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Original contribution

PBK/TOPK expression correlates with mutant p53 and affects patients' prognosis and cell proliferation and viability in lung adenocarcinoma☆

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Summary The PDZ-binding kinase/T-LAK cell–originated protein kinase (PBK/TOPK) is highly expressed in many types of tumors. However, its role in lung adenocarcinoma remains elusive. The aims of this study were to investigate the correlation between PBK/TOPK and mutant p53 in lung adenocarcinoma and to evaluate the effect of PBK/TOPK on cell proliferation and viability. Expression of PBK/TOPK and mutant p53 was detected in 127 cases of lung adenocarcinoma and was examined in the A549, GLC-82, and H358 lung adenocarcinoma cell lines by immunohistochemistry staining and Western blot assay. When PBK/TOPK expression was down-regulated by TOPK-specific siRNA in the A549 and GLC-82 lines, the effects of PBK/TOPK on cell proliferation, viability, and mutant p53 expression were evaluated. Expression of PBK/TOPK correlated positively with mutant p53 in both tumor tissues and cell lines. Kaplan-Meier survival analysis demonstrated that PBK/TOPK, mutant p53, lymph node metastasis, distant metastasis, high TNM stage, and poor tumor differentiation were associated with a poor prognosis. Cox multivariate analysis showed that PBK/TOPK, mutant p53, lymph node metastasis, and distant metastasis could each serve as an independent prognostic factor. After down-regulation of PBK/TOPK in the A549 and GLC-82 cell lines, mutant p53 expression was decreased, and cell proliferation and viability were significantly inhibited. Therefore, our results suggest that PBK/TOPK correlates with mutant p53 and affects cell proliferation and viability as well as prognosis in lung adenocarcinoma.

1. Introduction

Adenocarcinoma is the most common type of non–small cell lung cancer [1], and its incidence has been increasing in recent years [2]. Its pathogenesis remains unclear. The PDZ-

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binding kinase/T-LAK cell–originated protein kinase (PBK/TOPK) was originally found in a library of lymphokine-activated killer T (T-LAK) cell subtraction complementary DNA fragments [3]. PBK/TOPK is a 322-amino-acid MAPKK-like serine/threonine kinase that is hard to detect in normal tissues except in testicular and fetal samples [4,5]. The role of TOPK has been reported in different categories of tumors. For example, TOPK is involved with highly proliferative cells and tissues and is highly expressed in many types of tumors such as lymphoma, leukemia, breast cancer, Ewing sarcoma, and colorectal cancer [6–10]. High TOPK expression can promote cell proliferation [11–13] and prevent apoptosis [14,15] and is associated with a poor prognosis [16–19]. Moreover, TOPK expression may play an important role in the progress of cytokinesis and inflammation [20–22]. However, the detailed mechanism of TOPK signaling in lung adenocarcinoma remains unclarified.

TP53 is one of the most common tumor suppressor genes, whose mutation is closely associated with the formation and development of lung cancer [23]. Hu et al [24] found that high concentrations of TOPK contribute to tumor cell development and progression through suppression of p53 function. Nandi and colleagues [25] demonstrated that TOPK interacts with the tumor suppressor function of p53. However, it is unclear whether the role of TOPK in lung adenocarcinoma correlates with mutant p53. Therefore, we carried out this study.

2. Materials and methods

2.1. Study patients

We analyzed 127 specimens of surgically resected lung adenocarcinoma with no exposure to chemotherapy or radiotherapy before surgery that were harvested in 2001 to 2011 at Nanfang Hospital. These specimens were from 76 men and 51 women with a mean age of 58.4 years (range, 33-79 years). All specimens were reviewed by 2 pathologists. The clinicopathological characteristics included patients' sex and smoking status; tumor location, size, and differentiation; lymph node and distant metastasis; and TNM stage. Lung adenocarcinomas were staged and graded according to the 2009 World Health Organization/International Association for the Study of Lung Cancer classification [26]. The clinicopathological information was obtained through hospital records and telephone inquiries. The day of surgery was defined as the beginning of follow-up. A total of 113 patients with complete follow-up information were analyzed. The follow-up duration ranged from 1 to 103 months (mean, 36.1 months). This study was approved by the Southern Medical University Ethnics Committee.

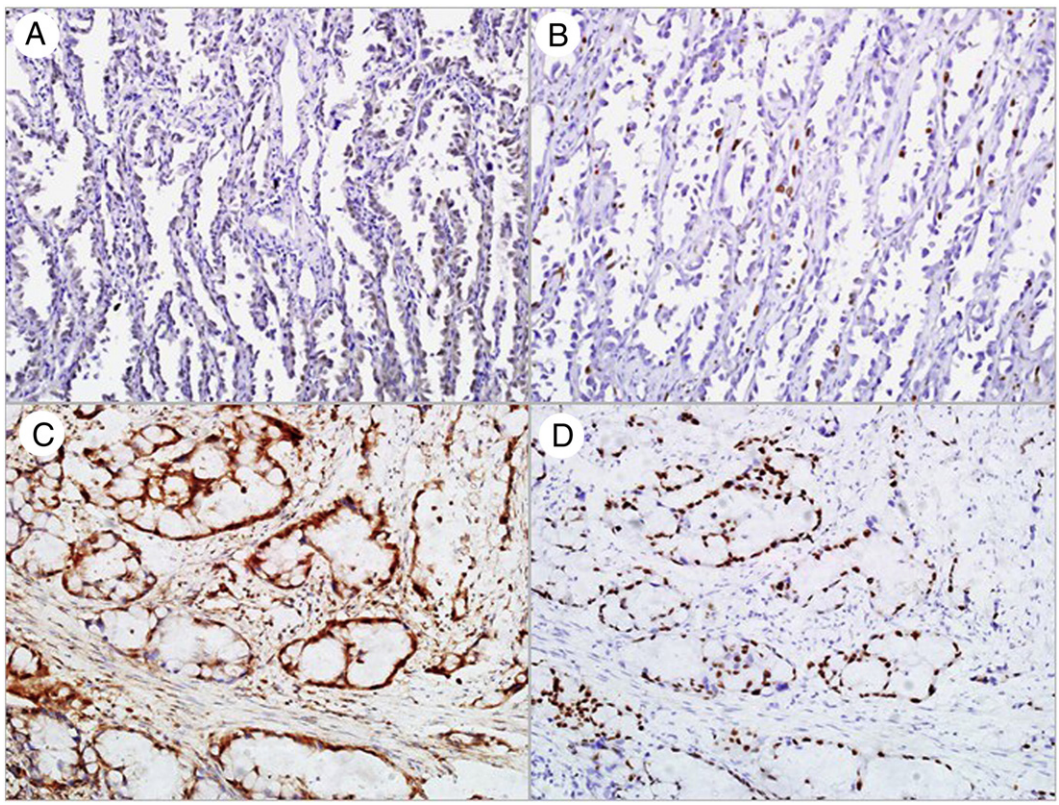

Fig. 1 Expression of PBK/TOPK and mutant p53 in lung adenocarcinoma tissues (original magnification ×40). A, Low expression of PBK/TOPK. B, Low expression of mutant p53. C, High expression of PBK/TOPK. D, High expression of mutant p53.