Секция «Экспериментальные исследования»

Hsp70 promotes the epithelial-mesenchymal transition in DLD1 human colon cancer cells.

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Colorectal cancer is the third most common tumor type worldwide and the second most fatal. Extremely high mortality of patients with this type of tumor is the increased metastatic activity of cancer cells associated with their phenotypic conversion within epithelial-mesenchymal transition (EMT). During this process epithelial cells activate a program to remodel their structure and achieve a mesenchymal fate. EMT is controlled by a few of transcription factors (Snail, Slug, Twist) regulating the expression of E-cadherin and vimentin. Among the factors contributing to colorectal cancer, is hyperglycemia which is usually associated with diabetes and mortality of which is elevating per se and increasing the risks of death of colorectal cancer. This study aimed to find additional links between above pathologies as the potential target for drug therapy. Therefore, the study of mechanisms of this relationship and also the identification of participants can lead to the emergence of new approaches in the treatment of colorectal cancer.

We explored the role of Hsp70 in EMT by analyzing the effect of the protein level on fundamental EMT markers. The DLD1 cell line with knockdown of Hsp70 and the substance U-133 were used to study the development of the EMT in cells with low and high levels of Hsp70 expression; to induce EMT the cells were kept on a medium with high glucose (80 mM) for a week. Thereafter, cell proliferation and migration were assessed using xCELLigence system and wound healing assay. We performed qPCR and western blotting to analyze the change in levels of mesenchymal and epithelial markers; the confocal microscopy was used to study localization of E-cadherin. The results indicated that high glucose and U-133 enhanced cell migration and the expression of transcriptional factors, whereas the level of E-cadherin was reduced. At the same time, the ability to migrate for DLD1shHsp70 decreases below the value typical of control cells, and there was no increase in the level of vimentin. Our results approved that reducing the expression of Hsp70 in carcinoma cells one can suppress EMT.

Then we studied the influence of Hsp70 inhibitors of on the EMT. We have chosen PES to suppress the chaperone activity of the protein and CL-43[1] to down-regulate its synthesis. Using the same methods we showed that the use of both inhibitors led to a decrease in the cell migration, as well as the recovery of E-cadherin expression together with a reduction in the level of EMT-modulating transcription factors.

We conclude that the elevation of Hsp70 expression can promote EMT, while using the chaperone inhibitors may reduce colorectal cancer cell metastasis.

This work was supported by Grant of Russian Scientific Foundation № 19-74-20161.

References

1) Nikotina A.D. et al. assigned to your manuscript by replying to this message. Discovery and optimization of cardenolides inhibiting HSF1 activation in human colon HCT-116 cancer cells.