Tiam1 high expression is associated with poor prognosis in solid cancers: a meta-analysis

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Abstract

Background: A number of studies have attempted to determine the prognostic value of T-cell lymphoma invasion and metastasis-inducing factor 1 (Tiam1) in patients with solid cancers, but the reported results were of inconsistency. Thus, we performed a systematic review and meta-analysis to exhaustively evaluate the prognostic role of Tiam1 expression in patients with solid cancers.

Methods: We retrieved literature published in between 1994 and April 22th, 2019 through searching PubMed, Web of Science and China national knowledge infrastructure (CNKI). Hazard ratios (HRs) coupled with 95% confidence intervals (95% CIs) were used to assess the relationship of Tiam1 expression and overall survival (OS), and disease-free survival (DFS).

Results: A total of 2647 patients with solid cancers in 20 studies were enrolled in our meta-analysis eventually. The pooled results showed that Tiam1 high expression was closely correlated with poor OS (HR = 2.17, 95% CI: 1.80–2.61, P = .000) and DFS (pooled HR = 1.95, 95% CI: 1.58–2.40, P = .000). Moreover, our subgroup analysis and sensitivity analysis demonstrated the reliability and stability of our pooled results.

Conclusion: In conclusion, this meta-analysis confirmed that Tiam1 higher expression positively correlated with OS and DFS, suggesting that Tiam1 may act as a valuable prognostic predictor and therapeutic target for patients with solid cancers. Nevertheless, in future more homogeneous and prospective studies should be performed to further support our findings.

Abbreviations: CI = confidence interval, DFS = disease-free survival, EMT = epithelial-mesenchymal transition; HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OS = overall survival, Tiam1 = T-cell lymphoma invasion and metastasis-inducing factor 1.

Keywords: cancer, meta-analysis, Tiam1, prognosis

1. Introduction

Cancer, as a severe public health problem, results in enormous economic burden worldwide. [1] It is very urgent to comprehensively elucidate its pathogenesis and develop effective therapeutic strategies. Growing evidence shows that the imbalance between oncogenes and tumor suppressor genes plays a pivotal role in transferring normal cells into malignant cells. [2–4] Hence, it is of great significance to identify these genes, clarify their functions in disease progression, and assess their prognostic role in cancer, for optimizing individualized therapy of cancer.

T-cell lymphoma invasion and metastasis factor 1 (Tiam1) was found in mice T lymphoma cells at the very start and then identified as a metastasis-associated-gene. [7–9] As a guanine nucleotide exchange factor, Tiam1 has been identified a specific activator of Rho-like GTPases Rac1. [8,9] Moreover, numerous studies demonstrated that the activation Tiam1-Rac signaling plays a crucial role in enhancing invasion and metastasis of various cancers. [10] Additionally, a recent study suggested that Tiam1 could activate Wnt/β-catenin signaling to facilitate thyroid cancer epithelial-mesenchymal transition (EMT)-mediated metastasis. [11] Metastasis is an essential hallmark of cancer that always confers poor oncologic outcomes. [12] In accordance with this, a large body of evidence supported that an increased Tiam1 expression predicted poor prognosis in patients with solid cancers. [13–18] Nevertheless, 2 early studies reported the inverse result that the increased Tiam1 expression correlated with a better prognosis. [17,19] Therefore, in the current study we performed a systematic review and meta-analysis to exhaustively assess the prognostic role of Tiam1 expression in solid cancers, aiming to provide evidence for the improved individualized therapy.

2. Materials and methods

The Institutional Review Board of 3201 Hospital, Xi’an Jiaotong University Health Science center approved this study. The current meta-analysis was conducted according to the Preferred Reporting Items for Systematics Reviews and Meta-Analyses guidelines. [20]
2.1. Search strategy
We retrieved literature published in between 1994 and April 22th, 2019 through searching PubMed, Web of Science and China national knowledge infrastructure (CNKI) using a search algorithm based on a combination of the following keywords:

1. “Tiam1” OR “T-cell lymphoma invasion and metastasis-inducing factor 1” OR “T lymphoma invasion and metastasis 1” AND
2. “tumor or tumor or cancer or carcinoma or adenocarcinoma or neoplasm or sarcoma or osteosarcoma or fibrosarcoma or rhabdomyosarcoma or glioma or glioblastoma or melanoma or retinoblastoma or choriocarcinoma or cholangiocarcinoma or teratoma or hepatoblastoma or nephroblastoma”.

The search strategy we used when searching PubMed was illustrated in Supplement 1. Reference lists from identified original studies and review articles were also carefully screened to identify additional eligible studies, which might be missed by electronic search strategies.

2.2. Selection and exclusion criteria
Studies included in this meta-analysis must met the following requirements:

1. Patients were diagnosed with solid cancer by pathological confirmation;
2. The expression of Tiam1 expression must be quantitatively detected using quantitative real-time polymerase chain reaction (q-PCR) or immunohistochemistry (IHC);
3. The relationship between Tiam1 expression and survival was explored;
4. The Hazard Ratios (HRs) and their 95% confidence intervals (CIs) for survival prediction based on Tiam1 expression level were readily available or could be calculated indirectly;
5. The most representative and most accurate study was considered to avert cohort overlapping when the same sample source was analyzed in multiple studies.

Studies satisfying the abovementioned inclusion criteria were further excluded if they had any of the following flaws:

1. Duplicated publications or data;
2. Animal or cell studies;
3. Erratum, conference, review articles, comments or letters;
4. Insufficient data or information to obtain HR;
5. Publications not written in Chinese or English.

2.3. Data extraction
The following data from the full texts of eligible studies were extracted: the first author, publication year, recruitment time study design, type of cancer, the number of cases, gender ratio, median age, tumor stage, method of detecting Tiam1 expression, cut-off value of Tiam1 overexpression, HRs of Tiam1 expression for OS and DFS, follow-up time and adjusted variables. If the HR for OS or DFS were calculated using both univariate and multivariate analyses, the latter was first chosen, considering that these results were adjusted for confounding factors. Besides, when a study did not provide the HRs, we estimated HRs and their corresponding 95% CIs from Kaplan-Meier curves using the Engauge Digitizer version 9.8 according to the method described by Parmar et al[21] and Tierney et al[22]. Any divergence in the extraction and explanation of all data was solved through discussion.

2.4. Quality assessment
The quality of the enrolled studies was independently assessed based on the Newcastle-Ottawa Scale (NOS) score.[23] In the NOS system, a score ≥6 was considered high quality.

2.5. Statistical analysis
HRs and their 95% CIs were pooled to estimate the effect of Tiam1 overexpression on survival. If the pooled HR exceeded 1 and its 95% CI did not intersect with the invalid line in the forest plot, the high expression of Tiam1 predicted a poor OS or DFS. Once the 95% CI intersect with the invalid line, the pooled HR was regarded of no significance. Inversely, the pooled HR less than 1 signified a better OS or DFS. The heterogeneity was examined using Cochrane Q test and Higgins’ I-squared, in which \( I^2 \geq 25\% \) was considered significant heterogeneity. We chose the random effects model to pool data when there was statistically significant heterogeneity. Otherwise, the heterogeneity could be neglected for its subtle influence, and the pooling analysis was conducted using a fixed effects model. Based on race, cancer type, the number of cases, detection method, adjusted TNM stage, and adjusted tumor differentiation, we conducted meta-regression analyses and subgroup analyses to determine the sources of heterogeneity and the reliability and stability of our pooled results. Additionally, sensitivity analysis was done by sequentially deleting single study to further verify the reliability and stability of our pooled results. The potential publication bias was evaluated by the funnel plot and Egger test,[24] \( P < .05 \) or \( I^2 \geq 25\% \) was regarded significant. Statistical analysis was fulfilled using STATA version 12.0 (StataCorp, College Station, TX).

3. Results
3.1. Study search and selection
We identified 324 records in PubMed, 247 records in Web of Science, 82 records in CNKI. We had a sum of 397 records after ruling out 256 duplicated publications. We then excluded 320 records which were review articles, letters, studies only with laboratory data, without survival analysis, or focusing irrelevant themes. We further removed 57 full-text articles based on the inclusion and exclusion criteria of this meta-analysis. The remaining 20 articles were ultimately identified as eligible ones and enrolled into this meta-analysis[13–19,25–37] (Fig. 1).

3.2. Study demographics
The main demographics of the 20 included studies are shown in Table 1. Fifteen different kinds of cancers were explored in our meta-analysis. All included studies were retrospective. Except 2 studies from Germany and USA, all studies were conducted in China. The sample size ranged from 76 to 217 across the included studies. A total of 20 included studies with 2647 patients reported HRs for OS, and 16 studies calculated HR using multivariate analysis. HRs for DFS were reported in 7 studies with 1048 patients and 4 studies provided HRs calculated using multivariate
analysis. Of all included studies, 18 studies assessed the Tiam1 expression using immunohistochemical staining method, while 2 studies did use polymerase chain reaction method. The cut-off values of Taim1 overexpression were not consistent across included studies. Each of the included studies was given less than 6 scores, suggesting all studies were high-quality enough for pooling analysis.

3.3. The prognostic significance of Tiam1 high expression in overall survival (OS) and disease-free survival (DFS) of cancer patients

HRs for OS were available in all 20 studies with 2647 patients. Because there was statistical heterogeneity in all the 20 datasets ($I^2 = 52.3\%$, $P = .003$), the overall pooled HR was calculated with the random-effects model. The forest plot results were shown in Figure 2, which suggested that Tiam1 high expression was linked with poor OS (HR = 2.17, 95\% CI: 1.80–2.61, $P = .000$).

HRs for DFS were available in 7 studies with 1048 patients. Because there was no statistical heterogeneity in all the 7 datasets ($I^2 = 41.9\%$, $P = .111$), the fixed-effects model was chosen to calculate the overall pooled HR. As shown in Figure 3, the overall pooled HR was 1.95 (95\% CI: 1.58–2.40; $P = .000$), suggesting that Tiam1 high expression was linked with poor DFS as well.

3.4. Meta-regression and subgroup analysis of heterogeneity for overall survival

We performed meta-regression analyses and subgroup analyses based on race, cancer type, the number of cases, detection method, adjusted TNM stage, and adjusted tumor differentiation, to investigate the sources of heterogeneity and determine whether the heterogeneity significantly affected the reliability and stability of the pooled HR for OS. As the results of meta-regression analyses showed, all these potential factors could not significantly interpret the heterogeneity for the pooled HR for OS (Fig. 4). However, in subgroup analysis we found that the heterogeneity completely vanished in group with adjusted tumor differentiation (HR = 2.59, 95\% CI: 2.145–3.127, $P = .000$; $I^2 = 0\%$, $P = .852$) (Fig. 4), hinting that tumor differentiation might account for a degree of heterogeneity, and Tiam1 higher expression had stronger efficacy in predicting prognosis in cancer patients with unanimous tumor differentiation. Additionally, our subgroup analysis showed that Tiam1 high expression was linked with poor OS in all groups, which verified the robustness of our overall pooled HR for OS.

3.5. Sensitivity analysis and publication bias

Sensitivity analysis by sequentially deleting single study was done to further verify the reliability of our synthesized results for OS and DFS. We found that no single study significantly changed the pooled HRs for OS (Supplement 2) and DFS (Supplement 3), further verifying the reliability of our pooled results. In addition, we applied Begg funnel plot and Egger test to evaluate the publication bias for OS. As shown in Figure 5, the shape of the funnel plots for OS was of symmetry. Moreover, the Egger test showed no statistical significance ($P = .752$). Thus, no publication bias for OS existed in this meta-analysis.

4. Discussion

A large number of studies indicated that an increased Tiam1 expression correlated with unfavorable oncologic outcomes in a wide range of solid cancers,[13–16,18,27,29,30] but some other studies reported a superior survival duration in cancer patients with an increased Tiam1 expression.[17,19] Therefore, in the current study we performed a systematic review and meta-analysis to exhaustively evaluate the prognostic role of Tiam1 expression in solid cancers, aiming to providing evidence for the improved individualized therapy.

In this meta-analysis, we scientifically pooled survival data of 2647 solid cancer patients enrolled in 20 clinical studies.

![Figure 1. Flowchart of study selection.](image)
| Reference   | SD      | RT      | Country | Type of Cancer | Case (No.) | M/F       | Median age (years) | TNM Stage | Detection method | Cut-off value of Taim1 overexpression | Survival end points | Follow-up (months) | NOS score | Adjusted variables |
|-------------|---------|---------|---------|----------------|------------|-----------|--------------------|-----------|------------------|-------------------------------------|--------------------|-------------------|-----------|-------------------|
| Liu 2014    | R       | 2002–2006 | China   | LC             | 98         | 53/45     | 57                 |        | HV              | Stained extent score > stained intensity score ≥ 4 | OS4M               | NA                | 7         | See, age, tumor size, tumor differentiation, TNM stage, lymph node status, EGFR expression, ALK expression |
| Zhu 2019    | R       | 2008–2011 | China   | LC             | 92         | 51/41     | NA                 |        | HV              | Stained extent score = 2 | OS2M               | NA                | 7         | See, age, tumor size, tumor differentiation, TNM stage, lymph node status, EGFR expression, ALK expression |
| Liu 2011    | R       | 2005–2009 | China   | ESCC           | 173        | 95/78     | NA                 |        | HV              | Stained extent score > stained intensity score ≥ 2 | OS4M               | Mean: 45           | 6         | NA                |
| Liu 2013    | R       | 2003–2006 | China   | NPC            | 217        | 163/54    | NA                 |        | HV              | Stained extent score > stained intensity score ≥ 4 | OS5M               | NA                | 8         | NA                |
| Qi 2009     | R       | NA      | China   | NPC            | 102        | 76/26     | NA                 |        | HV              | Stained extent score = 2/3 | DFS4M              | Mean: > 60         | 7         | See, age, TNM stage, Rac1 expression |
| Ding 2014   | R       | 1998–2000 | China   | NPC            | 140        | 104/36    | NA                 |        | HV              | Stained extent score > stained intensity score ≥ 3 | DFS2M              | Mean: 41.2         | 8         | See, age, tumor size, differentiation, T classification, lymph node status, distant metastasis |
| Wang 2015   | R       | 2003–2006 | China   | LSOC           | 98         | NA        | NA                 |        | HV              | Stained extent score > stained intensity score ≥ 4 | DFS4M              | Mean: 79           | 9         | NA                |
| Heuh 2011   | R       | 1994–1999 | China   | PTC            | 106        | 23/83     | 43.5               |        | HV              | Stained extent score > stained intensity score ≥ 4 | DFS3M              | Mean: 115.2        | 7         | See, age, tumor size, tumor multi-centrality, histological type, loco-regional recurrence |
| Yang 2015   | R       | 2001–2008 | China   | HNSCC          | 194        | 150/44    | 54.0               |        | HV              | Stained extent score > stained intensity score ≥ 5 | DFS3M              | Mean: 79           | 8         | NA                |
| Li 2016a    | R       | NA      | China   | BC             | 153        | 0/153     | NA                 |        | NA              | Stained extent score = 3 | DFS3M              | NA                | 8         | Age, menopausal status, molecular type, TNM stage, lymph node status, ER, Ki-67, PR and Her2 expression |
| Li 2016b    | R       | 2006–2010 | China   | OC             | 182        | 0/182     | NA                 |        | NA              | Stained extent score = 2/3 | DFS3M              | Mean: > 60         | 8         | Age, menopausal status, histological grade, metastasis, tumor stage |
| Yang 2017   | R       | 2004–2008 | China   | CC             | 174        | 0/174     | NA                 |        | 0-V            | Stained extent score = 3 | DFS4M              | Mean: 40           | 8         | Age, tumor differentiation, TNM stage, lymph node status, HPV infection |
| Wang 2018   | R       | 2010–2012 | China   | CC             | 84         | 0/84      | 41.3               |        | I–II            | Stained extent score > stained intensity score ≥ 4 | DFS6M              | NA                | 7         | Age, tumor size, histological grade and type, TNM stage, lymph node status, tumor depth |
| Kluth 2019  | R       | 2010–2011 | China   | CRC            | 193        | 111/82    | NA                 |        | PV              | Stained extent score = 2/3 | DFS4M              | NA                | 7         | Age, gender, tumor size, location, MIR-22 |
| Du 2012     | R       | 2000–2004 | China   | GCC            | 86         | 28/58     | NA                 |        | I–II            | Stained extent score > stained intensity score ≥ 4 | DFS6M              | NA                | 7         | Age, sex, lymphatic invasion, venous invasion |
| Ding 2009   | R       | 1999–2002 | China   | HCC            | 152        | NA        | NA                 |        | HV              | Stained extent score > stained intensity score ≥ 4 | DFS4M              | NA                | 8         | Age, gender, tumor size, tumor grade, liver cirrhosis, HBVAg status, metastasis, recurrence, serum AFP |
| Zhao 2011   | R       | 2000–2003 | China   | RCC            | 136        | 87/49     | NA                 |        | Intensity score of, 2 with at least 50% of malignant cells with positive Taim1 staining | DFS4M              | Mean: 36           | 7         | See, age, tumor size, tumor location, pathological status, T classification, lymph node status, TNM stage, lymph node status, Rac1 expression |

BC = breast carcinoma, OC = cervical cancer, CRC = colorectal cancer, ESCC = esophageal squamous cell carcinoma, GBC = gallbladder carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, Her2 = receptor tyrosine-protein kinase erbB-2, HNSCC = head and neck squamous cell carcinoma, IHCS = immunohistochemical staining, K = survival data was calculated from Kaplan-Meier survival curve, LC = lung cancer, LSCC = laryngeal squamous cell carcinoma, M = multivariable analysis, NA = not available, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, OC = ovarian carcinoma, PDAC = pancreatic ductal adenocarcinoma, PCR = polymerase chain reaction, PR = progesterone receptor, PTC = papillary thyroid carcinoma, RCC = renal cell carcinoma, RT = recruitment time, SD = study design.
Altogether, our overall pooled results showed that Tiam1 high expression was significantly associated with poor OS (HR = 2.17, 95% CI: 1.80–2.61, *P* = .000) and DFS (pooled HR = 1.95, 95% CI = 1.58–2.40, *P* = .000), verifying the value of Tiam1 high expression as an adverse prognostic factor in solid cancers. The overall pooled results may be challenged with the significant heterogeneity. Thus, to investigate the sources of heterogeneity and determine whether the heterogeneity significantly affected the reliability and stability of the overall pooled HR for OS, we performed meta-regression analyses and subgroup analyses based on race, cancer type, the number of cases, detection method, adjusted TNM stage, and adjusted tumor differentiation or grade. As the results of meta-regression analyses showed, all these potential factors could not significantly interpret the heterogeneity for the pooled HR for OS (Fig. 4). However, in subgroup analysis we found that the heterogeneity completely vanished in group with adjusted tumor differentiation (HR = 2.59, 95% CI: 2.145–3.127, *P* = .000; *I*^2^ = 0%, *P* = .852) (Fig. 4), hinting that tumor differentiation might account for a degree of heterogeneity, and Tiam1 high expression had stronger efficacy in predicting prognosis in cancer patients with unanimous tumor differentiation. Additionally, in general, our subgroup analysis showed that Tiam1 high expression was linked with poor OS in all groups, suggesting that the overall pooled HR for OS was reliable and stable. Furthermore, we also did sensitivity analysis by sequentially omitting single study and publication bias assessment to further verify the reliability and stability of our pooled results. From the results, we found that no single study significantly changed the overall pooled HRs for OS and DFS, and there was no significant publication bias, further demonstrating the robustness of our pooled results. Therefore, our comprehensive analyses strongly supported the notion that
Figure 3. Forest plot diagrams of hazard ratios for the prognostic value of Tiam1 in disease-free survival.

Figure 4. Meta-regression and subgroup analysis exploring the sources of heterogeneity and assessing the stability of the pooled hazard ratio for overall survival.
Tiam1 may be a useful prognostic biomarker for poor survival, suggesting Tiam1 could be explored as a promising therapeutic target for solid cancers.

The inverse association between Tiam1 expression and prognosis in patients with cancers may be interpreted by its roles in mediating tumor cell malignant phenotypes. First, as a metastasis-associated-gene, a large number of studies attested that Tiam1 could enhance tumor invasion and metastasis through activating Rac1. In addition, several recent studies also revealed that Tiam1 could facilitate epithelial-mesenchymal transition (EMT), a prerequisite for invasion and metastasis, of pancreatic,[13] lung,[35] cervical,[33] and thyroid[11] cancers. Second, Tiam1 has been reported to regulate tumor cell proliferation and apoptosis. Activation of Ras-MAP kinase signaling pathways play an important role in promoting tumor cell proliferation by facilitating cell cycle.[38–40] Tiam1-knockout mice were resistant to Ras-induced skin cancers, hinting that Tiam1 may be a responsive gene of Ras-MAP kinase signaling pathways and in implicated regulating tumor cell proliferation.[41] Consistently, many studies implied that Tiam1 overexpression exhibited an accelerative effect in regulating malignant cell proliferation in a wide range of cancers, including hepatocellular carcinoma,[42–44] oral cancer,[45] lung cancer,[35] esophageal cancer,[46,47] pancreatic cancer,[13,48] ovarian cancer,[49] cervical cancer,[33,50] colon cancer,[51–54] gastric cancer,[55] osteosarcoma,[56,57] nasopharyngeal cancer,[14] laryngeal cancer,[91] and cholangiocarcinoma.[50] Besides, lots of studies indicated that upregulation of Tiam1 could protect malignant cells from apoptotic death in esophageal cancer,[46,47] cervical cancer,[50] laryngeal cancer,[31] retinoblastoma,[59] and colon cancer.[33] Third, a few recent studies demonstrated that Tiam1 was able to promote of angiogenesis cervical[33] and lung cancer.[35] Fourthly, Tiam1 is involved in drug resistance of cancer cells. A most recent study showed that Tiam1 expression was significantly upregulated in colorectal cancer patients without positive response to chemotherapy and demonstrated that Tiam1 overexpression could induce drug resistance through promoting the stemness of colorectal cancer cells.[18] Similarly, it was also reported that Tiam1 participated in inducing resistance against doxorubicin in a 3D lymphoma model.[60] Taken together, all these evidence hold on to the notion that Tiam1 promote tumor progression by facilitating malignant cell invasion, metastasis, proliferation, angiogenesis, and drug resistance, as well as protecting malignant cells from apoptotic death, which could account for our findings in the current meta-analysis.

There are several limitations in our meta-analysis. First, all included studies were retrospective studies. In retrospective studies positive results were more likely to be reported than those with negative ones, which may cause bias. Second, most studies were conducted in China. Therefore, more clinical studies are required to further assess the prognostic value of Tiam1 in cancer patients from other countries. Thirdly, statistically substantial heterogeneity existed in the current meta-analysis. Accordingly, in future more homogeneous studies should be conducted to further validate our findings in this meta-analysis.

5. Conclusion

In summary, the current meta-analysis showed that Tiam1 higher expression positively correlated with shorter overall survival and disease-free survival, implying that Tiam1 may serve as a valuable prognostic indicator and treatment target for patients with solid cancers. However, more homogeneous and prospective studies should be conducted to further validate our conclusions in this meta-analysis.

Author contributions

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Figure 5. Begg funnel plot for publication bias assessment of the pooled hazard ratio for overall survival.
References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

[2] Hainaut P, Plymoth A. Targeting the hallmarks of cancer: towards a rational approach to next-generation cancer therapy. Curr Opin Oncol 2013;25:50–1.

[3] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.

[4] Huang YL, Wu JR, Fang M, et al. The role of ERCC1 and AFP gene polymorphism in hepatocellular carcinoma. Medicine (Baltimore) 2019;98:e15090.

[5] Xi Y, Zhang X, Yang Z, et al. Prognostic significance of Tiam1 expression in breast cancer: Protocol for a meta-analysis. Medicine (Baltimore) 2019;98:e14924.

[6] Zhang Y, Li Y, Jiang W, et al. The clinical significance of microRNA-122 in predicting the prognosis of patients with hepatocellular carcinoma: a meta-analysis validated by the Cancer Genome Atlas dataset. Medicine (Baltimore) 2019;98:e14810.

[7] Chiu CY, Leng S, Martín KA, et al. Cloning and characterization of T-cell lymphoma invasion and metastasis 2 (TIAM2), a novel guanine nucleotide exchange factor related to TIAM1. Genomics 1999;61:66–73.

[8] Bossier P, Huynh-Do U. The guanine nucleotide exchange factor Tiam1: a Janus-faced molecule in cellular signaling. Cell Signal 2014;26:483–91.

[9] Mertens AE, Roovers RC, Collard JG. Regulation of Tiam1–Rac signalling. FEBS Lett 2003;546:11–6.

[10] Minard ME, Kim LS, Price JE, et al. The role of the guanine nucleotide exchange factor Tiam1 in cellular migration, invasion, adhesion and tumor progression. Breast Cancer Res Treat 2004;84:21–32.

[11] Liu L, Wu B, Cai H, et al. Tiam1 promotes thyroid carcinoma metastasis by modulating EMT via Wnt/beta-catenin signaling. Exp Cell Res 2018;362:532–40.

[12] Aleckovic M, McAllister SS, Polyal K. Metastasis as a systemic disease: molecular insights and clinical implications. Biochem Biophys Acta Rev Cancer 2019;1872:89–102.

[13] Ding M, Li Y, Yang Y, et al. Elevated expression of Tiam1 is associated with poor prognosis and promotes tumor progression in pancreatic cancer. Oncol Targets Ther 2018;11:4367–75.

[14] Ding Y, Chen B, Huang J, et al. Overexpression of Tiam1 is associated with malignant phenotypes of nasopharyngeal carcinoma. Oncol Rep 2014;32:607–18.

[15] Ding Y, Chen B, Wang S, et al. Overexpression of Tiam1 in hepatocellular carcinomas predicts poor prognosis of HCC patients. Int J Cancer 2009;124:653–8.

[16] Du X, Wang S, Lu J, et al. Clinical value of Tiam1-Rac1 signaling in primary gallbladder carcinoma. Med Oncol 2012;29:1873–8.

[17] Huiec C, Lin JD, Yang CF, et al. Prognostic significance of Tiam1 expression in papillary thyroid carcinoma. Vrchow Arch 2011;459:587–93.

[18] Izumi D, Toden S, Ureta E, et al. Tiam1 promotes chemoresistance and tumor invasiveness in colorectal cancer. Cell Death Dis 2019;10:267.

[19] Walch A, Seidl S, Hermannsdorfer C, et al. Combined analysis of Rac1, IQGAP1, Tiam1 and E-cadherin expression in gastric cancer. Mod Pathol 2008;21:544–52.

[20] Molher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.

[21] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.

[22] Tierney JF, Stewart LA, Gersh K, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

[23] Yu W, Guo Y. Prognostic significance of programmed death ligand-1 immunohistochemical expression in esophageal cancer: a meta-analysis of the literature. Medicine (Baltimore) 2018;97:e11614.

[24] Yang J, Liu Y, Li B, et al. Prognostic significance of tumor length in patients with esophageal cancer undergoing radical resection: a PRISMA-compliant meta-analysis. Medicine (Baltimore) 2019;98:e15029.

[25] Li H, Cui X, Chen D, et al. Clinical implication of Tiam1 overexpression in the prognosis of patients with serious ovarian carcinoma. Oncol Lett 2016;12:3492–8.

[26] Li Z, Liu Q, Piao J, et al. Clinicopathological implications of Tiam1 overexpression in invasive ductal carcinoma of the breast. BMC Cancer 2016;16:681.

[27] Liu H, Shi G, Liu X, et al. Overexpression of Tiam1 predicts poor prognosis in patients with esophageal squamous cell carcinoma. Oncol Rep 2011;25:5841–8.

[28] Liu N, Tang LL, Sun Y, et al. MiR-29c suppresses invasion and metastasis by targeting Tiam1 in nasopharyngeal carcinoma. Cancer Lett 2013;329:181–8.

[29] Liu S, Li Y, Qi W, et al. Expression of Tiam1 predicts lymph node metastasis and poor survival of lung adenocarcinoma patients. Diagn Pathol 2014;9:69.

[30] Qi Y, Huang B, Yu L, et al. Prognostic value of Tiam1 and Rac1 overexpression in nasopharyngeal carcinoma. ORL J Otorhinolaryngol Relat Spec 2009;71:163–71.

[31] Wang S, Li S, Tang Q, et al. Overexpression of Tiam1 promotes the progression of laryngeal squamous cell carcinoma. Oncol Rep 2015;33:1807–14.

[32] Yang H, Cai YC, Cao Y, et al. The prognostic value of Tiam1 protein expression in head and neck squamous cell carcinoma: a retrospective study. Chin J Cancer 2015;34:614–21.

[33] Yang Y, Wu Q, Li N, et al. Upregulation of Tiam1 contributes to cervical cancer disease progression and indicates poor survival outcome. Hum Pathol 2018;75:179–88.

[34] Zhao L, Liu Y, Sun X, et al. Overexpression of T lymphoma invasion and metastasis 1 predict renal cell carcinoma metastasis and overall patient survival. J Cancer Res Clin Oncol 2011;137:393–9.

[35] Zhu G, Zhang Y, Wang Q, et al. The prognostic value of Tiam1 correlates with its roles in epithelial-mesenchymal transition progression and angiogenesis in lung adenocarcinoma. Cancer Manag Res 2019;11:1741–52.

[36] Li B, Li B, Sun H, et al. The predicted target gene validation, function, and prognosis studies of miRNA-22 in colorectal cancer tissue. Tumour Biol 2017;39:101428317692257.

[37] Wang J, Wang F, YYS. Expression and significance of T lymphoma invasion and metastasis inducing factor 1 in cervical cancer. Anhui Med Pharm J 2018;22:1689–93.

[38] Shapiro P. Ras-MAP kinase signaling pathways and control of cell proliferation: relevance to cancer therapy. Crit Rev Clin Lab Sci 2002;39:285–310.

[39] Sun H, Li Y, Sun B, et al. Atorvastatin inhibits insulin synthesis by inhibiting the Ras/Raf/ERK/CREB pathway in INS-1 cells. Medicine (Baltimore) 2016;95:e4906.

[40] Yoon JH, Kwon HJ, Lee HS, et al. RAS mutations in AUS/FLUS cytology: does it have an additional role in BRAFV600E mutation-negative nodules? Medicine (Baltimore) 2015;94:e4755.

[41] Malliri A, van der Kammen RA, Clark K, et al. Mice deficient in the Rac activator Tiam1 are resistant to Ras-induced skin tumours. Nature 2002;417:867–71.

[42] Chen G, Lu L, Liu C, et al. MicroRNA-377 suppresses cell proliferation and invasion by inhibiting Tiam1 expression in hepatocellular carcinoma. PLoS One 2015;10:e0117714.

[43] Chen JS, Su IJ, Leu YW, et al. Expression of T-cell lymphoma invasion and metastasis inducing factor 1 in cervical cancer. Anhui Med Pharm J 2015;34:614–8.

[44] Huang J, Ye X, Guan J, et al. Tiam1 is associated with hepatocellular carcinoma. Oncol Rep 2016;36:532–7.

[45] Malliri A, van der Kammen RA, Clark K, et al. Mice deficient in the Rac activator Tiam1 are resistant to Ras-induced skin tumours. Nature 2002;417:867–71.

[46] Chen G, Lu L, Liu C, et al. MicroRNA-377 suppresses cell proliferation and invasion by inhibiting Tiam1 expression in hepatocellular carcinoma. PLoS One 2015;10:e011774.

[47] Chen JS, Su IJ, Leu YW, et al. Expression of T-cell lymphoma invasion and metastasis 2 (TIAM2) promotes proliferation and invasion of liver cancer. Int J Cancer 2012;130:1302–7.

[48] Huang J, Ye X, Guan J, et al. Tiam1 is associated with hepatocellular carcinoma metastasis. Int J Cancer 2013;132:90–100.

[49] Zhou H, Kann MG, Mallory EK, et al. Recruitment of Tiam1 to Semaphorin 4D activates Rac and enhances proliferation, invasion, and metastasis in oral squamous cell carcinoma. Neoplasia 2017;19:65–74.

[50] Liu Y, Wang X, Jiang X, et al. Tumor-suppressive microRNA-10a inhibits cell proliferation and metastasis by targeting Tiam1 in esophageal squamous cell carcinoma. J Cell Biochem 2019;120:7843–57.
Liu H, Wang X, Shi G, et al. Tiam1 siRNA enhanced the sensitivity of sorafenib on esophageal squamous cell carcinoma in vivo. Tumour Biol 2014;35:8249–58.

Guo X, Wang M, Jiang J, et al. Balanced Tiam1-rac1 and RhoA drives proliferation and invasion of pancreatic cancer cells. Mol Cancer Res 2013;11:230–9.

Li J, Liang S, Jin H, et al. Tiam1, negatively regulated by miR-22, miR-183 and miR-31, is involved in migration, invasion and viability of ovarian cancer cells. Oncol Rep 2012;27:1835–42.

Yu M, Xu Y, Pan L, et al. miR-10b downregulated by DNA methylation acts as a tumor suppressor in HPV-Positive cervical cancer via targeting Tiam1. Cell Physiol Biochem 2018;51:1763–77.

He JH, Li YG, Han ZP, et al. The CircRNA-ACAP2/Hsa-miR-21-5p/Tiam1 regulatory feedback circuit affects the proliferation, migration, and invasion of colon cancer SW480 cells. Cell Physiol Biochem 2018;49:1539–50.

Liu L, Zhang Q, Zhang Y, et al. Lentivirus-mediated silencing of Tiam1 gene influences multiple functions of a human colorectal cancer cell line. Neoplasia 2006;8:917–24.

Jin H, Li T, Ding Y, et al. Methylation status of T-lymphoma invasion and metastasis 1 promoter and its overexpression in colorectal cancer. Hum Pathol 2011;42:541–51.

Minard ME, Ellis LM, Gallick GE. Tiam1 regulates cell adhesion, migration and apoptosis in colon tumor cells. Clin Exp Metastasis 2006;23:301–13.

Li Z, Yu X, Wang Y, et al. By downregulating TIAM1 expression, microRNA-329 suppresses gastric cancer invasion and growth. Oncotarget 2015;6:17559–69.

Hu J, Li G, Zhou S, et al. The downregulation of MiR-182 is associated with the growth and invasion of osteosarcoma cells through the regulation of TIAM1 expression. PLoS One 2015;10:e0121175.

Jin J, Cai L, Liu ZM, et al. miRNA-218 inhibits osteosarcoma cell migration and invasion by down-regulating of TIAM1, MMP2 and MMP9. Asian Pac J Cancer Prev 2013;14:3681–4.

Cheng W, Liu Y, Zuo Z, et al. Biological effects of RNAi targeted inhibiting Tiam1 gene expression on cholangiocarcinoma cells. Int J Clin Exp Pathol 2015;8:15511–26.

Subramanian N, Navaneethakrishnan S, Biswas J, et al. RNAi mediated knockdown of Tiam1 gene inhibits invasion of retinoblastoma. PLoS One 2013;8:e70422.

Ikram M, Lim Y, Baek SY, et al. Co-targeting of Tiam1/Rac1 and Notch ameliorates chemoresistance against doxorubicin in a biomimetic 3D lymphoma model. Oncotarget 2018;9:2058–75.