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Targeted delivery of cisplatin conjugates with arabinogalactan to tumor using aptamers

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Abstract. The effectiveness of targeted delivery of cisplatin conjugate with arabinogalactan to ascitic Ehrlich carcinoma in vivo using the target ligand, the AS42 aptamer, was studied in this work. Studies conducted on male ICR mice with ascitic Ehrlich carcinoma. Antitumor therapy was carried out with cisplatin and an arabinogalactan-platinum complex (AG-Pt) and an AG-Pt complex modified with aptamers to ascitic Ehrlich carcinoma cells. The toxicity of drugs was determined on the basis of biochemical parameters of blood in healthy mice after 5-fold administration. In our studies, cisplatin treatment of Ehrlich's ascitic carcinoma for 2 weeks led to the death of 6 out of 10 animals. The toxicity of the AG-Pt complex and the AG-Pt complex modified with the aptamer was not revealed. The number of tumor cells during therapy with cisplatin conjugates decreased by 10 times compared with the control. A new promising antitumor drug based on the standard drug cisplatin, which is more effective and less toxic, was presented in the work.

Key words: aptamers, cisplatin, arabinogalactan, targeted delivery, cancer.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

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Introduction

Cisplatin is a highly toxic but effective anticancer drug used to treat various types of malignant tumors. Encapsulation of this drug with polysaccharides (arabinogalactan) [1, 2] and its targeted delivery to the tumor are important ways to reduce its toxicity and increase bioavailability. Here we demonstrate the effectiveness of cisplatin/arabinogalactan targeted delivery to Ehrlich carcinoma in vivo using aptamer AS42 as a targeting ligand.

Material and methods

The cis-dichlorodiammineplatinum based on the interaction of cis-dichlorodiammineplatinum(II) with arabinogalactan was obtained according to the method [3]. Experiments were conducted on male ICR mice with ascites Ehrlich carcinoma. Antitumor therapy was carried out with cisplatin and an arabinogalactan-platinum complex (AG-Pt) and an AG-Pt complex modified with the aptamer AS42 specific to Ehrlich carcinoma cells. The introduction of drugs was carried out on the 3rd, 5th, 7th, 9th and 11th days of tumor development. The number of Ehrlich cells isolated from the abdominal cavity was counted in the Goryaev chamber. The dose of injected cisplatin in the group of mice that were injected with the pure cisplatin was 4 μg/g of animal weight, in the group of mice that were injected with the AG-Pt complex, the dose of cisplatin was 0.52 μg/g, in the composition of the complex modified with the aptamer, the dose of cisplatin was 0.26 μg/g. The toxicity of drugs was determined on the basis of biochemical parameters of blood in healthy mice after 5-fold administration.

Results and discussion

The results of studies of the complex of cisplatin with arabinogalactan indicate that the drug (Cis-AG) is not a mixture, but a product of the interaction of the cis-[Pt(NH3)2Cl2] salt with arabinogalactan (Fig.). In our studies, cisplatin treatment of Ehrlich's ascites carcinoma for 2 weeks led to the death of 6 out of 10 animals. When treated with the AG-Pt complex and the AG-Pt complex modified with aptamers all animals were alive. Mice after treatment with cisplatin did not have ascites cells (dose of cisplatin – 4 μg / g), while in non-treated control animals the tumor volume averaged 14.3×10^9 cells, in mice after treatment with the AG-Pt complex - 100 cells (dose of cisplatin – 0.52 μg/g), while the aptamer-modified AG-Pt complex has 83 cells (the dose of cisplatin is 0.26 μg/g). The toxicity of the AG-Pt complex and the AG-Pt complex modified with the aptamer was not revealed.

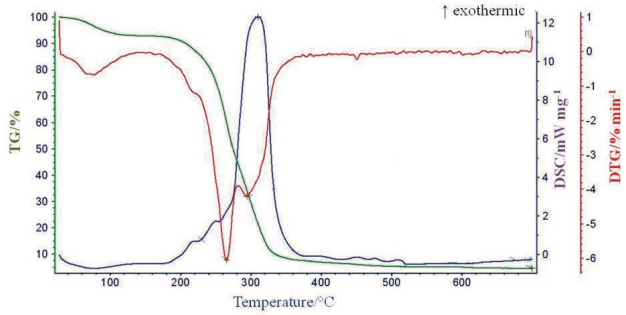

Figure. Thermogram of the drug obtained by the interaction of cis-[Pt(NH3)2Cl2] with arabinogalactan.

Conclusion

Conjugation of cisplatin with arabinogalactan and targeted delivery of the conjugate to the tumor using aptamers reduces the toxicity of cisplatin and increases its antitumor efficacy. Thus, a new promising antitumor drug based on the standard chemotherapeutic – cisplatin, which is more effective and less toxic, was presented in the work.

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