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Aberrant pattern of histone H4 modification in human lung carcinoma

A. Van Den Broeck[1], B. Eymin[1], D. Moro-Sibilot[1], S. Lantuejoul[1], C. Brambilla[1], E. Brambilla[1], S. Gazzeri[1]
[1]INSERM U823, Team 2, Grenoble, France

Post-translational modifications in the tails of nucleosomal core histones have a crucial role in chromatin packaging, gene expression and genome stability. Therefore, perturbation of this epigenetic information is likely to be involved in the development of cancer. Although some studies identified an altered activity of histone-modifying enzymes in tumors, little is known about the post-translational modifications of histones in these malignancies. By using immunohistochemistry, western blotting and specific antibodies, we have analyzed acetylation and methylation of histone H4 in normal lung and non small cell lung cancers. We found that cancer cells displayed a profound distorted pattern of histone H4 modifications with hyperacetylation of H4K5 or H4K8, hypoacetylation of H4K12 and H4K16 and loss of H4K20 trimethylation. Modification of histone H4 acetylation was not associated with size, stage and invasion of the tumors. Alteration of H4K20 trimethylation was frequent in squamous carcinoma and was observed in early precursors lesions in which the level of H4K20me3 staining strongly decreased with disease progression. In adenocarcinoma, the downregulation of H4K20me3 was less frequent but allowed the identification of a subgroup of stage I adenocarcinoma patients with reduced survival (p=0.024). By using quantitative RT/PCR we showed that loss of H4K20me3 was associated with the downregulation of Suv4-20h2 expression (p=0.019), a histone methyltransferase involved in telomere length maintenance. Our findings indicate an important role of histone H4 modifications in bronchial carcinogenesis and highlight H4K20me3 as a candidate biomarker for early detection and therapeutic approaches of lung cancer.

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Clinicopathologic aspects of SHP2 expression in gastric carcinoma

S.S. Kim[1], J.S. Kim[1], H.K. Kim[1], H.S. Chae[1], S.W. Han[2], O.R. Shin[3]
[1]Uijongbu St. Mary's Hospital, Internal Medicine, Uijongbu City, Korea; [2] Holy Family Hospital, Internal Medicine, Pucheon City, Korea; [3] Uijongbu St. Mary Hospital, Internal Medicine, Uijongbu City, Korea

Background: SHP2, a nonreceptor protein tyrosine phosphatase encoded by the PTPN 11gene, plays important roles in growth and cytokine signaling, and regulates numerous cellular processes. Deregulation of SHP2 can induce sustained intracellular signal-regulated kinase (ERK) activation through RAS-dependent and independent mechanism and related to carcinogenesis. Altered expression or mutation of SHP2 is linked to many malignant tumors including gastric cancer. This study was aimed to investigate the SHP2 expression in gastric cancer in association with clinicopathologic parameters. Materials and methods: We examined specimens taken from 92 cases of gastric cancer during gastrectomy. The expression of SHP2 protein was examined by immunohistochemistry. The intensity score of SHP2 was measured by comparing to its intensity in gastric mucosa from healthy person. Results: Intensity score of SHP2 was 0 in 14 cases (15%), 1 in 59 cases (64%), 2 in 19 cases (21%) with gastric carcinoma. The tubular carcinoma had significantly higher expression of SHP2 than signet ring cell type carcinoma (1.29 vs. 0.48, P=0.00). In the tubular carcinoma, the mean score was different according to the differentiation of tumor (well/moderately/poorly differentiated, 1.0/1.10/1.58 respectively; P=0.00). Lauren's intestinal type had higher expression than diffuse type carcinoma (1.26 vs.0.93; P=0.46). Advanced gastric cancer showed higher expression than early gastric cancer (1.14 vs. 0.86; P=0.03). In the tubular carcinoma, SHP2 score was well correlated with survival time (R=0.317; P=0.011). There was no difference of SHP2 expression according to TNM staging and location of the tumor in the stomach. Conclusion: SHP2 protein seems to be useful as tissue biomarker for the gastric carcinoma, especially in the tubular carcinoma.

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Prognosis of estrogen-regulated cathepsin D in pT2,3pN+ breast cancer

M. Markicevic[1], D. Nikolic-Vukosavljevic[1], Z. Neskovic-Konstantinovic[1]
[1]Institute of Oncology & Radiology of Serbia, Experimental, Belgrade, Serbia

The purpose of the study was to asses whether the expression of estrogen-induced protein cathepsin D might facilitate biological subgrouping of patients with breast carcinomas and its potential applicability in clinical oncology.

The study included 201 patients with histologically verified breast carcinomas. Clinico-pathological findings were classified according to age, menopausal status, tumor size, histological grade and regional lymph node status. Steroid hormone receptors' (ER and PR) as well as cathepsin D protein concentrations were assayed on the same breast tumor cytosolic extract in accordance with the recommendation of EORTC. The results were analyzed using non-parametric statistical methods.

A statistically significant direct correlation was observed between cathepsin D expression and auxiliary node status. The expression of cathepsin D protein was related to both ER and PR status. Baseline levels of cathepsin D expression were found in patients with steroid hormone receptor-negative status and either node-negative status (pN-) or tumors less than 2 cm (pT1). The highest cathepsin D protein level observed in these two ER, PR-negative TN-stage favorable subgroups was considered as the cut-off value (38,7 pmol/mg). This and higher values defined estrogen-regulated expression of cathepsin D. Evaluation of disease free interval in the first three years, among patients bearing pT2-3 pN+ carcinomas, revealed a statistically significant difference between estrogen-regulated and non-estrogen-regulated cathepsin D expression. A favorable course of disease was observed in patients with carcinomas expressing estrogen-regulated cathepsin D expression. This difference within pT2-3 pN+ subgroup of breast cancer patients was not caused by applied adjuvant treatment since chemo- or hormonal therapy, either alone or in combination, were evenly distributed among patients.

The results indicate possible role of cathepsin D in breast cancer prognosis by providing the tool to discriminate patients with different risk of disease progression. Our findings are also in accordance with the proposed role of cathepsin D in apoptosis, i.e. that cathepsin D overexpression stimulates induced apoptosis.

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Different EGFR expression between colorectal cancer tissue and adjacent normal mucosa

D.Y. Hwang[1], H.J. Lee[2], E.J. Jung[1]
[1]Korea Cancer Center Hospital, Dept of Surgery Section of Colorectal Surgery, Seoul, Korea; [2] Korea Cancer Center Hospital, Laboratory of Functional Genomics, Seoul, Korea

-Background: EGFR is involved in malignant transformation and tumor growth through PI3K-Akt and Ras-Raf-MAPK pathways that influence cell proliferation and survival. The treatment of cetuximab and bevacizumab in combination with chemotherapy has been active in patients with metastatic colorectal cancer. Nevertheless anti-tumor effects of cetuximab and bevacizumab, there is no establishment about a biological pathway to be responsible for anti-tumor effects of these agents and a marker to predict effects of these agents.

-Purpose: Colorectal cancer patients with EGFR negative tumor as determined by immunohistochemistry have responded with cetuximab. Targeted agents such as cetuximab and bevacizumab are targeted not on tumor but on molecules. Analysis about targeted molecules expression should be done using more consistent and quantitative method both in tumor and adjacent normal tissue. So we investigated gene expressions of EGFR using quantitative real time PCR in colorectal cancer tissues and corresponding normal mucosa.

-Methods: Fifty pairs of primary colorectal cancer and corresponding normal mucosa were analyzed in our study. RNA isolation were done from tissues to be stored at -80°C and gene expressions of EGFR were analyzed using Taqman probe by real time PCR.

-Results: EGFR was measurable in all samples both tumor and normal tissues. Median EGFR mRNA level is higher in normal mucosa than in colorectal cancer (8.94×10^{-3} vs. 4.97×10^{-3}, $p<0.0001$). There is a positive correlation for EGFR expression between colorectal cancer and normal mucosa (Spearman rank correlation, $r = 0.463$, $p<0.001$). In EGFR expression according to TNM stages, at stage I EGFR is more expressed in colorectal cancer than in normal mucosa, but at stage II-IV, EGFR is more expressed in normal mucosa than in colorectal cancer.

-Conclusions: Gene expressions of EGFR are measurable both colorectal cancer and normal mucosa and there is a positive correlation between colorectal cancer and normal mucosa. This suggests a common regulator for EGFR both in tumor and normal mucosa might be exist. Interestingly, at stage I EGFR overexpression in tumor switch over EGFR overexpression in normal mucosa at more advanced stage.