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ANTISENSE-BASED MARKER-DEPENDENT AGENTS FOR TARGETING HOUSEKEEPING GENES

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Introduction. Gene therapy holds significant promise in cancer treatment by offering targeted approaches to suppress disease-related genes. However, many existing therapies lack the specificity needed to differentiate between cancerous and normal cells, leading to potential off-target effects. While antisense oligonucleotide (ASO)-based therapies have been successfully developed for several genetic diseases, their application in cancer treatment is still limited due to challenges in selectivity and efficacy [1].

This study aims to address these limitations by developing marker-dependent antisense DNA agents that target housekeeping genes selectively based on the presence of specific oncomarkers. The research follows a structured optimization approach, progressing from the classical Antisense Releasing Cassette (ARC) to the enhanced 3T-ARC, culminating in a highly selective final design for ERBB2 oncomarker targeting Dync mRNA [2,3]. This approach seeks to improve the precision and therapeutic potential of ASO-based gene therapy in oncology.

Main Body. Gene therapy holds great potential for cancer therapy by providing targeted delivery of strategies that aim to inhibit genes associated with the disease. Most of the current therapies, however, do not have enough specificity and are thus unable to distinguish between normal and cancer cells, causing eventual off-target effects. Although ASO-based therapies have been developed for several genetic diseases, their use in oncological therapy is hampered by issues of low selectivity efficacy and efficiency or high cytotoxicity causing side effects.

Targeting housekeeping genes is a potentially effective approach to gene therapy, given that these genes are essential for cellular function and frequently play a significant role in cancer cell survival. In this work, we selected the DYNC mRNA as a target that codes for a protein participating in intracellular transport and force generation—a process essential for the maintenance of cellular integrity and function. Targeting this specific gene only in the presence of high ERBB2 oncogene expression we aim to attain high selectivity with the concomitant reduction in the risk of off-target effects [4].

Conclusions. The ultimately optimized design, which merges Antisense oligonucleotide Releasing Cassette (ARC) technology and is directed against DYNC mRNA, attained 73% cleaved of target mRNA in the present of Erbb2 compared with almost no activation in its absence. The strategy demonstrated enhanced activity and precise selectivity in targeting housekeeping genes, thereby offering a potentially useful therapeutic regimen characterized by minimal off-target effects. The findings validate the prospects of ASO-based gene therapy in cancer treatment, particularly via the marker-dependent targeting of housekeeping genes.

Список использованных источников:

1. J. H. Schulte, S. Horn, T. Otto, B. Samans, L. C. Heukamp, U.-C. Eilers, M. Krause, K. Astrahantseff, L. Klein-Hitpass, R. Buettner, A. Schramm, H. Christiansen, M. Eilers, A. Eggert and B. Berwanger // International Journal of Cancer. – 2008. – 122. – 699–704.

2. C. Y. Ooi, D. R. Carter, B. Liu, C. Mayoh, A. Beckers, A. Lalwani, Z. Nagy, S. De Brouwer, B. Decaesteker, T.-T. Hung, M. D. Norris, M. Haber, T. Liu, K. De Preter, F. Speleman, B. B. Cheung and G. M. Marshall // Cancer Research. – 2018. – 78. – 3122–3134.

3. S. A. Roth, Ø. H. Hald, S. Fuchs, C. Løkke, I. Mikkola, T. Flægstad, J. Schulte and C. Einvik // Oncotarget. – 2018. – 9. – 18160–18179.

4. E. Mogilyansky, I. Rigoutsos // Cell Death Differ. – 2013. – 20. – 1603–1614.