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Selected doxorubicin conjugates for anticancer therapy

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Abstract

Targeted drug delivery has received considerable attention in recent years, particularly concerning cancer chemotherapy. It seems to be an interesting strategy to overcome biological barriers, including the chemoresistance of cancer cells, and provide the delivery and controlled local release of a usually cytotoxic drug without damaging healthy cells and tissues.

The last few decades have seen impressive progress in the field of biomaterials. Researcher's efforts are aimed at developing a delivery platform that exhibits biocompatibility and increased drug transportation efficiency. The currently used carriers differ in size, charge, as well as the way how drug is coupled to the carrier. The most commonly used cargo platforms include polymer nanoparticles and their conjugates, liposomes, and lipid nanoparticles. Despite the wide range of intelligent biomaterials, they suffer from numerous drawbacks, i.e. low efficiency of drug delivery and release or toxicity to healthy cells. Therefore, there is a need for new, more effective carriers, in addition selectively targeting diverse types of cancer cells. The latter feature has significant clinical potential, but development of such carriers still remains a challenge.

The present dissertation aimed at designing, characterizing, and studying the biological activity of targeted drug carriers as potential tools for the delivery of an anticancer drug, doxorubicin, to cancer cells.

As a result of the current doctoral project, three systems for doxorubicin transportation have been developed: (1) fullerene-doxorubicin conjugate linked covalently via polyethylene (oxide), (2) a conjugate sensitive to the increased activity of matrix metalloproteinases, that is observed in neoplastic cells, and (3) lipid nanoparticles covalently linked with doxorubicin and encapsulated small interfering RNA to repress the bcl-2 gene, resulting in downregulation of the anti-apoptotic protein Bcl-2. All carriers were synthesized and subjected to in vitro experimental studies, utilizing several cancerous cell lines. Then, the most promising systems were additionally studied in vivo. Moreover, theoretical calculations were performed to characterize the developed systems in a more detailed way. The obtained results were in agreement with the experimental data. The outcomes coming from the in vitro and in vivo experiments evaluating the potential cytotoxic and therapeutic effects of the analyzed systems suggest that the enzyme-sensitive conjugate and lipid nanoparticles are promising doxorubicin carriers. The results of this doctoral dissertation contribute to the current knowledge regarding biomaterials as delivery systems used in anti-cancer therapy, as well as their potential role in medical applications and future clinical trials.