Dual effect of methylation of lncRNA genes on pathogenesis and metastasis of ovarian cancer

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Ovarian cancer (OvCa) is asymptomatic and still the most deadly cancer of the female genital tract worldwide. The discovery of noncoding RNAs (ncRNAs) involved in epigenetic processes opens up new opportunities in the study of the pathogenesis of cancer. Aberrant DNA methylation is an important mechanism for regulating the expression of both protein-coding and ncRNA genes. However, the role of methylation in the regulation of genes of long noncoding RNAs (lncRNAs) is still very little studied. So the aim of this work is to identify new hypermethylated lncRNA genes in ovarian tumors and their effect on OvCa metastasis. Using quantitative methylation-specific PCR and nonparametric Mann-Whitney test we observed a multiple and statistically significant ($p < 0.001$) increase in the methylation level of a group of lncRNA genes: MEG3, SEMA3B-AS1, ZNF667-AS1 and TINCR. All our resuts we found for the first time. Analysis of 19 samples of peritoneal metastases in comparison with paired primary tumors unexpectedly revealed a statistically significant decrease in the methylation level of the same 4 genes: MEG3 ($p = 0.004$), SEMA3B-AS1 ($p = 0.002$), TINCR ($p = 0.002$), and ZNF667- AS1 ($p < 0.001$). This phenomenon, which we discovered, is apparently associated with the participation of these lncRNAs in the regulation of plastic reversion of EMT - MET. So EMT - MET reprogramming of cells, a decrease in methylation of lncRNA genes activates the suppressive functions of lncRNAs, and may play a role in stabilizing the epithelial properties of secondary tumors. Thus, long ncRNAs have a dual effect on OvCa tumors and metastasis which is important for understanding the pathogenesis of OvCa and for finding new targets for therapy. The described effects of hypermethylated lncRNA genes on tumors and metastases (secondary tumors) of OvCa are under validation via expression studies. The work was supported by the grant from the Russian Science Foundation #20-15-00368.

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