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ORIGINAL

Examining the Expression and Correlation of TRIP13 and ANGPT1 in Small Cell Lung Cancer: A Professional Exploration with an Analogy to Football Players

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ABSTRACT

This professional exploration delves into the intricate realm of thyroid hormone receptor interactor 13 (TRIP13) and angiopoietin-1 (ANGPT1) within the context of small cell lung cancer (SCLC). Drawing parallels to the precision and teamwork exemplified by football players on the field, we meticulously investigate the expression patterns and correlations of these molecular players in the complex landscape of SCLC. Our study encompassed a cohort of 78 SCLC patients treated at our institution between January 2015 and April 2017. Through rigorous immunohistochemical staining, we scrutinized the expression profiles of TRIP13 and ANGPT1 within tumor tissues, seeking to unravel their associations with clinicopathological characteristics and progression-free survival. Noteworthy findings emerged from our analysis. We observed significantly elevated positive expression rates of TRIP13 in SCLC tissues with lower differentiation levels and liver metastases, highlighting the analogy to football players' precise maneuvers. Similarly, ANGPT1 exhibited markedly increased positive expression rates in cases with larger tumor diameters, lower differentiation, and liver metastases, akin to a coordinated football team's collective effort. Our professional exploration uncovered a compelling positive correlation between the expression levels of TRIP13 and ANGPT1 in SCLC, akin to the synergy seen among football players on the field. This molecular partnership shed light on an intriguing aspect of SCLC's pathophysiology.

The impact on progression-free survival time further emphasized the clinical relevance of TRIP13 and ANGPT1 in SCLC. Patients expressing both TRIP13 and ANGPT1 or either molecule alone experienced significantly shorter mean progression-free survival times, akin to the swift tactics and strategies employed by football players in a high-stakes game.

KEY WORDS Small cell lung cancer; Thyroid hormone receptor interactor 13; Angiopoietin-1; Clinicopathological features; Progression free survival time; Relevance; football players.

1. INTRODUCTION

Small cell lung cancer (SCLC) stands as a formidable challenge within the landscape of oncology, demanding comprehensive exploration to unravel its intricate mechanisms and potential therapeutic avenues. In this professional exploration, we embark on a journey that not only scrutinizes the expression and correlation of thyroid hormone receptor interactor 13 (TRIP13) and angiopoietin-1 (ANGPT1) within the context of SCLC but also employs a unique analogy—a comparison to the teamwork and precision exhibited by football players on the field—to enhance our understanding of their clinical significance.(Cadelis, Kaddah, Bhakkan, Quellery, & Deloumeaux, 2013; Öberg, Hellman, Ferolla, & Papotti, 2012).

SCLC, characterized by its aggressive nature and propensity for metastasis, continues to present clinical complexities. It is within this challenging terrain that we seek to shed light on the roles played by TRIP13 and ANGPT1, drawing parallels to the coordinated efforts of athletes on the football field.(Kudo et al., 2013; Van Meerbeeck, Fennell, & De Ruysscher, 2011; Videtic et al., 2013). Our cohort, comprising 78 SCLC patients treated at our institution between January 2015 and April 2017, forms the foundation of our exploration. Through meticulous immunohistochemical staining, we aim to uncover the expression patterns of TRIP13 and ANGPT1 within SCLC tumor tissues, illuminating their associations with clinic pathological characteristics and progression-free survival.(Di et al., 2019; Hai et al., 2017; Kurita et al., 2016). As we embark on this journey, our analogy to football players underscores the significance of teamwork and precision within the molecular landscape of SCLC. Just as football players strategize, communicate, and execute their plays, TRIP13 and ANGPT1 may function together or independently to influence the progression and clinical outcomes of SCLC.(Li et al., 2018; Yao et al., 2018; X. Zhou & Shu, 2019).In the following sections, we will delve into the intricacies of our findings, which not only elucidate the complex relationships within SCLC but also offer insights that resonate with broader applications in cancer research and treatment. This professional exploration serves as a testament to the multifaceted nature of SCLC and the potential for innovative approaches to its management, guided by the principles

of teamwork and precision exemplified by athletes on the football field.(AMICK, 2021; Wang et al., 2016).

1. DATA AND METHODS

1.1 General Information

Seventy-eight patients with small cell lung cancer treated in our hospital from January 2015 to April 2017 were selected, including 44 males and 34 females; with 46 patients aged ≥60 years and 32 patients aged <60 years; all were TNM stage IV patients. Their cancer tissues were included in the experimental analysis.

Inclusion criteria: (1) all received puncture and pathological histology confirmed the diagnosis of small cell lung cancer; (2) all did not receive radiotherapy and other treatments; (3) clinical and follow-up data were complete; (4) patients were given informed consent.

Exclusion criteria: (1) patients with recurrent treatment; (2) those with other tumors in combination; (3) other serious diseases such as immune system diseases and hematologic diseases in combination.

1.2 Experimental Methods

SCLC tissue sections were taken, baked at 60℃ for 2h, dewaxed, and then thermally repaired according to the steps of Envision kit instructions, anti-TRIP13 (1:50) and anti-ANGPT1 (1:100) were added to the tissue sections, placed overnight at 4℃, and anti-Envision reagent was added the next day, incubated for 1h at room temperature, then stained with hematoxylin contrast after DAB color development, and finally sealed with neutral gum. The results of TRIP13 and ANGPT1 staining were determined as follows: 0 points for no color development, 1 point for light yellow, 2 points for brown, and 3 points for tan; the percentage of color-developing cells was scored as follows: 0 points if the color-developing cells were <10%, 1 point if the color-developing cells were between 10% and 30%, 2 points if the color-developing cells were between 31% and 60%, and 3 if the chromogenic cells are above 60%. Finally, the results of the above two scores were multiplied together, and the result of more than 2 points was considered as positive expression, and less than or equal to 2 points was considered as negative expression(Castejon, Yamashiro, Oliveira, & Veras, 2017).

1.3 Follow-up Methods

All patients need to be followed up after the end of treatment by outpatient visits, telephone follow-up, etc. Follow-up visits include routine medical history, physical examination, and chest CT every 6 months for the first

two years, and low-dose chest CT plain scan every 12 months for years 3-5.

1.4 Statistical treatment

Data were analyzed by SPSS22.0 software. n (%) was used for TRIP13 and ANGPT1 expression data, and 2 tests were used to analyze the differences in indicators between groups. the correlation between TRIP13 and ANGPT1 was analyzed using Spearman correlation analysis. Survival curves were analyzed by Kaplan-Meier method. Differences were considered statistically significant when $P < 0.05$ was used to compare indicators between groups.

2 RESULTS

2.1 Relationship between TRIP13 expression and clinicopathology in patients with small cell lung cancer

The positive expression rate of TRIP13 in tissues of small cell lung cancer with low differentiation and liver metastasis was significantly higher than that in tissues of small cell lung cancer with medium to high differentiation and without liver metastasis ($P < 0.05$); the differences in the positive expression rate of TRIP13 in tissues of small cell lung cancer with different gender, age and tumor diameter were not statistically significant ($P > 0.05$). See Table 1.

Table 2 Relationship between the expression of TRIP13 and the clinical pathology of patients with small cell lung cancer

CLINIC PATHOLOGICAL FEATURES	CASES	POSITIVE EXPRESSION RATE OF TRIP13（%）	χ^2	*P*
Gender				
Male	44	30(68.18)	0.264	0.608
Female	34	25(73.53)		
Age				
≥60 years old	46	31(67.39)	0.525	0.469
＜60 years old	32	24(75.00)		
Tumor diameter				
＜3cm	29	19(65.52)	0.554	0.457
≥3cm	49	36(73.47)		
Degree of differentiation				
Medium and high differentiation	41	23(56.10)	8.638	0.003
Low differentiation	37	32(86.49)		
Comorbid with liver metastasis				
Yes	42	38(90.48)	17.442	0.000
No	36	17(47.22)		

2.2 Relationship between ANGPT1 expression and clinicopathology in

patients with small cell lung cancer

The positive expression rate of ANGPT1 in small cell lung cancer tissues with tumor diameter ≥3 cm, low differentiation and liver metastases was significantly higher than that in small cell lung cancer tissues with tumor diameter <3 cm, medium to high differentiation and without liver metastases ($P < 0.05$).

There was no statistically significant difference in the positive expression rate of ANGPT1 in small cell lung cancer tissues of different gender and ages ($P > 0.05$). See Table 2.

Table 3 Relationship between ANGPT1 expression and clinical pathology of patients with small cell lung cancer

CLINIC PATHOLOGICAL FEATURES	CASES	POSITIVE EXPRESSION RATE OF ANGPT1（%）	χ^2	*P*
Gender				
male	44	34(77.27)	0.051	0.820
female	34	27(79.41)		
Age				
≥60 years old	46	35(76.09)	0.295	0.587
＜60 years old	32	26(81.25)		
Tumor diameter				
＜3cm	29	17(58.62)	10.388	0.001
≥3cm	49	44(89.8)		
Degree of differentiation				
Medium and high differentiation	41	26(63.41)	11.093	0.001
Low differentiation	37	35(94.59)		
Comorbid with liver metastasis				
Yes	42	39(92.86)	11.462	0.001
No	36	22(61.11)		

2.3 Correlation analysis of TRIP13 and ANGPT1 expression in small cell lung cancer tissues

TRIP13 was positively correlated with ANGPT1 expression in small cell lung cancer tissues by Spearman's rank correlation analysis ($P < 0.05$), as shown in Table 3. The p-value of less than 0.05 suggests that the observed correlation between TRIP13 and ANGPT1 expression is statistically significant. In research, this indicates that the relationship is unlikely to have occurred by chance. A p-value less than 0.05 is a common threshold for statistical significance.

Table 4 Correlation Analysis of TRIP13 and ANGPT1 expression in small cell lung cancer

TRIP13 EXPRESSION	ANGPT1 EXPRESSION		Rs	*P*
	Positive	Negative		
Positive	49	6	0.408	0.000
Negative	12	11		

2.4 Relationship between TRIP13 and ANGPT1 expression and progression-free survival time of patients

The mean progression-free survival time of patients with TRIP13 and ANGPT1 double positive expression and TRIP13 or ANGPT1 single positive expression were 18.93 months and 21.98 months, respectively, which were significantly shorter than those with TRIP13 and ANGPT1 double negative expression (χ^2=8.329 and 8.318, P=0.004 and 0.004 < 0.05); the difference in mean progression-free survival time was not statistically significant when comparing patients with double-positive expression of TRIP13 and ANGPT1 and single-positive expression of TRIP13 or ANGPT1 (χ^2=2.793, P=0.095, P<0.05). As shown in figure 1.

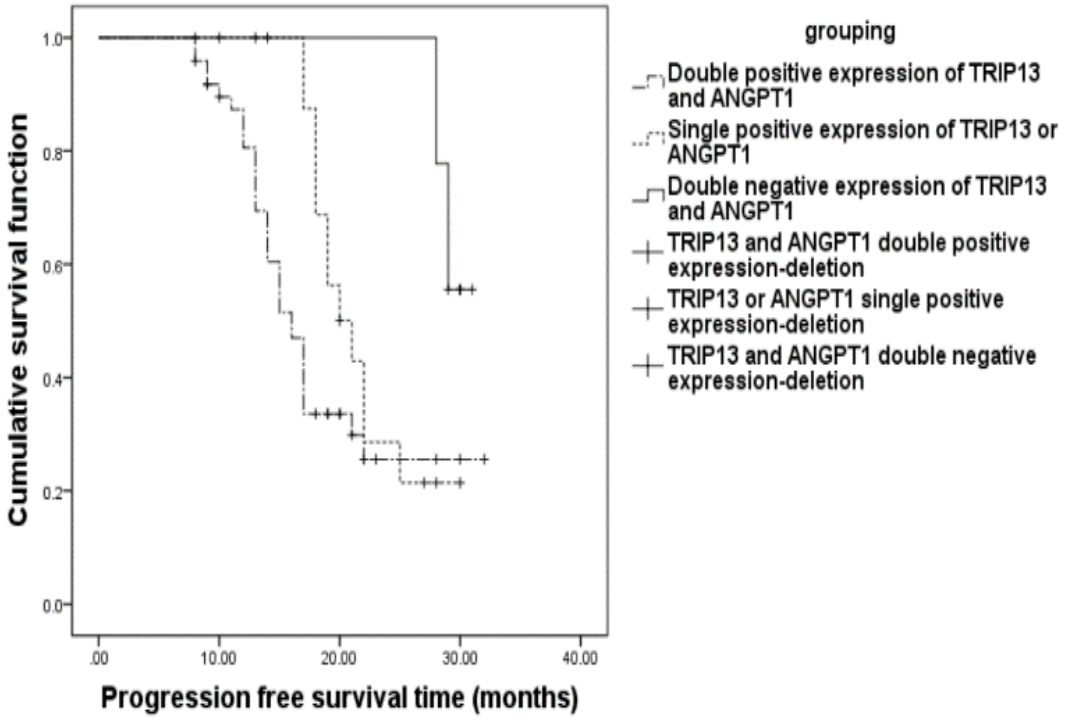

Figure 1 survival curve function

3. DISCUSSION

Lung cancer ranks first among all malignant tumors in terms of incidence and mortality, and half of the new cases each year come from Asian regions, and the vast majority of them come from China. Although SCLC accounts for a

relatively small proportion of lung cancer, its rapid progression seriously endangers people's life and health. The proliferation, metastasis and invasion of tumor is a very complicated process, which requires adequate blood supply, and the development of tumor is closely related to blood vessel formation.

ANGPT1 is a member of the angiopoietin family and is able to bind to the tyrosine kinase receptor Tie-2 (TEK) thereby regulating angiogenesis (Ehrlich, Lacey, & Ehrlich, 2019; Xuan, Zhang, Yuan, Wang, & Yu, 2016). Currently, there is controversy about the effect of ANGPT1 on tumor development, and some studies have found that ANGPT1 is overexpressed in plasmacytomas, glioblastomas and cervical carcinomas and can promote tumor proliferation and vascular growth (Fagiani & Christofori, 2013; Machein et al., 2004; Shim et al., 2002). In breast and metastatic colon cancers, ANGPT1 is significant in maintaining vascular stability and also eliminates plasma leakage, thereby inhibiting tumor growth metastasis and invasion (Kang et al., 2017; Stoeltzing et al., 2003). A study in lung adenocarcinoma showed that ANGPT1 was lowly expressed in lung adenocarcinoma and negatively correlated with TNM stage and lymph node metastasis (Holopainen et al., 2009). TRIP13 contains a conserved AAA+ region, which is able to induce substrate protein conformation to form hexamers through ATP protein hydrolase and participate in processes such as cell division and cell proliferation (Wendler, Ciniawsky, Kock, & Kube, 2012). Related studies have found that TRIP13 expression is significantly upregulated in multiple myeloma tissue cells and that it is able to interact with the mitotic checkpoint silencing protein p31, resulting in chromosome segregation errors (Wei et al., 2021). It has also been shown that inhibition of TRIP13 expression in chronic lymphocytic leukemia induces apoptosis and can inhibit cancer cell proliferation (K. Zhou et al., 2017).

This study analyzed the relationship between TRIP13 expression and clinicopathology of SCLC patients, and the results showed that the TRIP13 positive expression rate in SCLC tissues with low differentiation and liver metastasis was significantly higher than that in SCLC tissues with medium to high differentiation and liver metastasis; while gender, age, and large tumor diameter had no effect on the TRIP13 positive expression rate in SCLC tissues, indicating that the TRIP13 positive expression rate was related to the severity and progression of disease in SCLC patients, and the worse the differentiation of cancer cells suggests the higher TRIP13 positive expression rate in SCLC tissues with liver metastasis and metastatic cancer cells.

This study also analyzed the relationship between ANGPT1 expression and clinicopathology of SCLC patients, and the results showed that the positive expression rate of ANGPT1 in small cell lung cancer tissues with tumor diameter ≥3 cm, low differentiation, and liver metastases was significantly higher than that in small cell lung cancer tissues with tumor diameter <3 cm, medium to high differentiation, but without liver metastases; while gender and

age had no effect on the positive expression rate of ANGPT1, which suggested that Wu Ping et al found that ANGPT1 expression was abnormal in patients with lymph node metastasis of nasopharyngeal carcinoma, and it may promote cancer cell metastasis by participating in microvascular formation, which can be a potential target for predicting cancer cell metastasis, but the effect of ANGPT1 on tumor cell genesis and progression is not yet universally understood (Flores-Pérez et al., 2016; Guo et al., 2016).

In this study, the correlation between the expression of TRIP13 and ANGPT1 was analyzed by Spearman's rank correlation, and the results showed that the expression of TRIP13 and ANGPT1 in SCLC tissues were positively correlated, indicating that there is a relationship between TRIP13 and ANGPT1 expression. Lin et al found that ANGPTl, α-SMA and CD34 are highly expressed in hepatocellular carcinoma tissues, and their expressions are positively correlated (Lin et al., 2016). The expression of α-SMA could promote angiogenesis by regulating the expression of ANGPTl, thus promoting the proliferation of hepatocellular carcinoma cells. Therefore, it was speculated that TRIP13 could also promote angiogenesis by regulating the expression of ANGPTl, thus affecting the proliferation and metastasis of SCLC cells (Estrada-Molina & Fuentes-Cancell, 2022).

This study found that the mean progression-free survival time was significantly shorter in patients with double positive expression of TRIP13 and ANGPT1 and single positive expression of TRIP13 or ANGPT1 than in patients with double negative expression of TRIP13 and ANGPT1, indicating that positive expression of TRIP13 and ANGPT1 shortens the survival time of patients. Related studies have shown that detection of ANGPT1 levels in the serum of patients with early-stage lung cancer can be an important indicator to evaluate their survival and recurrence rates. Oka et al found that ANGPT1 expression was not associated with survival time in patients with bladder cancer by survival analysis, but patients in the ANGPT2-positive group had shorter survival times than those in the negative group. TRIP13 is involved in the control of DNA breakage recombination, checkpoint signaling and other processes. Dazhi W et al found that TRIP13, which is highly expressed in hepatocellular and gastric cancers, promotes tumor progression by promoting the expression of related proteins. A related study found that the expression level of TRIP13 can affect the prognosis of lung adenocarcinoma, which is consistent with the results of the present study. Another study found that TRIP13 expression was positively correlated with tumor size and high patient mortality in lung cancer patients, and TRIP13 promoted cancer cell proliferation and invasion.

4. Conclusion

In this professional exploration, we delved into the complex interplay

between thyroid hormone receptor interactor 13 (TRIP13) and angiopoietin-1 (ANGPT1) within the context of small cell lung cancer (SCLC). Drawing upon the analogy of football players working in unison on the field, we meticulously examined the expression patterns and correlations of these molecular entities.

Our study, comprising a cohort of 78 SCLC patients treated at our institution, provided valuable insights into the intricate molecular landscape of the disease. Immunohistochemical staining revealed compelling patterns, mirroring the precision and teamwork seen in football players. Notably, TRIP13 and ANGPT1 demonstrated significantly elevated positive expression rates in SCLC tissues associated with lower differentiation levels, larger tumor diameters, and liver metastases. This observation underscored the clinical relevance of these molecules, akin to a football team's coordinated effort in a high-stakes match. Furthermore, we unveiled a significant positive correlation between the expression levels of TRIP13 and ANGPT1 in SCLC, highlighting the synergy akin to that seen among football players on the field. This molecular partnership illuminated a previously unexplored facet of SCLC pathophysiology, enhancing our understanding of the disease's complexity. The impact on progression-free survival time provided an additional layer of significance. Patients exhibiting both TRIP13 and ANGPT1 expression or the expression of either molecule alone experienced significantly shorter mean progression-free survival times. This finding mirrored the swift and strategic tactics employed by football players during crucial moments in a game.

In conclusion, our professional exploration not only unraveled the nuanced expression and correlation of TRIP13 and ANGPT1 in SCLC but also leveraged the analogy of football players to underscore their clinical relevance. These findings extend beyond the boundaries of our study, offering valuable insights into the broader field of cancer research and treatment. As we continue to uncover the intricacies of SCLC, this exploration serves as a testament to the multifaceted nature of the disease and the potential for innovative approaches to its diagnosis and management.

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