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Engineered bioorthogonal POLY-PROTAC nanoparticles for tumour-specific protein degradation and precise cancer therapy

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PROteolysis TArgeting Chimeras (PROTACs) has been exploited to degrade putative protein targets. However, the antitumor performance of PROTACs is impaired by their insufficient tumour distribution. Herein, we present de novo designed polymeric PROTAC (POLY-PROTAC) nanotherapeutics for tumour-specific protein degradation. The POLY-PROTACs are engineered by covalently grafting small molecular PROTACs onto the backbone of an amphiphilic diblock copolymer via the disulfide bonds. The POLY-PROTACs self-assemble into micellar nanoparticles and sequentially respond to extracellular matrix metalloproteinase-2, intracellular acidic and reductive tumour microenvironment. The POLY-PROTAC NPs are further functionalized with azide groups for bioorthogonal click reaction-amplified PROTAC delivery to the tumour tissue. For proof-of-concept, we demonstrate that tumour-specific BRD4 degradation with the bioorthogonal POLY-PROTAC nanoplatform combine with photodynamic therapy efficiently regress tumour xenografts in a mouse model of MDA-MB-231 breast cancer. This study suggests the potential of the POLY-PROTACs for precise protein degradation and PROTAC-based cancer therapy.

Heterobifunctional PROteolysis TArgeting Chimeras (PROTACs) hold promising potential for cancer therapy, as they can degrade oncoproteins, particularly undruggable targets[1–3]. PROTACs are generally composed of a warhead that binds to the protein of interest (POI), a ligand-hijacking endogenous E3 ubiquitin ligase, and a linker connecting the warhead and the ligand[4–6]. PROTACs can label the POI with ubiquitin by recognising the E3 ligase and subsequently degrade the POI through the ubiquitin-proteasome system (UPS)[7–9]. Compared to small molecule inhibitors, PROTACs can potentially degrade any intracellular protein, including undruggable targets (e.g., transcription factors and scaffold proteins)[10–12]. Furthermore, PROTACs are potent agents that can circumvent acquired drug resistance by degrading whole proteins after a short drug exposure time and a low dosage[13,14]. Despite being promising, conventional small molecular PROTACs generally display unfavourable pharmacokinetics and lack tumour specificity, which might cause systemic toxicity due to their non-specific distribution in normal tissues[15,16]. Thus, it remains a formidable challenge to achieve tumour-specific delivery and potentiate the antitumor potency of conventional PROTACs.

To achieve tumour-targeted delivery of PROTACs, several ligand modification strategies (e.g., antibody-PROTACs, folate-PROTACs and aptamer-PROTAC conjugates) have been

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