New Phenomenon

Syk is low-expressed in non-small-cell lung cancer and inversely correlates with patient’s survival

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The protein tyrosine kinases (PTKs) are a group of enzyme proteins that can phosphorylate substrate protein tyrosine residues, and are involved in many signal transduction pathways. They also play an important role in the control of cell differentiation, proliferation, and spreading. A recent study has found that Syk, as a tumor suppressor of PTKs, is closely related to tumor invasion and metastasis [1]. Syk has been also showed to have potential inhibitory effect in breast, gastric, and pancreatic cancers [2−4]. Sung et al. [5] found that in the mouse mammary gland, loss of one Syk allele profoundly increased proliferation, ductal branching, and invasion of epithelial cells through the mammary fat pad during puberty, and that mammary carcinoma developed after 1 year. An increasing number of clinical studies have revealed a correlation between reduced Syk expression and increased risk of metastasis formation, and Syk is assigned as a potential new prognostic marker in different tumor types [6]. In this study, we examined the expression of Syk in non-small-cell lung cancer (NSCLC) and analyzed its association with the prognosis.

The study approved by the Ethics Committee of the Second Hospital of Shandong University included 70 patients (54 males, 16 females; median age of 61 years, ranged from 41 to 76 years) with NSCLC that were diagnosed in the Department of Thoracic Surgery, the Second Hospital of Shandong University. In 70 cases, 28 were diagnosed as adenocarcinoma, 36 squamous-cell carcinoma and 6 large-cell carcinoma. According to Primary Lung Cancer Diagnostic and Treatment Practices (2001), 13 cases belonged to stage I, 33 stage II, 19 stage III, and 5 stage IV. None of the patients received radiation or chemotherapy before surgery. All patients were followed up from January 2007 to December 2010. Tumor tissues were taken from primary tumor area, avoiding necrosis and inflammatory areas. Adjacent tissues were from 2 cm next to the tumor material, and normal lung tissues from 5 cm next to tumor margin. Pathological examination showed no carcinoma cells. Syk expression was immunohistochemically examined using mouse anti-human Syk monoclonal antibody (NeoMarkerS, Fremont, USA) under a light microscope. Three fields of cells were counted, respectively at ×400 magnification to determine whether the cells were positive for Syk, and the percentage of stained cells was averaged. Specimens were regarded as Syk negative if <5% of the cells were stained, 5%−25% as ‘+’, 25%−50% as ‘++’, and >50% as ‘+++’ according to many previous reports [7,8].

The results showed that brown particles could be seen in the cytoplasm in Syk-positive cells under a light microscope (Fig. 1). Syk expression rates were 5.7%, 95.7%, and 100% in tumor, adjacent lung cells, and normal lung cells, respectively. The positive rates were 5.6% in squamous-cell carcinoma, 3.6% in adenocarcinoma, and 16.7% in large-cell carcinoma (P = 0.394). Syk expression rate in NSCLC tumor cells was significantly lower compared with those in normal lung tissue and adjacent lung tissue (P < 0.05), while there was no difference between adjacent lung tissue and normal lung tissue. These results are similar to previous reports about Syk expression in other types of malignant tumors [4]. However, unlike those reported in previous studies, the Syk expression rates among patients of different pathologic types, differentiation, and clinical stages did not reveal any statistically significant differences. A previous study showed [6] that Syk expression was negatively correlated with differentiation and clinical stages of malignant tumors such as pancreatic cancer, esophageal squamous cell carcinoma, and endometrial cancer. We also noticed that the positive rate of Syk expression in our study was much lower than those reported in previous literatures. This may be explained by the following factors: very low expression of Syk in NSCLC, small sample size, and experimental techniques. Large sample volume and other experimental methods are needed for further study. Other associations between Syk expression and lymph node metastasis, tumor size, and tumor node metastasis have been reported [9], and the results also need further validation. In our study, 47 patients survived >3 years, and Syk expression in this group (8.57%) was higher than that with
survival time of ≤3 years (0%) (Table 1). The prognosis of patients with lung cancer is related to multi-factor, multi-indicators, and mutual effects among various indicators. Syk is only one of the indicators and further studies are needed to elucidate its interactions with other factors [10,11] and its expression in metastatic lymph nodes [12]. Syk expression in most solid tumors has been reported to inversely correlate with patient's survival [13]. Our study also confirmed that low expression of Syk inversely correlates with patient's survival.

Syk may play a role in suppressing the growth and metastasis of NSCLC. Our results suggest that up-regulating Syk expression might prolong the survival time of patients with NSCLC, and these may serve as part of the basis for NSCLC gene therapy. However, the following issues should be addressed to reveal the molecular mechanism of Syk’s tumor suppressive function: (i) relationship between transduction network and tumor; (ii) regulation mechanisms in the tumor; (iii) Syk specific positioning and functional differences in tumor; and (iv) Syk subtypes detection and functional studies.

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References


