RESEARCH ARTICLE

Clinicopathological Significance of DLC-1 Expression in Cancer: a Meta-Analysis

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Abstract

Background: Recent reports have shown that DLC-1 is widely expressed in normal tissues and is down-regulated in a wide range of human tumors, suggesting it may act as a tumor suppressor gene. We conducted a meta-analysis to determine the correlation between DLC-1 expression and clinicopathological characteristics in cancers. Materials and Methods: A detailed literature search was made for relevant publications from PubMed, EMBASE, Cochrane library databases, Web of Science, CNKI. The methodological quality of the studies was also evaluated. Analyses of pooled data were performed and odds ratios (ORs) were calculated and summarized. Results: Final analysis was performed of 1,815 cancer patients from 19 eligible studies. We observed that DLC-1 expression was significantly lower in cancers than in normal tissues. DLC-1 expression was not found to be associated with tumor differentiation status. However, DLC-1 expression was obviously lower in advance stage than in early-stage cancers and was more down-regulated in metastatic than non-metastatic cancers. Conclusions: The results of our meta-analysis suggested that DLC-1 expression is significantly lower in cancers than in normal tissues. Aberrant DLC-1 expression may play an important role in cancer genesis and metastasis.

Keywords: DLC-1 expression - metastasis - meta-analysis - cancer

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Introduction

Distant metastasis is always occurred in advanced cancer and is proved to be the leading cause of cancer mortality, so it is a predominant issue to understand the molecular mechanisms that enables this phenomenon in cancer biology. Metastasis suppressor gene deregulation was certified to play a key role in metastasis and several new metastasis suppressor genes have been fond and studied in cancers. DLC-1, a member of the deleted-in-liver cancer family of proteins which includes DLC-1, DLC2 and DLC3, was first identified as a tumor metastasis suppressor gene in hepatocellular carcinoma (Yuan et al., 1998). The human DLC-1 gene is localized on chromosome 8p21-22 and encodes a 1,091 amino acid protein that is highly homologous to the rat p122-RhoGAP, which is a GTPase-activating protein(GAP) for Rho family proteins (Homma and Emori, 1995). Rho family proteins play essential roles in regulating cytoskeletal organization, cell adhesion, and cellcycle progression (Etienne-Manneville and Hall, 2002; Moon and Zheng, 2003; Tcherkezian and Lamarche-Vane, 2007). It was determined that DLC-1 is widely expressed in normal tissues and is down-regulated in a wide range of tumor tissues.

Underexpression of DLC-1 was associated with either heterozygous deletions of the DLC-1 gene or hypermethylation of the gene promoter region (Guan et al., 2006; Seng et al., 2007; Guan et al., 2012). Recent studies have extensively investigated DLC-1 expression and function in many human cancers, including liver, breast, lung, ovarian, kidney, colon, stomach, prostate, nasopharynx, Gallbladder and so on (Guan et al., 2006; Peng et al., 2006; Zhang et al., 2009; Hua et al., 2010; Yufei et al., 2010; Fan and Shi, 2011; Yun et al., 2011; Fang et al., 2012; Quanrui and Zhimei, 2012; Peng et al., 2013; Ren et al., 2013; Yang et al., 2013a; Yang et al., 2013b; Feng et al., 2014; Mingrui et al., 2014; Qin et al., 2014; Yufei et al., 2014; Yujie et al., 2014; Zhefeng et al., 2015). Wang Y reported that DLC-1 is an important regulator of TGF-β responses and DLC-1 overexpression suppressed bone metastasis of breast cancer (Wang et al., 2014). Ren reported that the expression of DLC-1 was closely related with the metastasis and invasion of ovarian carcinoma (Ren et al., 2013). However, controversies still exist due to the limited number of patients in individual studies. In addition, the association between DLC-1 expression and clinical significance has not been thoroughly investigated. In this study, we pooled and analyzed the published clinical investigations regarding the effect of DLC-1 on cancer patients.

Materials and Methods

Search strategy and selection criteria

The following electronic databases were searched for relevant articles without any language restrictions:

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PubMed (data from 1966 to March 2015), Excerpta Medica dataBASE (EMBASE) (data from 1980 to March 2015), Cochrane library databases (up to March 2015), Web of Science (1945-2015) and China National Knowledge Infrastructure databases (CNKI). The search items are as follows: "cancer or tumor or neoplasm or carcinoma," "*expression*," "*DLC-1 or DLC-1 or deleted-in-liver cancer 1*," "*prognosis or prognostic or outcome*."

The criteria that an eligible study had to meet were as follows: (1) DLC-1 expression evaluated in primary cancer tissues, (2) researchers revealed the relationship between DLC-1 expression and cancer clinicopathological parameters and prognosis, and (3) studies provided sufficient information to estimate odds ratio (OR) and 95 % confidence interval (CI) about prognosis . The exclusion criteria included the following: (1) letters, reviews, case reports, conference abstracts, editorials, expert opinion and (2) all publications regarding in cell lines and animal models.

Data extraction and methodological assessment

Two authors (Jiang and Li) independently reviewed and extracted data from eligible studies. Disagreements were resolved by discussion with a third reviewer (Luo). The following information was recorded for each study: the first author name, year of publication, sample source, number of cases, clinicopathological parameters, cancer tumor node metastasis stage, immunohistochemical staining method, antibody source, percentage rate of expression, and follow-up. Data for study characteristics and clinical responses were summarized and the data turned into table format. Heterogeneity of investigation was evaluated to determine whether the data of the various studies could be analyzed for a meta-analysis.

For the methodological evaluation of the studies, three investigators read through each publication independently and assessed and scored them according to REMARK guidelines and the ELCWP quality scale (Steels et al., 2001; McShane et al., 2005). Any discrepancies or disagreements were discussed, and if consensus could not be achieved, a third reviewer resolved the issue.

Statistical analysis

Analysis was conducted using the STATA 12 (StataCorp LP, College Station, TX, USA) and Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). Heterogeneity among studies was evaluated by I^2 inconsistency test and χ^2-based Cochran's Q statistic test (Higgins et al., 2003). When heterogeneity was not an issue (I^2<50% or p≥0.05), a fixed-effect model was used to calculate parameters. If there was substantial heterogeneity (I^2 ≥50% or p<0.05), a random-effects model was used to pool data and attempted to identify potential sources of heterogeneity based on subgroup analyses. The pooled odds ratio (OR) was estimated for the association between DLC-1 expression and clinicopathological features. All reported p values were two-sided and p<0.05 was considered statistically significant.

The possibility of publication bias was assessed using the Begg test and visual inspection of a funnel plot (Begg and Mazumdar, 1994; Egger et al., 1997) We also performed the Duval and Tweedie nonparametric "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis (Higgins and Thompson, 2002).This method considers the possibility of hypothetical "missing" studies that might exist, imputes their ORs, and recalculates a pooled OR that incorporates the hypothetical missing studies as though they actually existed.

Results

Eligible studies and characteristics

Two hundred and eighty-eight publications were identified by the search method as described above. Two hundred and sixty-nine of those were excluded due to being non-original articles (review), or studies irrelevant to the current analysis. Eventually, based on the above inclusion and exclusion criteria, nineteen studies were included in this meta-analysis, as shown in Figure 1. total of 1815 tumor patients were enrolled. Their basic characteristics are summarized in Table 1.

The correlation of CXCR4 expression with clinicopathological features

Increased DLC-1 expression in cancers

We first determined whether DLC-1 expression is significantly higher in cancers than in normal tissues. The pooled OR from nineteen studies including 1182 cancers and 633 normal tissues is shown in Figure 2. There was no significant heterogeneity (I^2=0.0%, p=0.782), and the pooled OR was performed using a fixed model (OR=0.441, 95% CI=0.374-0.520, p=0.000), which indicated that DLC-1 expression is significantly lower in cancers than in the normal tissues.

The role of DLC-1 expression in cancer progression

We then analyzed 810 cancer patients pooled from thirteen studies to assess whether DLC-1 expression in cancers was associated with advanced stage. As shown in Figure 2, aberrant DLC-1 expression was significantly lower in advanced cancers (stages III and IV) than in early-stage cancers (stages I and II) (OR=0.435, 95% CI=0.332-0.570, p=0.000) by fixed model (I^2=0.0%, p=0.993). In addition, as shown in Figure Supplement 1, aberrant DLC-1 expression was not significantly lower in poorly and moderately differentiated cancers than in highly

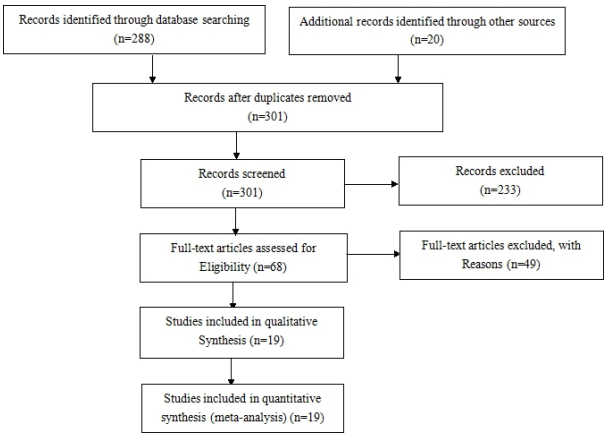

Figure 1. Flow Chart of Study Selection

Table 1. Basic Characteristics of the Included Studies

Study	Cancer	Year	Coutry	Patients		Gender		Methods	Tumor stage		Lymph node metastasis	Antibody source
				Experimental	control	Experimental (male/femal)	control (male/femal)		I–II	III–IV		
Yiyu Qin	gallbladder cancer	2014	China	28	34	NR	NR	IHC	NR	NR	NR	Santa Cruz
Wang Quanrui	gallbladder carcinoma	2012	China	48	15	15\33	5\10	IHC	18	30	20	Santa Cruz
Xiangling Feng	Nasopharyngeal Carcinoma	2014	China	35	14	26\19	10\4	IHC	12	23	NR	BD
Dan Peng	Nasopharyngeal Carcinoma	2006	China	41	16	30\11	12\2	RT-PCR	NR	NR	NR	NR
Fang Ren	ovarian carcinoma	2013	China	75	25	0\75	0\25	IHC	32	43	33	Santa Cruz
Dong Mei fan	epithelial ovarian carcinomas	2011	China	76	20	0\76	0\20	IHC	16	60	31	Abcam
Ren Fang	epithelial ovarian cancer	2012	China	62	22	0\62	0\22	IHC	20	42	24	Santa Cruz
Tang Hua	gastric carcinoma	2010	China	98	20	53\45	NR	IHC	37	61	57	Abcam
Che Yang	gastric carcinoma	2013	China	43	20	33\10	NR	IHC	13	30	27	Gene Tex
Feng Yun	breast cancer	2011	China	61	30	0\61	0\30	IHC	31	30	43	Abcam
Liu Yufei	breast cancer	2010	China	52	42	0\52	0\42	IHC	30	22	33	Santa Cruz
Ming Guan	Prostate Cancer	2006	Greece	27	10	27\0	10\0	RT-PCR	10	17	NR	NR
Haixia Peng	Primary Colorectal Cancer	2013	China	137	48	64\73	30\18	RT-PCR	NR	NR	NR	NR
Liu yufei	papmary thyroid carcinoma	2014	China	40	40	6\34	NR	IHC	23	17	22	Abcam
Yang Zhefeng	hepatic cancer	2015	China	60	60	51\9	NR	IHC	28	32	9	NR
Zhai Yujie	non-small cell lung cancer	2014	China	48	48	36\12	NR	IHC	22	26	19	Abcam
Song Mingrui	cervical squamous cell carcinoma	2014	China	102	20	0\102	0\20	IHC	48	54	34	Santa Cruz
Cailing Yang	cutaneous squamous cell carcinoma	2013	China	87	87	NR	NR	IHC	NR	NR	NR	Santa Cruz
Tao Zhang	Cell Renal Cell Carcinoma	2009	China	62	62	42\21	NR	IHC\RT-PCR	41	21	NR	Santa Cruz

*IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; NR, not reported

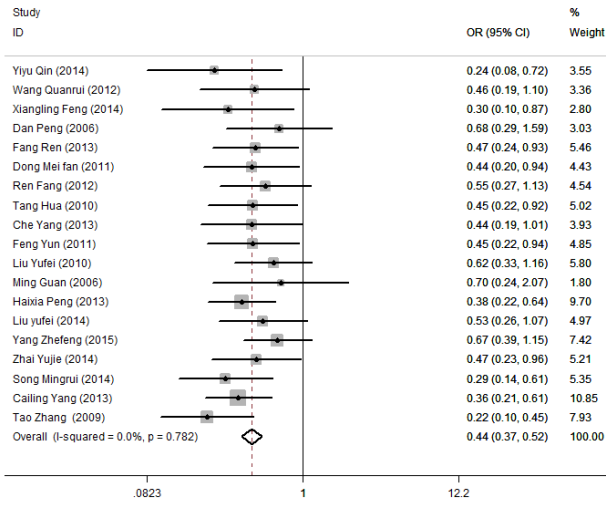

Figure 2. The Pooled OR of DLC-1 Expression from Nineteen Studies Including 1182 Cancers and 633 Normal Tissues (OR=0.916, 95% CI=0.552-1.519, *p*=0.734). Abbreviations: OR, odds ratio; CI, confidence interval; DLC-1, deleted in liver cancer-1

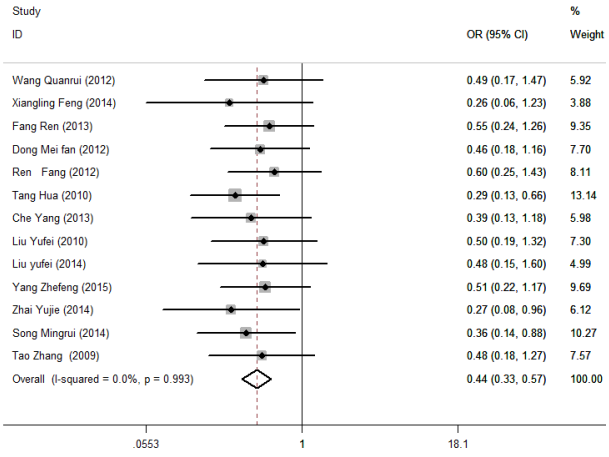

Figure 3. DLC-1 expression was Significantly Lower in Advanced Cancers (stages III and IV) than in Early-Stage Cancers (Stages I and II) Pooled from Thirteen Studies Including 810 Cancer Patients. Abbreviations: OR, odds ratio; CI, confidence interval; DLC-1, deleted in liver cancer-1

differentiated cancers (OR=0.916, 95% CI=0.552 - 1.519, *p*=0.734). These results suggest that DLC-1 expression may not associate with tumor's differentiated status, but may play an important role in cancer progression and development.

The role of DLC-1 expression in metastatic cancers

We then analyzed 744 cancer patients pooled from twelve studies to assess whether DLC-1expression in cancers was associated with lymphoma metastatic status. As shown in Figure 3, there was no significant heterogeneity (I^2=0.0%, *p*=0.910) among studies and the pooled OR was performed using a fixed model. Aberrant DLC-1 expression was significantly lower in metastatic cancers than in nonmetastatic cancers (OR=0.432, 95% CI=0.323 -0.579, P=0.000). The result suggests that DLC-1 expression is strongly correlated with metastatic status in cancer patients.

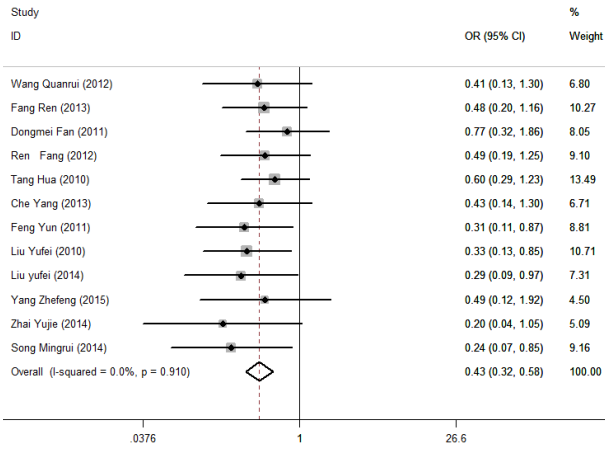

Figure 4. DLC-1 expression was Significantly Lower in Metastatic Cancers than in Nonmetastatic Cancers Pooled from Twelve Studies Including 744 Cancer Patients (OR=0.432, 95% CI=0.323 -0.579, P=0.000). Abbreviations: OR, odds ratio; CI, confidence interval; DLC-1 deleted in liver cancer-1

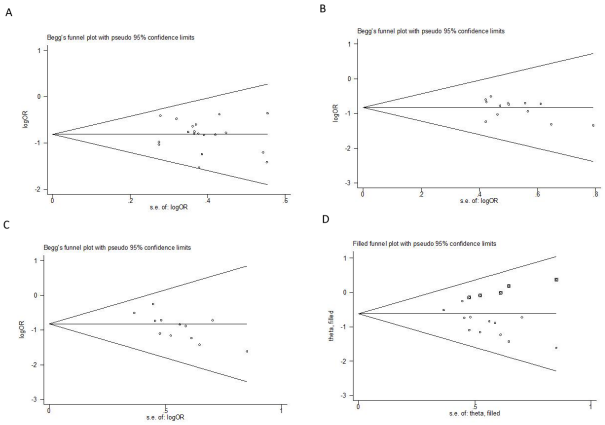

Figure 5. The Funnel Plots of Publication Biases in the Meta-Analysis of DLC-1 Expression and Clinicopathological Features. (A) The funnel plot from nineteen studies compared cancers and the normal tissues, there is no significant publication bias (*p*=0.441). (B) The funnel plot from thirteen ten studies in determing DLC-1 expression for different stages of cancers, there is no significant publication bias (*p*=0.161). (C) The funnel plot from twelve studies determined the relationship between DLC-1 expression and metastatic status in cancers (*p*=0.011). (D) The funnel plot with Trim and Fill from seventeen studies determined the relationship between DLC-1 expression and metastatic status in cancers

Sensitivity analyses and publication bias

A sensitivity analysis, in which one study was removed at a time, was conducted to assess the stability of the results. The pooled ORs were not significantly changed, indicating the stability of our analyses. Two funnel plots were largely symmetric (Figure 4A-B) suggesting there were no publication biases in the meta-analysis of DLC-1 expression in cancers (*p*=0.441) and DLC-1 expression with cancer progression (*p*=0.161). Visual inspection of the Begg funnel plot revealed asymmetry in the analysis of DLC-1 expression with cancer metastasis (Figure 4C), and the Begg test was also statistically significant (*p*=0.011). This indicated the possibility of publication bias. Because of this, we undertook a sensitivity analysis using the trim and fill method (Duval and Tweedie, 2000), which

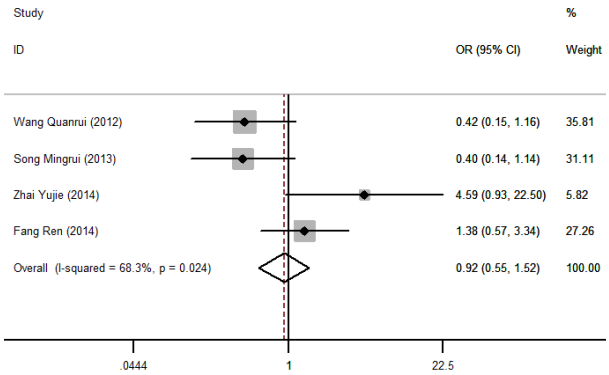

Figure Supplement 1. DLC-1 Expression was not Significantly Lower in Poorly and Moderately Differentiated Cancers than in Highly Differentiated Cancers (OR=0.916, 95% CI=0.552 - 1.519, *p* = 0.734).
Abbreviations: OR, odds ratio; CI, confidence interval; DLC-1, deleted in liver cancer-1

conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies produce a symmetrical funnel plot (Figure 4D). The pooled analysis incorporating the hypothetical studies continued to show a statistically significant association between DLC-1 expression and cancer metastasis (OR=0.537, 95% CI=0.416-0.693, P=0.000)

Discussion

To date, there have been some studies describing the precise expression and prognostic impact of DLC-1 in cancers. However, the roles and clinical significance of DLC-1 expression in cancers have not been thoroughly investigated. We conducted the meta-analysis to determine the correlation between DLC-1 expression and clinicopathological characteristics in cancers. Analyses of the pooled data showed that cancers had a significantly lower DLC-1expression than normal tissues (OR=0.435, 95% CI=0.332-0.570, *p*=0.000). Recent studies have shown that down-regulation or inactivation of the DLC-1 gene during tumor development appears to be primarily due to aberrant methylation at the gene promoter. In an early study, the promoter methylation was proved to major responsible for down-regulation of DLC-1 by screening several cell lines derived from HCC, prostate tumors and colon (Yuan et al., 2003). Then the analysis of 73 surgical samples of HCC showed that the level of DLC-1methylation in highly invasive HCC was significantly higher than in low invasion cases (Liu, 2008). A recent methylation analysis of 68 patients with pancreatic ductal adenocarcinoma showed that DLC-1 hypermethylation strongly correlated with lymph node metastasis (Xue et al., 2013). Promoter methylation and LOH result in DLC-1 inactivation in nasopharyngeal tumors (Feng et al., 2014). Still, more studies are needed to reveal the relationship betweeen DLC-1 expression and promoter methylation, and the affect of promoter methylation on clinicopathological features.

DLC-1 also played an important role in cancer progress and metastasis. This meta-analysis pooled the data and showed that aberrant DLC-1 expression was significantly lower in metastatic cancers than in nonmetastatic cancers (OR=0.432, 95% CI=0.323-0.579, P=0.000) and in advanced cancers (stages III and IV) than in early-stage cancers (stages I and II) (OR=0.435, 95% CI=0.332 - 0.570, *p*=0.000) ,while aberrant DLC-1 expression was not significantly lower in poorly and moderately differentiated cancers than in highly differentiated cancers (OR=0.916, 95% CI=0.552-1.519, *p*=0.734). The results suggest that DLC-1 expression play an important role in cancer progression and metastasis even not in cancer differentiation. Because of limited studies involve in cancer differentiation analysis, the differentiation result is not certain and need more new evidence to prove it. The mechanism that DLC-1 expression inhibits cancer progression was focused on DLC-1 interaction proteins. Members of the tensin family of focal adhesion proteins were identified the first DLC-1 binding partners and the impact of this interaction has been examined in HCC, NSCLC and breast carcinoma cells (Yam et al., 2006; Qian et al., 2007). Other proteins, like phosphatase and tensin homolog (PTEN), p120Ras-GAP (RASA1) and S100A10 are also studied in several cancers and targeting prooncogenic proteins activated by DLC-1 down-regulation was thought to be therapeutically effective for the suppression of cancer progression and metastasis (Heering et al., 2009; Yang et al., 2009; Yang et al., 2011).

Consistent results were shown in sensitivity analyses, and no evidence of heterogeneity was found. This meta-analysis met publication bias issues when analyze the association between DLC-1 expression and cancer metastasis. We undertook a sensitivity analysis using the trim and fill method to remove publication bias and the pooled analysis after adjusted continued to show a statistically significant association between DLC-1 expression and cancer metastasis. This study has several potential limitations. First, the possibility of information and selection biases as well as unidentified confounders could not be completely excluded because all of the included studies were observational. Second, the searching strategy was restricted to articles published in English and Chinese. Articles with potentially high-quality data that were published in other languages were not included. Third, the samples and studies were limited by a presence of heterogeneity between other studies.

In conclusion, 0ur meta-analysis showed that DLC-1 expression was significantly lower in cancers than in normal tissues. The aberrant DLC-1 expression plays an important role in cancer carcinogenesis and metastasis. Thus, it is safe to say that the remarkable potential of DLC-1 could serve as a prognostic biomarker for cancer patients. Further large-scale studies, especially multicenter, could serve well-matched cohort will provide more insight into the role of DLC-1 in the prognosis and clinical implementation of cancer patients.

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