STRESZCZENIE W JĘZYKU ANGIELSKIM

The ultimate goal of modern anti-cancer therapy is to achieve the appropriate therapeutic effect and to ensure complete remission of the disease, with subsequent limiting of adverse effects associated with systemic chemotherapy and reducing the drug resistance of cancer cells. A number of literature reports present a significant potential of compounds characterized by a membrane activity in increasing the intracellular concentration of anticancer drugs, as well as demonstrates the possibility of using nanomaterials as biocompatible and highly effective drug carriers. Considering this, it is suggested that the employment of natural antimicrobial peptides (AMPs) and/or their synthetic analogs from ceragenin group (CSA), as well as the use of iron oxide-based magnetic nanoparticles as drug carriers may constitute an innovative therapeutic approach, applicable in modern oncological therapy.

The aim of this study was to determine the anti-tumor activity and the mechanism of action of magnetic nanoparticles functionalized by analogs of cationic antibacterial peptides from the ceragenin group against breast cancer cells. To achieve this goal, the LL-37 peptide, being the only representative of the natural antimicrobial peptides (AMPs) from the cathelicidin family occurring in the human body, and its synthetic steroid analog, ceragenin CSA-13, the best-known representative of this class of compounds, were immobilized on the surface of iron oxide-based magnetic nanoparticles to develop nanosystems with membrane activity (MNP @ LL-37 and MNP @ CSA-13).

The research was performed using MCF-7 (ATCC® HTB-22 ™) and MDA-MB-231 (ATCC® HTB-26 ™) breast cancer cell lines. Colorimetric and cytofluorimetric methods were used to assess the cytotoxicity of the analyzed compounds. The analysis of mechanism of action, including the assessment of apoptosis degree and DNA fragmentation, evaluation of alternations in mitochondrial potential of cells, activation of caspases, as well as the intensity of reactive oxygen species generation and quantitative changes in intracellular glutathione levels was carried out by flow cytometry and fluorescence microscopy. The intracellular internalization and location of tested cells within the treated cancer cells were determined using confocal microscopy. At each stage of the research, the activity of membrane active compounds was compared with the activity of the agents immobilized on the surface of magnetic nanoparticles, as well as with the activity of unmodified iron oxide-based nanoparticles.

In this study, a statistically significant reduction in survival of breast cancer cells in the response to treatment with synthetic analog of AMPs, ceragenin CSA-13 and its magnetic counterpart immobilized on the surface of magnetic nanoparticles i.e. MNP@CSA-13 was observed. Above was determined by disruption of the oxidative balance of cancer cells, a decrease in the activity of antioxidant factors followed by induction of oxidative stress, an increase in mitochondrial membrane permeability, depolarization of the mitochondrial membrane and caspase activation. It was also shown that immobilization of ceragenin on the surface of iron oxide-based magnetic nanoparticles and thus the use of nanostructures as drug carriers, significantly increases the antitumor activity of analyzed analog, mainly by enhanced intracellular internalization with subsequent increase in agent intracellular concentration and by exacerbation of alternation in the oxidative balance of cancer cells. Above observations suggests a possible employment of magnetic nanoparticles-based nanosystems in therapy of drug resistant cancers.

The results obtained during this research indicate the possibility of the employment of synthetic analogs of AMPs from ceragenins group in an effective eradication of cancer cells, suggest the possibility of development of innovative tumor therapies based on the membrane-active compounds and their nanosystems, and justify further research in this area.