ABSTRACT

Targeted drug delivery for the treatment of diseases like cancer is a major challenge because of the side effects associated with the available treatment options. A competent delivery system is needed that can address the challenges associated with the delivery of molecules to the target sites. The structural proteins of many viruses can self-assemble spontaneously into virus-like particles (VLPs) under appropriate conditions, which makes them potentially effective nanocarriers for drug encapsulation and delivery.

We have exploited the inherent advantages of an insect nodavirus, Flock House Virus (FHV), to engineer a targeted nano-vehicle for site-specific peptide functionalization, hydrophobic drug encapsulation, and targeted delivery in melanoma and colorectal cancer models, establishing a modular framework for receptor-directed nanotherapeutics.

Since FHV lacks mammalian cell tropism, making use of thiol-maleamide-based conjugation, we have devised a method to attach targeting peptides to FHV virus-like particles (VLPs) via polyethene glycol based crosslinker. The attachment of the peptides transformed the VLPs' lack of tropism and enabled them to selectively bind with the receptors overexpressed on cancer cells. The optimised conjugation protocol ensured the particles' symmetry and overall stability. Further, the natural affinity of FHV for hydrophobic molecules has been utilized for encapsulating hydrophobic chemotherapeutic drugs, like doxorubicin, by transient destabilization and re-stabilization of the capsid via modulation of Ca^{2+} concentration. The resulting modified VLPs exhibited high drug-loading capacity and pH-responsive release behaviour, with minimal leakage at physiological pH and accelerated release under acidic endosomal conditions.

These modified drug encapsulated VLPs have demonstrated controlled and sustained cytotoxic effect primarily through apoptosis in comparison to the rapid and non-controlled cell death induced by free drug. The drug-encapsulated VLPs display high anticancer efficacy in the murine colorectal model, leading to tumour suppression and improved survival. Effective targeted delivery of chemotherapeutic drugs via VLP-based nano-vehicles is expected to address some of the primary challenges associated with cancer therapy. Our work in the growing field of virus nanoparticles opens avenues for engineering ligand-receptor-oriented targeted drug delivery vehicles for cancer therapy.