POLYMER NANOTHERAPEUTICS FOR OOVERCOMING DRUG RESISTANCE DURING CANCER TREATMENT

ETRYCH Tomáš, BRAUNOVÁ Alena, CHYTIL Petr, ŠÍROVÁ Milada, HEINRICH Anne Kathrin, MÜLLER Thomas, MÄDER Karsten

Institute of Macromolecular Chemistry AS CR, v.v.i., Prague, Czech Republic, EU
Institute of Microbiology AS CR, v.v.i., Prague, Czech Republic, EU;
Martin-Luther-University Halle-Wittenberg, Halle, Germany, EU

Abstract

Beside the development of novel low-molecular-weight anti-cancer agents, new formulations of "classic" cytostatic drugs, so called drug delivery systems (DDS), including their encapsulation into liposomes and nanoparticles or covalent binding to water-soluble polymers and micelles, appear to be a very promising strategy. Described micellar and star polymer-drug conjugates are high-molecular-weight (HMW) drug conjugates designed for enhanced passive tumor accumulation and release of drug in the acidic milieu of a tumor.

The therapeutic efficacy of the conjugates is based on three mechanisms of selectivity toward solid tumors: I) drug accumulation in tumors driven by enhanced permeability and retention (EPR) effect, which results in almost 100 times higher concentration of drug in the solid tumor than in normal tissue, II) pH-dependent release of drug from polymer-drug conjugate, which releases free drug more efficiently at a lower pH in tumors, and III) significant overcoming of drug resistance. The tumor-to-blood and tumor-to-muscle ratio for star and micellar polymer-doxorubicin conjugates increased with time, demonstrating that the conjugates passively accumulate within a tumor mass due to the EPR effect. The anti-tumor activities of linear, micellar and star copolymers containing Dox were compared using a well-defined model of experimental malignant tumor, mouse EL4 T cell lymphoma or various human xenograph models, inoculated in conventional mice or athymic nude mice. The highest efficacy, highest percentage of LTS, was achieved during the treatment with micellar and star conjugates. Moreover, we observed that the pH-sensitive polymer-drug conjugates have the potential to induce excellent antitumor effect without apparent adverse effects in treatment of highly chemotherapy resistant tumor models.

ACKNOWLEDGEMENTS:

This work was supported by the project ''BIOCEV – Biotechnology and Biomedicine Centre of the Academy of Sciences and Charles University'' (CZ.1.05/1.1.00/02.0109), from the European Regional Development Fund and by the Czech Science Foundation (project No. 15-02986S).

Author did not supply full text of the paper.