), the recently reported lysosome-targeting chimeras (LYTACs), and related technologies could specifically identify and degrade the target proteins by hijacking the inherent protein degradation pathways in cells. Thus, it has drawn great attention in medicinal chemistry and chemical biology.

Some extracellular and membrane-associated proteins are key agents in cancer, aging-related diseases, autoimmune disorders, etc. Thus, they are considered to be an important class of drug targets. Therefore, a general strategy to selectively degrade these proteins will offer new opportunities for drug discovery.

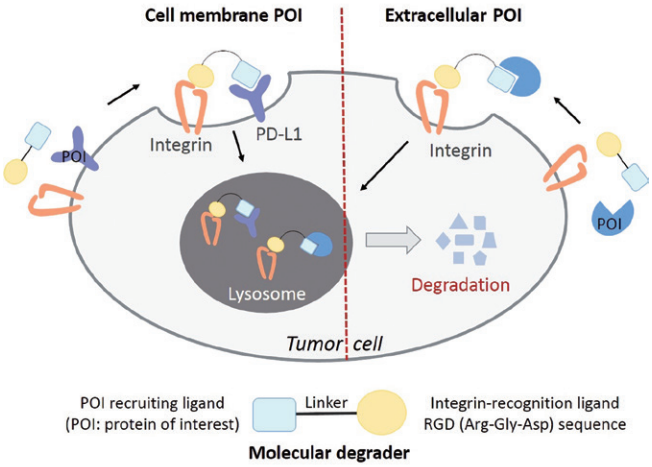
Recently, a research team led by Prof. FANG Lijing, Prof. CHEN Liang, and Prof. LI Hongchang from the Shenzhen Institute of Advanced Technology (SIAT) of the Chinese Academy of Sciences has reported a novel integrin-facilitated lysosomal degradation (IFLD) strategy to degrade extracellular and cell membrane proteins using bifunctional compounds as molecular degraders.

This work was published in the *Journal of the American Chemical Society* on Nov. 24.

By conjugating a target protein-binding ligand with an integrin-recognition ligand, the resulting molecular degrader proved to be highly efficient in inducing the endocytosis and subsequent lysosomal degradation of extracellular or cell membrane proteins through forming a ternary complex between the target protein and integrin on the cell surface.

Since $\alpha_v\beta_3$ integrin is usually overexpressed in tumors, the IFLD strategy is particularly attractive for the targeted degradation of cancer-relevant proteins.

Compared with antibody-, nanobody-, and aptamer-based technologies, bifunctional molecules possess several advantages as protein degraders, such as small size, no immunogenicity, and controllable pharmacological and pharmacokinetic properties. The availability of small molecule inhibitors for many disease-related proteins also provides convenience for designing IFLD molecular degraders.



Integrin-facilitated lysosomal degradation (IFLD) strategy for extracellular or membrane proteins using bifunctional compounds as molecular degraders. (Image by Prof. FANG)

As demonstrated in the development of BMS-L1-RGD, an efficient programmed death-ligand 1 (PD-L1) degrader validated both *in vitro* and *in vivo*, the IFLD strategy expands the toolbox for the regulation of secreted and membrane-associated proteins, thus has great potential in chemical biology and drug discovery.

Contact:
ZHANG Xiaomin
Email:xm.zhang@siat.ac.cn

(SIAT)

Reference

Zheng, J., He, W., Li, J., *et al.* (2022). Bifunctional Compounds as Molecular Degraders for Integrin-Facilitated Targeted Protein Degradation. *Journal of the American Chemical Society, 144*(48), 21831–21836. doi:10.1021/jacs.2c08367