Reduction of non-specific interactions in systems based on PAMAM dendrimers for targeted MRI contrast agent delivery

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Introduction

Non-invasive specific diagnosis of tumor diseases can be achieved by using imaging technics like MRI with contrast agents. Low-molecular contrast agents, suffer from rapid elimination from blood vessels, leading to a rapid decrease in the concentration of the substance. In this regard, it is required to apply higher concentrations of contrast agents, which increases the cost and toxicity of the procedure [1]. For this purpose, it is more suitable to use high-molecular contrast agents, like polyamidoamine (PAMAM) dendrimers with conjugated chelated forms of Gd(III) on its surface. The use of dendrimers which have a lot of terminal surface groups makes it possible to conjugate a large number of chelate groups on the surface, increasing the local concentration of the contrast agent, which greatly increases the relaxation and effectiveness of contrast agent [2]. For more selective tumor contrast, vector molecules which are directed at overexpressed tumor markers on the surface of cancer cells, such as alpha-fetoprotein (AFP) [3], may be used.

Materials and Methods

PAMAM-DOTA conjugate were synthesized using PAMAM-NH2 dendrimers (generations G2 and G3) and DOTA-NHS ester. Conjugation of vector molecule (third domain of AFP (3DAFP)) were done through carbodiimide intermediate. Size and zeta-potential of both products (DOTA-PAMAM G2.0 and DOTA-PAMAM G3.0) were characterized by dynamic light scattering (DLS) and electrophoresis. The number DOTA groups conjugated onto each dendrimer surface were determined by ^{1}H NRM and MALDI-TOF. After chelation the amount of gadolinium were determined by atomic-emission spectroscopy. Specific and non-specific interaction between cells and dendrimers were tested in vitro on MCF-7 and SCOV-3 cell lines.

Results

Synthesized DOTA-PAMAM G2.0 and DOTA-PAMAM G3.0 had an average diameter of 6 to 18 nm and zeta potential in range from +33.8±5.12 mV to -21.8±2,48. The results of 1H NRM shows expected level of DOTA to dendrimer surface and atomic emission spectroscopy data reveals chelation of Gd(III) ions by all DOTA groups. The results of non-specific interactions between PAMAM-DOTA-Gd(III) showed increase of dendrimer binding to cell surface with high positive surface charge, negatively charged macromolecules showed reduced binding. At the same time, negatively charged dendrimers conjugated with 3DAFP showed increased specific binding and accumulation in MCF-7 and SCOV-3 cell lines.

Conclusion

Non-specific interactions of PAMAM-DOTA-Gd(III) greatly depends from zeta potential of macromolecule. Dendrimers with more positive zeta potential binds to the cells non-specifically due to negative charge of cell walls. Negatively charged dendrimers interact with cells less but with addition of vector molecule specifically binds to tumor cells without non-specific binding. This work was supported by the grant of Russian Foundation for Basic Research (No. 18-29- 09022\18).

References

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