Abstract

Chemotherapy is still the most widely used anti-cancer treatment. The majority of chemotherapeutics inhibit proliferating cells generally, not selectively cancer cells. The side effects associated with chemotherapy can be partly limited by conjugating a cytotoxic drug with a polymer nanocarrier. Such binding facilitates solubility in aqueous solutions, reduces systemic toxicity; and passively targets the drug directly into the tumour through the enhanced permeability and retention (EPR) effect.

This thesis focuses on testing polymer conjugates based on N-(2-hydroxypropyl)methacrylamide (HPMA) carrying cucurbitacin D (CuD), a naturally occurring compound with potential anti-cancer activity. The mechanism of action is not elucidated yet, but several studies have depicted the inhibitory effect on signal transducer and activator of transcription 3 (STAT3) transcription factor. A STAT3 signalling pathway is overexpressed in several cancer cell lines and is also involved in the differentiation of myeloid-derived suppressor cells (MDSCs).

We examined the therapeutic effect of the HPMA copolymers based on CuD in combined therapy with other polymer chemotherapeutics. CuD conjugates have shown in vitro cytotoxic effect on several model cancer cell lines. The combination with conjugates carrying doxorubicin (Dox) reduced tumour growth in the course of *in vivo* therapy. Moreover, the effect of CuD-based conjugates on blocking the MDSC-mediated immunosuppression over the course of the Dox-based combined therapy was studied.

Keywords: cancer; immune-oncotherapy; cucurbitacin D; STAT3 signalling pathway; MDSCs; HPMA copolymers