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SELECTION OF NOVEL TARGET GENES FOR ANTISENSE OLIGONUCLEOTIDE-BASED THERAPY IN COLORECTAL CANCER *

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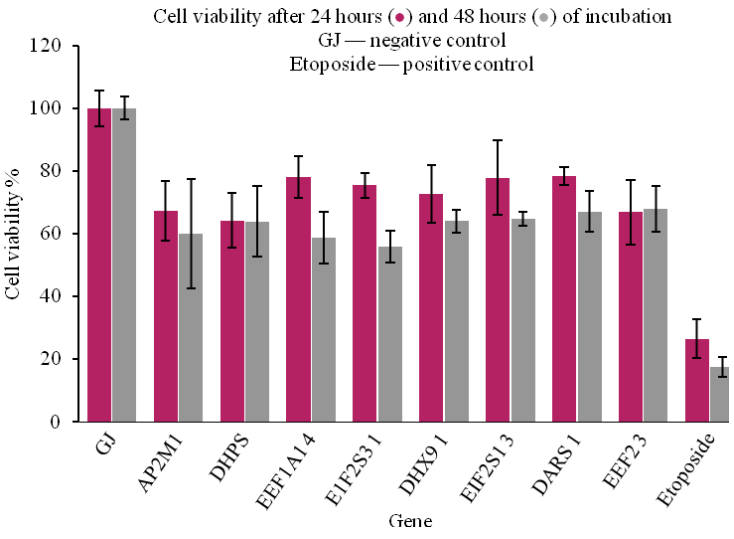
Abstract

Potential housekeeping genes were selected to test cytotoxicity of antisense oligonucleotides (ASOs) in colorectal cancer cells. Eight ASOs showed 33–44 % cell viability reduction in HCT-116 cell line. The agents that showed the greatest cytotoxicity were selected for further examinations.

Cancer is one of the leading causes of death worldwide and colorectal cancer is one of the most aggressive and difficult cancers to treat. Traditional methods of its treatment, such as radiation and chemotherapy, are associated with side effects and a high probability of recurrence. In this regard, new methods and approaches in treatment are currently being developed. One of the potential methods is gene therapy, which makes it possible to inhibit tumor development using antisense oligonucleotides (ASO) that suppress the expression of housekeeping genes in cancer cells [1]. ASOs are short sequences of nucleic acids that selectively hybridize with the messenger RNA (mRNA) target, which activates RNase H1, which cleaves the ASO/RNA duplex. As a result of mRNA's cleavage, essential proteins encoded by this mRNA are not formed, which potentially leads to activation of programmed cell death — apoptosis [2]. One of the most significant challenges for cancer gene therapy is the choice of a suitable target that will lead to cell death instead of suppressing proliferation

The aim of this research is to investigate the cellular response to antisense oligonucleotides targeting housekeeping genes in HCT 116 cancer cell line (human colorectal carcinoma). To determine targets in HCT-116 cell line, online databases such as DepMap and OGEE, which provide information on essential genes in diverse cell lines, were used. As a result, the following 13 housekeeping genes were selected for further examinations: DHX8, DHX9, CSE1L, DARS1, DHPS, COPB1, AP2M1, DYNC1I2, EEF1A1, EEF2, EIF2S1, EIF2S3, PSMB2. To conduct primary screening of the targets MTT cytotoxicity test for 24- and 48-hours transfections was carried out. Based on obtained MTT results, 8 ASOs showed 32–44 % cell viability reduction and were selected for further secondary screening: AP2M1, DHPS, EEF1A1, E1F2S3, DHX9, DARS 1, EEF2 (see figure).



Results of MTT cytotoxicity test for the most efficient agents

Obtained results point out potential usage of ASOs in colorectal cancer treatment. Further experiments are going to be conducted to prove the efficiency of our selected ASOs, to confirm the gene knockdown, and to investigate the type of resulting cell death, in order to select the best agent to treat colorectal cancer.

References

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