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Protein arginine methyltransferase 5 in the pathomechanism of human lung cancer

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Cancer accounts for 35 percent of deaths, of which various types of lung cancer are the leading causes of death. Genetic mutations, epigenetic modification and the altered gene expressions of tumor suppressors can promote the development of lung cancers. As the diagnostic methods evolve for genetic and biomarkers, specific tumor-specific mutations can be identified that allow individualized targeted therapy. Protein arginine methyltransferase 5 (PRMT5) is a potential protooncogene that results in the inhibition of gene expression through symmetric dimethylation of histone proteins. PRMT5 is regulated by RhoA-activated protein kinase (ROK) and myosin phosphatase (MP) through its Thr80 activating phosphorylation site. PRMT5 mutations and modifications as potential tumor markers were analyzed by biochemical, molecular biological, and genomic studies in human samples in human planocellular and adenocarcinoma lung tumors. Genomic DNA was isolated from control (out-of-infiltration zone) and tumor tissue samples and the vicinity of the PRMT5 regulatory site was sequenced to identify possible mutations. Tissue samples were analyzed by semi-quantitative Western blot analysis to assess the expression levels and post-translational modifications of myosin phosphatase subunits, PRMT5, and histone proteins. While the level of the catalytic subunit of myosin phosphatase was unchanged, that of the regulatory subunit (MYPT1) decreased, and the phosphorylation of the MYPT1 inhibitor Thr696 regulatory site was significantly increased in tumor samples compared to non-tumor samples. The expression levels of PRMT5 and histone did not change in the tumor samples, however, Thr80 phosphorylation and symmetric dimethylation of histone, which indicate PRMT5 activity, were also increased. Analyzing the patient database, we found that genetic and posttranslational changes correlated with the stage of lung tumors. Our results suggest that disruption of the MP-PRMT5-histone signaling pathway plays a role in the development of lung tumors and further investigation is a promising target for tumor diagnosis. Our results suggest the tumor suppressor role of MP via inhibition of PRMT5 thereby regulating gene expression through histone arginine dimethylation.

Keywords: lung cancer, methylation, phosphorylation, myosin phosphatase, posttranslational modification