PATOLOGIA SPERIMENTALE

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Background. Surfactant protein D, also known as SP-D, is a collagenous glycoprotein encoded by SFTPD gene belonging to the collectins family (collagen-containing C-type lectin). SP-D is a pattern recognition molecule that has pulmonary as well as extra-pulmonary localization ¹. In addition to its canonical role in the maintenance of surfactant homeostasis in the lung, SP-D plays a critical role as regulator of immunity and inflammation ². We have performed a bioinformatics analysis to investigate whether SP-D can be considered as a potential prognostic marker for human epithelial malignancies by focusing on carcinomas of the lung, stomach, breast and ovary. Subsequently, by immunohistochemistry, we have investigated the expression of SP-D in the same healthy human tissues and in their malignant counterparts.

Methods. For the bioinformatics analysis we used Oncomine, a cancer microarray database (www.oncomine.org), which allowed evaluating the expression level of SFTPD gene in different types of cancer and to compare the differences in mRNA level between normal and neoplastic tissues ³. The prognostic significance of SP-D expression and survival in lung, gastric, breast and ovary cancer were analyzed by Kaplan–Meier plotter (www.kmplot.com) ⁴. Immunohistochemistry (IHC) on formalin-fixed and paraffin-embedded (FFPE) samples was performed using a polymer detection method.

Results. In lung cancer we detected a significantly lower SP-D mRNA expression both in adenocarcinoma and squamous cell carcinoma than in the normal pulmonary parenchyma (p < 0.05). Moreover SP-D mRNA expression was positively related with the overall survival rate of lung cancer patients, even lung adenocarcinomas and squamous cell carcinomas were analyzed separately (Fig. 1A). IHC staining for SP-D confirmed a different expression in the healthy pulmonary parenchyma and in both histotypes of lung cancer. Consistently, the same bioinformatic analysis applied to gastric and breast cancer revealed a lower SP-D mRNA expression in gastric adenocarcinoma, even stratified into diffuse-, intestinal-, and mixed-type adenocarcinomas by Lauren’s classification (p < 0.05) and in invasive ductal breast carcinomas compared to gastric mucosa and normal ductal mammary epithelium, respectively (p < 0.05). SP-D mRNA expression was negatively related to an overall survival rate of the patients with gastric cancer (p = 0.0001) (Fig. 1B). If stratified by Lauren’s classification, SP-D mRNA expression was negatively related to the overall survival rate of patients with intestinal-type adenocarcinoma (p = 0.00091), without distant metastasis and Her2-negative (p = 0.0023) (Fig. 1B). In invasive ductal breast carcinomas, we observed a negative association between SP-D mRNA expression and a favorable prognosis in patients with Luminal-A grade-1 and -2 cancers (respectively p = 0.01 and p = 0.0059) (Fig. 2A). IHC staining for SP-D confirmed its lower expression in gastric adenocarcinomas and invasive ductal breast carcinomas than in the normal gastric mucosa and ductal mammary epithelium, respectively. As far as ovarian cancer was concerned, a higher SP-D mRNA expression was detectable in duct than in normal ovary (p < 0.05). This data was also confirmed by real-time PCR in primary cells isolated from four samples each of human ovarian serous cystadenocarcinoma and normal ovarian tissues. SP-D mRNA expression showed a negative relationship with both overall or progression-free survival (respectively p = 0.016 and p = 0.0035) rates of patients with serous cystadenocarcinoma, if stratified by stage I and -2 (Fig. 2B). Furthermore, IHC staining for SP-D confirmed a higher expression in serous cystadenocarcinoma compared to the normal ovarian parenchyma.

Conclusions. We conclude that, while in lung cancer it might be considered as a favorable prognostic factor, in gastric, breast, and ovarian cancers SP-D might have a different clinicopathological significance, representing an unfavorable prognostic factor. The apparently conflicting role of this pattern recognition receptor might find explanation on the heterogeneous immune contexts of the investigated tumors, which arise in the setting of dramatically different inflammatory milieus. Correlation between the levels of SP-D and patients’ outcome requires further investigation. Our results in silico analyses, candidate SP-D as potential novel marker with prognostic significance in epithelial malignancies, which actual impact deserves to be investigated in forthcoming ad-hoc-designed studies.

References

TRANSCRIPTOME SEQUENCING OF THE TRANSITION FROM NORMAL EPITHELIUM TO INVASIVE CANCER REVEALS INSIGHTS INTO THE CARCINOGENESIS OF HPV+ AND HPV- VULVAR NEOPLASIA

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Background. Vulvar Squamous Cell Carcinoma represents a rare neoplasm with bimodal distribution by age and complex pathogenesis. This neoplasm often affects fragile patients with