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Perspective

Advanced Delivery System for Improved Medication Distribution during Phase Separation in the Treatment of Cancer

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DESCRIPTION

Understanding biological processes has drawn more and more attention to Liquid-Liquid Phase Separation (LLPS). Condensates produced by LLPS offer particular local conditions for a variety of cellular functions. Utilizing this phenomenon to interfere with cell activity has significant potential for biomedical applications now that the function of LLPS within cells has been clarified. The recently discovered phase separation phenomena in living things were previously restricted to the intracellular space because LLPS requires a congested environment inside of cells. This reduces the potential for LLPS in the development of drugs. An innovative method for treating cancer is the Antibody Drug Conjugate (ADC), which combines monoclonal antibodies with anticancer cytotoxic chemicals for targeted cancer cell delivery. ADCs have had considerable clinical success, and the FDA has approved a number of medications.

However, a significant issue is the drug to Antibody Ratio (DAR) limitation caused by the constrained number of thiol- or amine-groups present on the antibody surface. A challenge for reagent preparation and efficacy assessment is heterogeneity or aggregation, which might result from the production of more copies of a medication. A small therapeutic window and safety problems result from the requirement of low DAR, which limits the choice of the payloads within severely hazardous medicines. To achieve a higher DAR and more efficacies, some organisations have attempted to create new multivalency hydrophilic linkers, such as the Fleximer platform. As an alternative, we created PEDS using LLPS of simple units, which can condensate into homogeneous coacervates holding amounts of payloads, rather than creating a huge complex ADC molecule with high DAR. PEDS consists of two components that can co-phase separate: a Targeting Component (TC) and a Drug Component (DC).

The system is very modular, and each component, including the co-phase separation pair, linkers, the targeting molecule, and the payload, can be changed to deliver different molecules into different tissues. The Single-Chain Variable Fragment (scFv) of cetuximab, which targets the epidermal growth factor receptor (EGFR), and a negatively charged peptide, poly glutamate (polyE), were combined in this report for the anticancer drug delivery. Our positive charged glycine-lysine repeat peptide (polyGK) for DC was chemically attached to the linkers with Monomethyl Auristatin F (MMAF), a commonly used ADC payload that prevents tubulin polymerization.

When combined together, it has been demonstrated that PolyE and PolyGK can phase split due to electrostatic interactions15. As soon as it is administered, TC attaches to the target protein on the cell surface, the DC phase separates with TC to form a condensate, and then the condensates are spontaneously internalised into the targeted cells by the EGFR, leading to cell death. The *E. coli* system was used to express the TC protein, which was then purified using metal affinity resin. Cyanine 3 (Cy3) monosuccinimidyl ester was used to chemically stain it for imaging. In DC, we first used Enhanced Yellow Fluorescent Protein (EYFP) as the fictitious payload for imaging purposes to confirm whether phase separation occurs. Similar to before, this pseudo-DC protein was produced and purified.

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