Autophagy-tethering compounds may open new directions in targeted drug discovery

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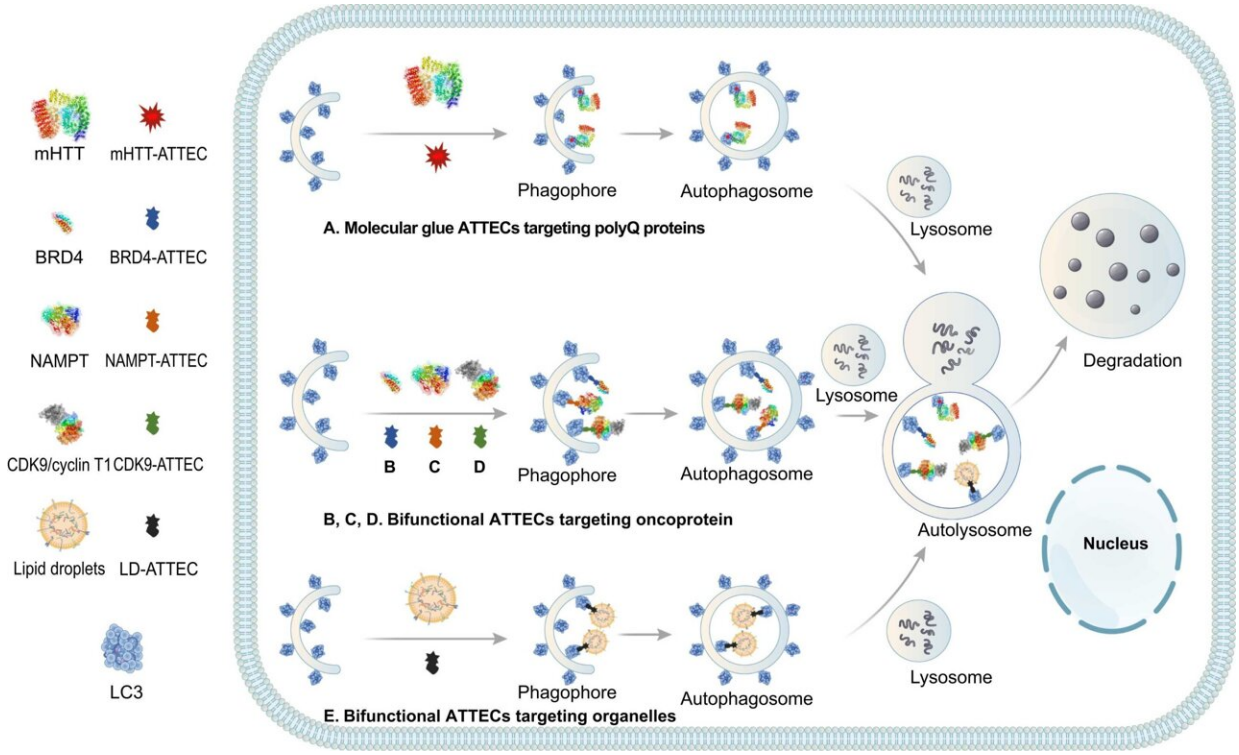

(A) Molecular glue ATTECs are targeting polyQ proteins in neurodegenerative disorders. (B) Bifunctional ATTECs targeting oncoprotein BRD4. (C) Bifunctional ATTECs targeting oncoprotein NAMPT. (D) Bifunctional ATTECs targeting oncoprotein CDK9/cyclin T1. (E) Bifunctional ATTECs targeting lipid droplets. Credit: Science China Press

Human genetic and mechanistic studies reveal thousands of pathogenic

proteins that may serve as potential targets for small-molecule drugs. Meanwhile, the conventional method of drug discovery through inhibitors hinges on the "druggability" of targets—a criterion determined by measurable biochemical activities and accessible binding sites.

The occupancy of these sites directly or indirectly impacts these functions. An encouraging strategy for circumventing the challenge of "druggability" involves leveraging endogenous degradation pathways to eliminate the targeted protein, a concept known as targeted protein degradation (TPD).

Proteolysis-targeting chimeras (PROTACs) currently stand as the predominant approach within TPD. They facilitate the transient formation of a ternary complex, bringing the E3 ligase to the target protein, thereby inducing polyubiquitination (polyUb) of the protein and its subsequent proteasomal degradation. Thus, PROTACs are dependent on the ubiquitin-proteasome pathway, which is incapable of degrading certain categories of targets.

Compared to the ubiquitin-proteasome pathway, the macroautophagy pathway is capable of degrading various categories of targeting, including even organelles.

In recent years, researchers from Fudan University in China have developed a new TPD strategy called autophagy-tethering compounds (ATTECs), which directly harnesses the macroautophagy pathway for the degradation and demonstrated their capability of degrading both protein targets and organelles.

In recent years, several independent labs have also worked on this new strategy and developed ATTECs targeting various targets of different diseases, from neurodegeneration to cancer.

In this recently published review paper from the group that originally developed ATTECs, the authors provided thorough discussions of multiple dimensions of ATTECs, focusing on their mechanisms of action and potential applications in drug discovery.

The research is published in the journal *Medicine Plus*.

More information: Yu Ding et al, Perspectives of autophagy-tethering compounds (ATTECs) in drug discovery, *Medicine Plus* (2024). DOI: 10.1016/j.medp.2023.100004