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New System Triggers Cellular Waste Disposal

Established treatments for cancer and other diseases often focus on inhibiting harmful enzymes to mitigate their effects. However, a more innovative approach has emerged: harnessing the cell's natural waste disposal system not just to deactivate but to entirely eradicate these proteins. Researchers at CeMM have already demonstrated the efficacy of this approach through two distinct methods. Now, in collaboration with colleagues from the University of Dundee in Scotland, they unveil a third system capable of targeting and disposing of previously inaccessible proteins. Their groundbreaking findings have been published in the journal Nature.

Living cells resemble highly organized small towns - in addition to energy production, transportation systems, and construction, cells also require efficient waste disposal. Most proteins, which shape and sustain cellular function, have only a limited half-life and must eventually be disposed of, along with defective and unwanted proteins. This vital task falls upon specialized enzymes known as ubiquitin ligases, which tag obsolete proteins for degradation, guiding them to the cellular recycling center, the proteasome. Ubiquitin, acting as molecular label, ensures the targeted proteins are efficiently processed for disposal.

Yet, cells are not always able to recognize and mark every harmful protein with ubiquitin accordingly. Many diseases such as cancer or neurodegenerative diseases like Alzheimer's can only arise because harmful proteins accumulate in cells. This is where the research of Georg Winter's group at CeMM comes in: with a technique called "targeted protein degradation," harmful or otherwise unwanted proteins can be marked with ubiquitin and destroyed in the proteasome, effectively reprogramming the cell's waste disposal system.

So far, this has worked in one of two ways: either by introducing a chemical agent (so-called PROTACs) into the cell, which attaches to one side of the protein to be degraded and to the ubiquitin ligase on the other side, thereby directly linking the two and marking the undesired protein for degradation. Or, by introducing a kind of "molecular glue" into the cell, which attaches to the ligase and thereby induces it to recognize and mark the unwanted protein for degradation. In the new study, now published in Nature (DOI: 10.1038/s41586-024-07089-6), the team led by Georg Winter (CeMM) and Alessio Ciulli (University of Dundee) has revealed a third way that combines both of these existing strategies: so-called "intramolecular bivalent glues" (IBGs) attach to two points on the protein to be degraded, slightly bending it and thereby altering its surface. This alteration is recognized by a ubiquitin ligase, thus marking the protein for degradation.

"This method opens up completely new possibilities for the development of drugs that can be used against cancer, among other diseases" says Georg Winter. "Together with other targeted protein degradation methods, this could potentially treat many diseases that have previously been undruggable." "So far, we often discover drugs that lead to targeted protein degradation only by chance. However, the better we understand how this system works, the closer we come to being able to design such drugs deliberately," says Matthias Hinterndorfer, a postdoctoral researcher in Georg Winter's research group. Therefore, the new discovery provides important insights into the mechanisms and therapeutic opportunities of targeted protein degradation.

Pictures attached
Photo: Georg Winter (left) and Matthias Hinterndorfer (right) © CeMM/Anna Yuwen
Graphic: Schematic model of showing the different modes of molecular recognition with traditional monovalent glues and bivalent PROTACs versus intramolecularly bivalent glue as revealed in this work (© Hsia, Hinterndorfer & Cowan et al., Nature 2024)
The Study "Targeted protein degradation via intramolecular bivalent glues" was published in *Nature* on February 21, 2024. DOI: 10.1038/s41586-024-07089-6
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The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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