ABSTRACT

The aim of the presented thesis is to introduce modern molecular methods that may contribute to deepening our knowledge of pulmonary carcinogenesis. Furthermore, we would like to point out the significance of immunohistochemistry in differential diagnostics of the most common primary pulmonary and pleural neoplasms.

Lung carcinoma of all histological subtypes is a result of stepwise accumulation of genetic and epigenetic changes, including allelic losses (LOH), chromosomal instability and imbalance, oncogene and tumor suppressor gene mutations, epigenetic silencing by promotor hypermethylation or aberrant gene expression guidinig cell proliferation. In our study, certain genetic changes were detected in squamous cell carcinomas (SCC) of the lung, their precancerous lesions as well as in normal bronchial mucosa in a selected group of heavy smokers with limited ventilation. We investigated the relation between molecular changes of LOH type in chromosomal regions harbouring mismatch repair genes and cell cycle regulators and human telomerase reverse transcriptase (hTERT) mRNA expression. We also evaluated the relation between these molecular changes and histologic pattern in bronchial mucosa in this patient group. hTERT mRNA expression analysis in correlation with LOH in bronchial mucosa of heavy smokers suggests that it represents one of the first events in the multistep process of pulmonary SCC carcinogenesis. Autofluorescence bronchoscopy, a novel sensitive imaging method for detection of premalignant bronchial lesions, has not shown higher effectivity in comparison to standard white light bronchoscopy. Nevertheless, this method may assist to obtain valuable information concerning evolution of bronchial preinvasive lesions and early carcinomas. We believe that it may contribute to the identification of reliable and sensitive molecular markers of invasive carcinoma in the future.

Diffuse malignant mesothelioma (MM) represents only 0,16 % of all malignant tumours, but is the most common primary pleural malignancy. From the pathologist's point of view, its significance resides in histological differential diagnosis towards adenocarcinoma metastasizing or infiltrating into the pleura, especially of primary lung origin. Immunohistochemistry plays an essential role in this field. In the long term, new antibodies with increased diagnostic sensitivity and specificity, and eventual prognostic or therapeutic significance, are searched for. From a broad scale of relevant immunohistochemical markers, we validated a panel combining „positive" (calretinin and D2-40) and „negative" markers (MOC-31 and TTF-1) with the highest sensitivity and specificity. Our further work comprises the analysis of immunohistochemical expression of carboanhydrase IX (CAIX), a member of metalloproteinases regulating pH homeostasis. Its positivity was observed in virtually all MM as well as in normal and reactive mesothelia and in various metastatic carcinomas. Our results suggest that CAIX may neither be used as a reliable diagnostic marker of malignancy in pleural effusions nor a differentiation tool between neoplastic (mesothelioma) and reactive mesothelial proliferations. Nevertheless, these data support the concept of organ selective isoenzyme-specific CAIX inhibition as a potential target in patients with advanced MM.