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EDITORIAL

Leveraging glypican-3 (GPC3)-mediated lysosome-targeting chimeras (GLTACs) for targeted membrane protein degradation

Targeted protein degradation (TPD) has transformed drug discovery by eliminating disease-causing proteins rather than merely inhibiting their activity. Proteolysis-targeting chimeras (PROTACs) have significantly advanced this field by using bifunctional small molecules to recruit E3 ubiquitin ligases to degrade proteins of interest. However, PROTACs, relying on the ubiquitin-proteasome system, predominantly target cytosolic and nuclear proteins, but they struggle to degrade membrane or extracellular proteins. To address this gap, scientists have developed lysosome-targeting chimeras (LYTACs), which consist of an antibody or peptide binding the target protein, linked to a ligand that binds a cell-surface lysosomal trafficking receptor. By bridging a target protein on the cell surface to a lysosome-shuttling receptor, LYTACs are internalized into the cell and delivered to lysosomes, where acidic enzymes degrade various membrane proteins. In essence, LYTACs broaden the druggable proteome, allowing researchers to modulate "undruggable" targets that PROTACs and traditional inhibitors cannot touch.

A recent proof-of-concept study led by Professor Chunquan Sheng from the Second Military Medical University reported an innovative lysosomal degradation modality: GPC3-mediated lysosome-targeting chimeras (GLTACs)[1]. GLTACs harness a tumor-specific cell-surface receptor, glypican-3 (GPC3), as the vehicle to deliver target proteins to the lysosome *via* endocytosis. GPC3 is an oncofetal antigen expressed in >70% of patients with hepatocellular carcinoma (HCC) while minimally present in normal adult liver tissues. The research leveraged this property to design bifunctional molecules that bind both GPC3 and the proteins of interest (POI). In effect, a GLTAC functions as a molecular matchmaker: one end attaches to GPC3, the other end latches onto the target protein, forming a GPC3−GLTAC−POI ternary complex. Once the GLTAC brings the target into proximity of GPC3 on the cell surface, the entire complex is internalized into the cell and trafficked to the lysosome, where the target protein is degraded.

The study demonstrated successful GLTAC-mediated degradation of several membrane proteins, including PD-L1, *c*-Met, and FGFR1. One notable example was the design of **WP0**, a GLTAC degrader linking the GPC3-targeting peptide **TJ12P1** with the PD-L1 inhibitor **BMS-202** through the 1,2,3-triazole linker. PD-L1 normally sits on tumor cell surfaces where it dampens immune attacks. Blocking PD-L1 with antibodies is a successful cancer immunotherapy strategy, but removing PD-L1 from the tumor cell surface could provide an even more durable immune activation. Using GPC3 as the delivery handle, the GLTAC degrader **WP0** efficiently delivered PD-L1 into lysosomes and effectively eliminated it (HepG2 cells DC_{50} = 0.38 μmol/L, D_{max} = 83%; Caco-2 cells DC_{50} = 0.55 μmol/L). In HepG2 cells, **WP0** induced the aggregation and colocalization of PD-L1 with GPC3, forming the PD-L1-**WP0**-GPC3 ternary complex. In HepG2 cells, **WP0** treatment led to a restoration of T cell-mediated tumor cell killing − essentially unmasking the cancer cells to the immune system. The GLTAC concept was also expanded to degrade *c*-Met and FGFR1, another two membrane proteins implicated in cancer. These corresponding GLTAC degraders successfully reduced levels of their target receptors, showcasing the scope of the GLTAC degradation approach for different classes of membrane proteins. Importantly, the degraders were selective − they acted on tumor cells expressing GPC3, sparing normal cells that lack this receptor. This tumor specificity is a key advantage, showing the potential for fewer side effects since the degradation machinery is directed mainly at cancer cells.

The implications of this work are significant. By coupling a disease-specific "address label" (GPC3) with a protein binder, GLTACs open a pathway to target membrane proteins that were previously difficult to touch. Instead of using a conventional inhibitor or antibody to block a membrane receptor's activity, GLTACs literally dispose of the entire receptor. This could overcome cases where simply inhibiting a receptor is insufficient or where mutations render traditional inhibitors ineffective.

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Moreover, GLTACs illustrate how targeting a degradation pathway can translate into functional outcomes. In the PD-L1 case, degradation led to enhanced immune destruction of tumor cells, a result that blockade alone might not fully achieve. Overall, the featured study establishes GLTACs as an innovative addition to the targeted protein degradation arsenal, expanding the therapeutic possibilities for membrane proteins.

The development of GLTACs marks a conceptual and technological advancement in targeted degradation. Conceptually, it demonstrates the value of choosing a disease-specific internalization pathway — in this case, exploiting an oncofetal antigen (GPC3) to achieve cell-selective protein knockdown. This is an evolution of the LYTAC concept, addressing previous concerns about on-target side effects in normal tissue. By narrowing the lysosomal targeting to tumor cells, GLTACs align well with the precision medicine ethos of hitting cancer cells while sparing normal cells. Technologically, the GLTAC molecules were assembled by conjugating relatively small components. This yields a degrader that is smaller and potentially more drug-like than large antibody-based LYTACs. Smaller size can translate to better tissue penetration and easier manufacturing and characterization. It also sidesteps some challenges of antibody–drug conjugates (ADCs), such as heterogeneity in attachment sites and stoichiometry.

Despite these advances, there are still several challenges facing the researchers. GLTACs require co-expression of GPC3 and the target protein on the same cell, but it means GLTACs would not work in contexts where the target protein is on cells that do not express GPC3. In contrast, a generic LYTAC could, in principle, degrade a given target in any cell type. There is also the question of immunogenicity and stability: while smaller than antibodies, peptide-based chimeras can still trigger immune responses or be degraded in circulation. The GLTAC study validated specificity in cell culture, but moving to animal models and ultimately humans will require ensuring that the GPC3-binding peptide doesn't unintentionally bind to other proteins or cause unanticipated side effects. Furthermore, tumor heterogeneity could pose a hurdle. Cancer cells that do not express GPC3 strongly might escape the GLTACs therapy. The GLTAC approach minimizes the risk by using a receptor largely absent from normal cells, but if applied to other receptors one must be cautious of perturbing normal biology. In summary, GLTACs advance the field by solving some problems (tumor-specific targeting, smaller degraders) while still facing the general challenges inherent to any new therapeutic modality.

In conclusion, lysosome-targeting degradation strategies exemplified by GLTACs represent a step forward to therapeutically manipulate the proteome. The featured GLTAC study showcases the power of merging specificity using a tumor-specific receptor for degradation of the "undruggable" membrane proteins. As the field progresses, we can expect even more refined degradation approaches that are safer, more potent, and more precise.

Reference

1. Fang YX, Zhu YJ, Wang W, Xia ZW, He SP, Dong GQ, et al. GPC3-mediated lysosome-targeting chimeras (GLTACs) for targeted degradation of membrane proteins. *Acta Pharm Sin B* 2025;**15**:2156–69.

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