

bronchopulmonary carcinoid tumors in relation to the immunohistochemical expression of Bcl-2 family proteins Bax and Bcl-2 and correlate it with clinical and histopathological variables. We analyzed Bax and Bcl-2 expression in 44 patients subjected to resection of bronchopulmonary carcinoid tumor, using immunohistochemistry technique. This study involved 43.2% men and 56.8% women with an average age of 38.8 years. Considering the tumor size they presented a mean of 28.3 mm. Bax and Bcl-2 proteins were expressed in 16 (36.4%) and 22 (50.0%) tumors, respectively. Univariate analysis found significance between positive immunostaining for Bax and lymph node metastasis ($P=0.024$) and death ($P=0.024$). There was no significant relation between Bcl-2 expression and the study's variables. The association between Bax and lymph node metastasis is important in clinical practice, once they may determine the prognosis of bronchopulmonary carcinoid tumor. Further series are required to fully assess the role of Bcl-2 family protein expression in these tumors, reaffirming the relevance of apoptosis studies.

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PUBLICATION

Heparanase expression in lung carcinoid tumors by immunohistochemistry

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At present, there is no immunohistochemistry marker that reliably predict which pulmonary carcinoid will behave aggressive. So, we focus our studies to investigate a possible new marker for lung carcinoid tumors and we choose heparanase, an endo- β -glucuronidase, that seems to be involved in tumor development promoting degradation of heparan sulfate proteoglycans. We analyzed heparanase expression in 40 patients subjected to resection of lung cancer comparing with 28 normal lung tissues obtained from non neoplastic area at the same patients. Immunohistochemistry assay was performed using polyclonal antibody HPA2-C17 (Santa Cruz). We analyzed 10 microscopic fields at a magnification of 400x using ImageLab 2000 software. The variables considered were: sex, age, specific localization, histologic criteria, tumor size, presence of metastasis and percentage of positive cells for heparanase expression. Association between variables was assessed by univariate analysis by Students t-Test for parametric variables using the SPSS10 software. This study involved 59% men and 41% women with an average of 39.16 years old; 88% of lung carcinoids represented typical tumors; however, 12% were atypical. Tumor size mean was 29.55 mm and only 30% of the patients had metastasis. We observed a significant difference between heparanase expression and lung carcinoids comparing with normal tissues ($p<0.0001$), since 75% of carcinoids tumors were positive for heparanase immunohistochemistry, while 100% of normal tissues were negative. In addition we also obtained a relation between tumor size ($p<0.0001$) and heparanase expression ($p=0.022$) in atypical lung carcinoids. This study validated the importance of heparanase expression to explore the presence of lung carcinoid. In addition, we conclude that atypical lung carcinoids presented a higher heparanase expression and bigger tumor size when compared with typical carcinoids which are less aggressive tumor. (Supported by FAPESP, CAPES and NEPAS).

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PUBLICATION

Methylenetetrahydrofolate reductase (MTHFR) polymorphisms affect chemotherapy response in lung cancer patients

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A growing body of evidence indicates that folate status during chemotherapy might influence chemoresponse and long-term survival. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme crucial to the folate pathway. This study investigated whether the previously described SNPs *MTHFR* C677T and *MTHFR* A1298C have an influence on chemotherapy response in lung cancer patients. In both SNPs, the variant allele is

known to reduce enzyme activity, causing aberrant methylation among other possible effects. For 349 Caucasian patients with primary lung cancer (162 SCLC, 187 NSCLC) that were recruited in the Thoraxklinik Heidelberg from 1999 to 2004, the response to first line chemotherapy after the 2nd cycle was assessed according to the response evaluation criteria in solid tumours (RECIST). DNA was isolated from peripheral blood and genotyped for *MTHFR* polymorphisms by PCR followed by fluorescence based melting curve (LightCycler[®]) analysis. Genotype frequencies were compared in responders (complete or partial tumour remission) and non-responders (stable or progressive disease). Presence of at least one *MTHFR* 1298 C variant allele was significantly associated with better chemoresponse (OR 0.26, 95% CI 0.11 – 0.61) in SCLC patients who received etoposide, while no correlation was observed for the *MTHFR* 677 variant allele in the same group (OR 1.31, CI 0.57 – 3.02). One previous study (Alberola et al., Clin Lung Cancer, 2004) examined the influence of the *MTHFR* C677T polymorphism on chemoresponse in NSCLC patients and found no significant differences. In contrast, we found the presence of at least one *MTHFR* 677 T allele to be significantly predictive of a better outcome in NSCLC patients who received chemotherapy with either cis- or carboplatin (OR 0.44, CI 0.21–0.92), while the *MTHFR* A1298C polymorphism showed no significant correlation in this group.

In conclusion, different variant alleles, both associated with reduced enzyme activity, were found associated with favourable chemotherapy response in the two main groups investigated. Whether this predictive function of the two *MTHFR* polymorphisms is the result of different mechanisms affecting enzyme activity or is due to differences between the two histological groups of SCLC and NSCLC tumours or due to the different choices of chemotherapeutic drugs remains to be further investigated. Funded in part by the "Deutsche Krebshilfe" (H.D., B.J.)

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PUBLICATION

Increased risk for non-small cell lung cancer in carriers of a genetic functional variant in leptin gene

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Background: Leptin is a pleiotrophic hormone with angiogenic and proliferative potential. The long isoform leptin receptor is present in the lung, suggesting a possible peripheral action of this hormone in that organ. Leptin is further associated to the development of several cancer types in organs where it interact with cell receptor.

Material and methods: In this study, 140 patients with histological diagnose of Lung Cancer and 341 healthy controls were genotyped for a leptin gene functional variant (*LEP*-2548 G/A).

Results: In this study, the homozygous AA genotype of the polymorphism in the 5' flanking region of the leptin gene was found to be associated to lung cancer ($P=0.011$). This overexpressing genotype increased by 2-fold the risk for non-small cell lung cancer ($P=0.015$). Age-adjusted logistic regression analysis in men indicates an association of AA genotype with all lung cancer cases (OR, 3.23; 95%CI, 1.49–7.02), non-small cell lung cancer type (OR, 3.41; 95%CI, 1.54–7.59), and the histological subtypes squamous cell carcinoma (OR, 3.19; 95%CI, 1.26–8.13) and adenocarcinoma (OR, 4.29; 95%CI, 1.64–11.72). Furthermore, multivariate logistic regression analysis confirmed the AA genotype (OR, 2.57; 95%CI, 1.34–4.92), male gender (OR, 13.16; 95%CI, 6.86–25.24) and age over 63 years (OR, 2.27; 95%CI, 1.41–3.66) as risk factors, demonstrating the independent association of AA genotype and lung cancer development. Kaplan-Meier analysis showed a younger age for lung cancer onset in AA carriers, in comparison to non-AA carriers (log rank test, $P=0.023$).

Conclusions: This study provides evidence of a role for the genetic *LEP* functional variant in non-small cell lung cancer. Our results suggest an etiopathological role for leptin in lung cancer and support the hypothesis of *LEP* functional polymorphism influence in cancer behaviour.

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PUBLICATION

Relationship between expression of xiap protein in operable non-small cell lung carcinomas and apoptosis index and postoperative prognosis

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Background: Dysregulation of apoptosis plays an important role in carcinogenesis, tumor progression, and resistance to chemotherapy. X-linked inhibitor of apoptosis (XIAP) is considered to be the most potent