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BIOMARKER-DEPENDENT ANTISENSE RELEASING CASSETTE TARGETING GFP

Салимова А. А. (ИТМО)**, Дрозд В. С.** (ИТМО)**, Эльдиб А. А.** (ИТМО)
Научный руководитель – профессор, кандидат химических наук, Колпащиков Д. М.
(University of Central Florida)

Введение. Cancer remains one of the leading causes of death. Traditional methods of cancer treatment, such as radiotherapy and chemotherapy, tend to have many side effects and significantly reduce patients' quality of life due to lack of selectivity. Gene therapy is a promising tool against cancer, but it also has some limitations, one of which is the low selectivity of gene therapy agents. To overcome this disadvantage of gene therapy, we are developing agents based on antisense oligonucleotides (ASO). ASO is one of the most successful approaches in gene therapy. It is already used in the treatment of monogenic diseases [2]. ASO is a class of DNA molecules specifically binds to the target RNA and cleaves it with the help of the enzyme RNase H. The main problem with using ASO in cancer therapy is that ASO itself is not selective and can't distinguish between cancerous and healthy cells [1].

Основная часть. Our goal is to create a selective gene therapy tool based on ASO. It will be selective for cancer cells, i.e. it will have a part that senses cancer markers and activates the therapy only in the presence of cancer markers. The target RNA for the drug will be a housekeeping gene that is essential for the cell's vital activity, so its suppression will cause a cancer cell to undergo apoptosis.

For that purpose, we developed ASO releasing cassette. It consists of 4 oligonucleotides, one of which carries in itself a classical ASO for the RNA of green fluorescent protein (GFP). When the cassette meets the mRNA of oncomarker KRAS (gene that is commonly mutated in 25% of cancers), the oligonucleotides holding ASO form a hairpin and release a part that consists of classical ASO. This ASO binds to GFP target. The target later will be replaced with house-keeping gene. This approach allows us to reach classical ASO’s efficacy (85-90%) in the presence of oncomarker.

Selectivity of the construct towards cells containing the oncomarker was demonstrated in physiological conditions and in cells. However, the efficacy of the cassette was reduced. This is because one of the oligonucleotides holding the ASO part doesn't form a strong harpin and can't release a complete ASO, so only half of the ASO is released. The next step would be to increase the efficiency of the cassette by improving harping of the oligonucleotides.

Выводы. Cassette for releasing ASO is a promising tool in cancer therapy. It can be adapted to different types of cancer and targeted to different housekeeping genes, making the technology highly personalized.

Список использованных источников:

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