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FOXG1 Expression is Positively Associated With Metastasis of Carcinoma: Evidence From A Meta-Analysis

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Abstract

FOXG1 is a new member of tumor-associated oncogenes, which participates in cell differentiation and bone matrix formation. Role of FOXG1 in tumor metastasis is not consistent in clinical reports. To explore the theoretical basis for screening prognostic indicators in tumor diagnosis and treatment, this study systematically evaluates the association of FOXG1 expression and tumor metastasis. Data from published case-control studies on FOXG1 expression and metastasis were collected up to September 2018. The databases of Pubmed, Chinese National Knowledge Infrastructure, Springer and Cochrane Library were selected with keywords "FOXG1" or "FBI-1" or "LRF" or "ZBTB7" or "OCZF" or "tumor" and "tumor metastasis" to identify articles published in Chinese or English. Review manager V.5.3 software was used to estimate OR and corresponding 95% Cl and for statistical analysis. The combined OR and 95% Cl for the cumulative metastatic rate in the FOXG1 expression cases versus those in the FOXG1-negative cases were evaluated by using fixed-effects and random-effects models.1593 cases from 19 articles, including 1147 cases with FOXG1 expression and 446 cases without FOXG1 expression, were statistically analyzed. The cumulative metastatic rates were 57.98% (665/1147) in cases with FOXG1 expression and 41.48% (185/446) in those without FOXG1 expression. The combined OR for the cumulative metastatic rates were 1.99 (95% CI 1.58 to 2.50) in the fixed-effects model (I2=45%). FOXG1 expression is positively associated with metastasis in the tumor, especially lymph node metastasis. Therefore, the detection of FOXG1 may be an effective and feasible means for predicting metastasis.

Keywords: FOXG1; Metastasis; Carcinoma; Meta-analysis

Introduction

FOXG1, also known as FBI-1 (factor binding IST protein 1), LRF (leukemia/ lymphoma related factor), OCZF (osteoclast derived zinc finger rat homolog) and ZBTB7(zinc finger and broad complex, tramtrack and brica), is a POK (Poxvirus and Krüppel-type) protein family member that has a critical function in tumor pathogenesis discovered in recent years [1]. FBI-1 was originally identified as a protein that binds specifically to an HIV type 1 promoter element that activates the transcription of the HIV-1 promoter [2]. FOXG1 is located in human chromosome 19p13.3, containing two exons and two introns, and encoded by ZBTB7 gene, which encoding product consists of an NH2-terminal BTB/POZ domain and COOH-terminal fourKrüppel-type zinc fingers. FOXG1 is, to our knowledge, the first ARF-specific (Alternative reading frame, ARF) transcriptional repressor to be identified [1,3,4]. POK protein is a transcriptional repressor involved in embryonic development, differentiation, proliferation, anti-apoptosis, and oncogenesis [5-8]. Besides, FOXG1 was implicated in adipogenesis, osteoclastogenesis, and fatty acid synthesis [9]. FOXG1 might induce multifaceted cellular signaling pathways such as ARF-MDM2-p53 or Rb-E2F1 to play a crucial role in oncogene transformation [3,10,11]. It could regulate cell cycle by repressing ARF gene expression or down-regulate apoptosis rate by repressing transcription of the Rb gene and significantly affect the tumorigenesis and development of carcinoma. Compared with the study of Jeon BN, Yonglin Chen et al. had drawn different conclusions about the correlation between FOXG1 and tumor metastasis [5]. They suggested that the expression of FOXG1 may affect the differentiation of the tumor. However, there was no

evidence of nodal metastasis and distant metastasis associated with the expression of FOXG1. The cumulative metastasis rate is an essential index for evaluating the prognosis in tumor patients. As far as we know, it is still short of the investigation data of large sample and clinical meta-analysis for the correlation between FOXG1 expression and tumor metastasis. With the cumulative published evidence, we hypothesize that FOXG1 expression promotes the metastasis, and it is thus one of the negative prognostic factors of carcinoma.

Materials and Methods

Literature research strategy for identification of studies

Databases of Pubmed, the Springer and Cochrane library (without a language limitation) and Chinese National Knowledge Infrastructure (CNKI, in Chinese) were searched, covering the period from 20 June 2007 to 30 September 2018. The terms 'FOXG1' or 'FBI-1' or 'LRF' or 'ZBTB7' or 'OCZF' or 'tumor' and 'tumor metastasis' were used as the search keywords, with a result of 42 papers found. Another eight qualified articles on this topic were identified by a hand search of the references of retrieved articles. Studies testing the association between FOXG1 expression and tumor metastasis were included if the following criteria were met: (1) The article was published as a randomized case-control study (2) The study reported the OR (odds ratio) and 95% CI (confidence interval) or reported the results about FOXG1-positive expression and metastasis that conduce to calculate OR,95% CI and P value. FOXG1-positive expression was defined as those that directly expressed a case as positive, or expressed a case as high expression when only cases of high or low expression are provided, or scored a case with FOXG1-positive cells greater than 10% of the carcinoma cells, or scored a case with pathological evaluation greater than 3, including the score of the degree of cell pigmenting and percentage of positive cells. (3) Methods of cases were RT-PCR (reverse transcription polymerase chain reaction), western blot or immunohistochemistry. (4) The selected cases included patients with histology proved to be cancer. (5) The metastatic lesions included local lymph node metastasis and distant metastasis. The exclusion criteria included the following: (1) the articles were non-randomized control study. (2) As for overlapping data from the same researchers, we got in touch with the authors and discussed with them to reach an agreement or just selected the ones with the maximum number of cases. (3) The literatures have not been published. (4) Results of the studies, the significant publication bias was found. After a preliminary search, we reviewed those 50 papers carefully in accordance with the criteria above, and finally selected 19 articles for further analysis.

Article evaluation and data extraction

The literatures were retrieved, screened, extracted and cross-checked independently by two reviewers. This meta-analysis study followed the steps of consensus on the quality control requirements of meta-analysis reports written by Moher *et al*. [12] The following information on each study was extracted and recorded from the articles: the name of the first author; year of publication; literature sources; histological types of the tumor; number of observed cases; Ethnicity of source of cases; the related factors of expression of FOXG1 in tumor; statistical methods; randomness and reliability of study and publication bias. The ethnicity was categorized as Caucasians, Chinese, and Koreans. The analysis was based on one researcher used an advanced research data table to extract data, while another examined the results. If there was any disagreement between the two reviewers, a discussion was held in the group to reach an agreement.

Statistical analysis

The OR, 95% CI and Z value (Hypothesis testing of combined effect size) were used as the association indicator to analyze the results, performed by Review manager 5.3 program. Both fixed-effects and random-effects models were utilized to calculated OR and 95% CI for the association between FOXG1 expression and metastasis. The association was determined by comparison between the metastasis rates in the FOXG1 expression cases and the FOXG1 negative cases. The combined OR and 95% CI were calculated and used forest plots to analyze data. It was considered to be statistically significant when 95% CI did not include 1. If the OR was larger than 1, it indicated that the metastasis rate in FOXG1 expression cases was higher than that in FOXG1-negative cases, and vice versa. A χ2-based Q test and I^2 statistics were used to assess the statistical heterogeneity between researches. If the P value is larger than 0.10 and I^2 less than 50%, the homogeneity between studies is insignificant; indicating that the fixed-effects model (the Mantel-Haenszel method) can be used to calculate the combined OR. Otherwise, the source of heterogeneity should be searched, and the random-effects model (the DerSimonian-Laird method) would be preferable. Publication bias was evaluated with Egger's funnel plot. The Z test was carried out to compare the cumulative metastasis rate in FOXG1 expression cases with that in FOXG1-negative cases. It was considered to be statistically significant when $P<0.05$.

Results

Characteristics of studies

According to the criteria of inclusion and exclusion, 19 case-control studies were available for analysis, with a total sample size of 1593 cases. All 19 articles provided precise data on FOXG1 expression and metastasis in cancer patients. Five articles were published in English, which can be searched in full text in the Pubmed database [9,13-16]. The remaining 14 articles were published in Chinese [4,5,17-28]. Although these Chinese papers cannot be retrieved in full text at present in English databases, they were included because they were clinical randomized controlled trials, and their data were relatively completed, and the data represented the largest population that had liver cancer, esophageal cancer, gastric cancer, lung cancer, especially NPC (Nasopharyngeal carcinoma) in China. Several experimental

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methods were used by researchers to detect FOXG1 expression, including immunohistochemistry, western blotting, and PCR. Two articles reported additional information on distant organ metastasis.

The characteristics of the cases are summarized in table 1. There were 1593 cases, among which 1147 cases were with FOXG1 expression, and 446 cases were without FOXG1 expression,850 cases had metastasis, and 743 cases were without metastasis. FOXG1 expression rate and the cumulative metastasis rate in tumor tissues were 72.00% (1147/1593) and 53.36% (850/1593), respectively. The FOXG1 expression cases had a cumulative metastasis rate of 57.98% (665/1147) that was higher than 41.48% (185/446) in FOXG1-negative cases.

Table 1: Case-control studies on FOXG1 expression and tumor metastasis.

Publication Year	First Author	Publication	Total			Pokemon+			Pokemon-		
			Case no	Pokemon+ (%)	Met+ (%)	Case no	Met case	Met (%)	Case no	Met case	Met (%)
2007	Zhao ZH	**Chin J Lung Cancer**	92	66	71.74	66	36	54.6	26	11	42.31
2007	Cui M	**J Clin Surg**	52	37	71.15	37	24	64.9	15	5	33.33
2008	Wu Y	**Shandong medical journal**	50	27	54	27	12	44.4	23	6	26.09
2008	Liu HF	**Journal of Harbin Medical University**	54	40	74.07	40	30	75	14	6	42.86
2009	Li ZM	**Shandong medical journal**	65	46	70.77	46	33	71.7	19	6	31.58
2010	Qu H	**Cancer Invest**	125	84	67.2	84	43	51.2	41	17	41.46
2010	Li ZM	**Journal of Zhengzhou University (Medical Sciences)**	76	45	59.21	45	33	73.3	31	11	35.48
2010	Cao GC	**Journal of Nanjing University (Natural Sciences)**	28	13	46.43	13	10	76.9	15	11	73.33
2011	Zu X	**Breast Cancer Res**	182	158	86.81	158	97	61.4	24	16	66.67
2012	Fang F	**Cancer**	129	112	86.82	112	50	44.6	17	9	52.94
2014	Liu SM	**Journal of Chengde Medical College**	60	43	71.67	43	29	67.4	17	7	41.18
2014	Zhao ZH	**Progress in Modern Biomedicine**	52	35	67.31	35	22	62.9	17	13	76.47
2014	Zhao Y	**Med Oncol**	66	50	75.76	50	30	60	16	4	25
2014	Chen YL	**Gansu Science and Technology**	99	64	64.65	64	34	53.1	35	20	57.14
2015	Huo H	**Shanghai Jiaotong University (Medical Science)**	75	59	78.67	59	47	79.7	16	8	50
2015	Ma L	**Chinese Journal of Histochemistry and Cytochemistry**	93	60	64.52	60	40	66.7	33	14	42.42
2016	Jiang HB	**Shandong medical journal**	62	42	67.74	42	21	50	20	3	15
2016	Chen YC	**Shandong medical journal**	55	37	67.27	37	17	46	18	3	16.67
2018	Joo JW	**Anticancer Res**	178	129	72.47	129	57	44.2	49	15	30.61
Total case no/combined rate			1593	1147	72	1147	665	58	446	185	41.48

In the 19 articles, there were 413 cases of breast cancer in four articles,250 cases of gastric cancer in three articles, 304 cases of colorectal cancer in three articles,210 cases of squamous cell carcinomas in three articles(155 were diagnosed with esophageal squamous cell carcinoma in two articles, and 55 were diagnosed with squamous carcinoma of larynx in one article),209 cases of lung cancer in three articles(157 were diagnosed with non-small-cell lung cancer in two articles, and 52 were diagnosed with small cell lung cancer in one article),179 cases of liver cancer in two articles(50 were diagnosed with primary carcinoma of liver in one article and 129 were diagnosed with hepatocellular carcinoma in one article)and 28 cases of carcinoma of gastric cardia in one

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article. After double-blind identification and discussing with the original author, 967 cases, including breast cancer (413 cases), gastric cancer (250 cases) and colorectal cancer (304 cases), were classified as adenocarcinoma. And 210 cases, including 155 cases of esophageal squamous cell carcinoma and 55 cases of laryngeal squamous cell carcinoma, were classified as squamous cell carcinoma. According to the above classification, there were 13 articles on adenosquamous carcinoma, including ten articles on adenocarcinoma and three articles on squamous cell carcinoma.

Adenocarcinoma accounts for 60.70% (967/1593). Squamous carcinoma accounts for 13.18% (210/1593). Among the 1593 cases, 182 were American, 1233 were Chinese,178 were Koreans. The Chinese patients account for 77.40% of the total cases. The age distribution for the patients at diagnosis was from 22 to 85 years, and the mean age was 53.5 years (Table 1).

The association of FOXG1 expression with metastasis in tumors

The OR and 95% CI for the association of FOXG1 expression with metastasis calculated in this study are provided in figure 1 (with the fixed-effects model) and figure 2 (with the random-effects model). The results of the amalgamation heterogeneity test were$P$=0.02, I^2= 45% by combining analysis. The combined OR (95% CI) for the association of FOXG1 expression with metastasis was 1.99 (1.58 to 2.50) calculated by the fixed-effects model, suggesting that the expression of FOXG1 was associated with tumor metastasis, and the high expression of FOXG1 was highly indicative of tumor metastasis. The two combined OR were statistically significant (Z =5.87, P 0.00001, Figure1 displayed). In the individual study, fifteen of the nineteen articles gave an OR greater than 1, and the remaining four articles gave an OR less than 1. In this analysis, if the OR was greater than 1, there was a greater tendency for metastasis to occur with FOXG1 expression; whereas when the OR was less than 1, there was a lower tendency for metastasis to occur with FOXG1 expression. With the fixed-effect model, I^2= 45%, it can be considered that the theoretical effect size is fixed. Even if there is a difference in the effect size among the original studies, it may cause by the sampling error, so the fixed-effect model can be used to evaluate the combined effect size. Due to the evaluation results are statistically significant, the test results of the random-effect model are used as a reference.

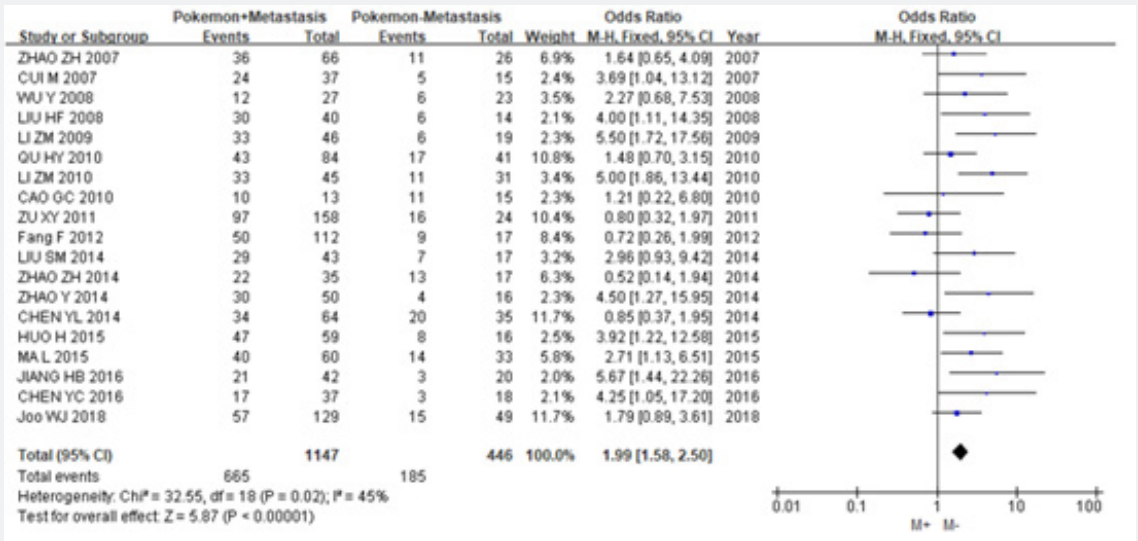

Figure 1: OR for the association of Pokemon expression with metastasis in tumors with the fixed-effects model.

Test of heterogeneity

The heterogeneity accompanying the fixed-effects model between studies was checked. As seen in figure 3, the result of χ2test was 32.55 with 18d.f., P=0.020 and I^2=45%. The test demonstrated a moderate heterogeneity that accompanied the fixed-effects model between studies.

Sensitivity and stability analysis

The influence of a single study was investigated by omitting one study on the overall analysis. The omission of any study made no significant difference, indicating that the result was statistically reliable. Moreover, the result of the fixed-effects model was statistically similar to the result of the random-effects model, suggesting the stability and sensitivity of this analysis.

Test of publication bias

The study of each indicator was preliminarily estimated for the potential publication bias by drawing funnel maps, and we further used Egger's funnel plots to assess the possible publication biases. Figure 4 displayed a more symmetrical funnel plot, suggesting that there was no obvious publication bias in this meta-analysis.

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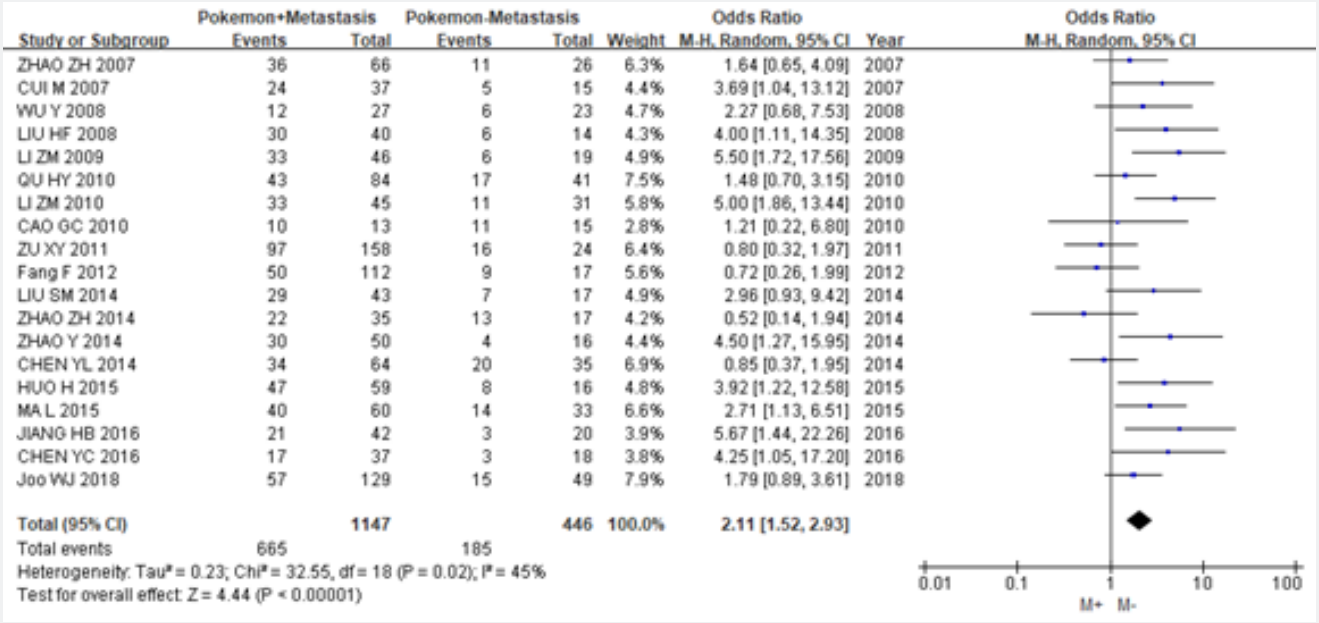

Figure 2: OR for the association of FOXG1 expression with metastasis in cancer with the random-effects model.

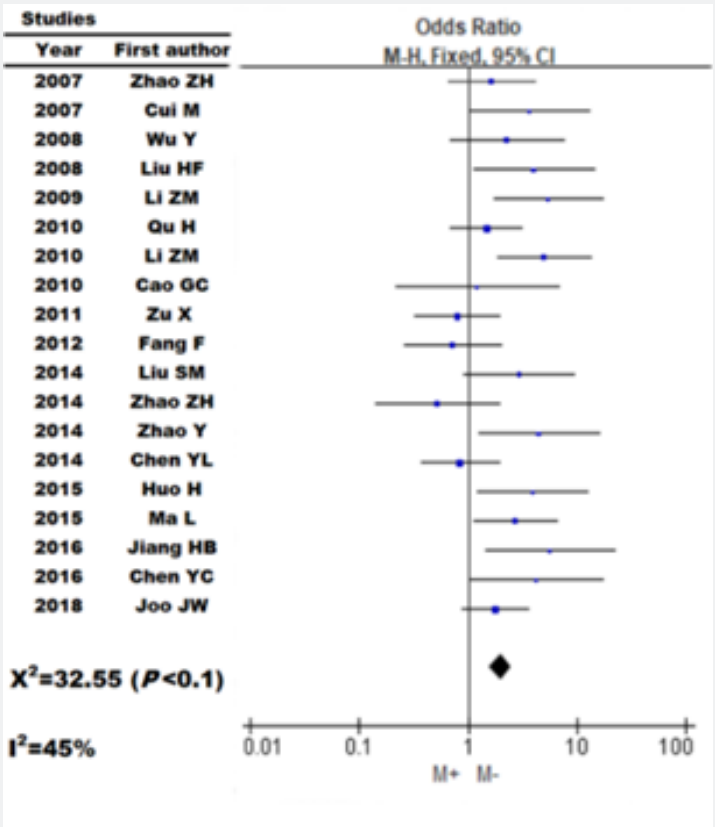

Figure 3: Heterogeneity between studies accompanying the fixed-effects model.

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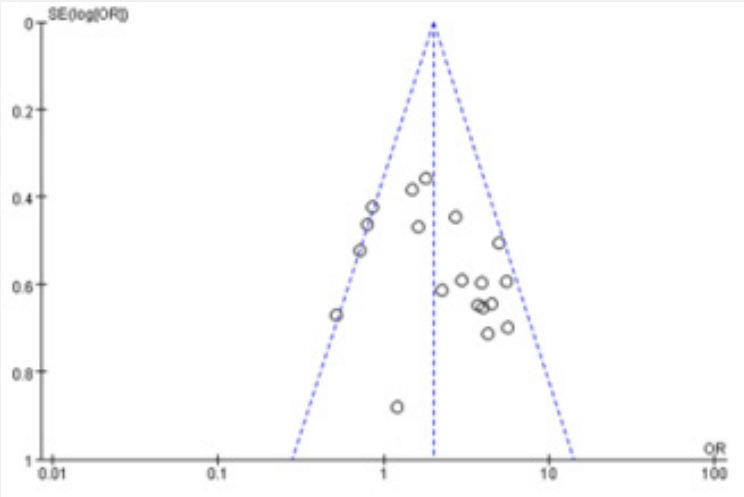

Figure 4: Eegger's funnel plot for publication bias test.

Discussion

In recent studies, POK protein has been found to be functionally varied in different stages of development and differentiation of stem cells, blood cells, tumor cells, and other cells. FOXG1 induces tumorigenesis by suppressing the ARF/p53 pathway in cancers of the breast, lung, colon, and bladder. That is, FOXG1 protein can take part in the regulation of p53 pathway to play a carcinogenic role by inducing apoptosis, promoting cell proliferation and malignant transformation and selectively inhibiting the tumor suppressor protein ARF and its agonist [29]. FOXG1 gene silencing interferes with cell proliferation signaling pathway and promotes human non-Hodgkin's lymphoma Raji cells apoptosis by lowering the expressions of BCL-6 (B-cell lymphoma 6 protein) and mutant p53 gene and protein [30]. It suggests that FOXG1 may be associated with a series of signaling networks of cell cycle and apoptosis. Maeda T et al. indicated that FOXG1 was closely linked to embryonic development, cell differentiation and the origin of cancer stem cells in the study of hematopoietic stem cells and liver cancer cells [31,32]. Therefore, FOXG1 was assumed to be a relay regulator of carcinomas, which might be located at the rate-limiting sites upstream of various proto-oncogenes and tumor suppressor genes, and play a central role in regulating cell pathways and functions, tumorigenesis and transformation [8].

As a result of the sample size limitation for the individual studies, broad agreement on the association between FOXG1 expression and metastasis in carcinoma has not already been reached. Some studies reported that FOXG1 expression promotes metastasis, and others reported that FOXG1 has no impact on metastasis. To overcome the sample size limitation, we performed a meta-analysis of the association of FOXG1 expression with the risk of metastasis based on a systematic review of 19 case-control studies including 1593 cases in this study. The results of the study proved that the expression of FOXG1 is positively associated with an increased risk of metastasis and some interesting revelations as follows.

FOXG1 expressed in the cytoplasm is closely related to tumor metastasis

Results from different studies suggest that FOXG1 can be expressed in the cytoplasm and nucleus. Combined with the results of FOXG1 protein localization in those studies, four articles showed that FOXG1 is localized in the nucleus and its expression is not related to lymph node metastasis, published by Zhao Zhihong, HongyanQu, Chen Yonglin *et al* [4,5,16,21]. Interestingly, the expression of FOXG1 in the nucleus is not necessarily independent of tumor metastasis. In 19 articles, Ma Li and Jiang Haibin *et al*. suggested that FOXG1 can express in the cytoplasm and nucleus, and is closely associated with tumor metastasis, which was consistent with the results of Yi Tianjin *et al*. [17,19,33]. The results of Cui Ming's studies on breast cancer suggested that FOXG1 can be expressed in the cytoplasm and nucleus, and the overexpression of FOXG1 in the nucleus positively correlated with the axillary lymph node metastasis of breast cancer [28]. The results also accord with the supposition that FOXG1 expressed in the nucleus is not necessarily independent of metastasis. We also found that literatures, relating to FOXG1 expression and metastasis, suggested that it mainly expressed in the cytoplasm [20,23]. Among them, the primary localization of FOXG1 protein in the cytoplasm of gastric cancer was detected by immunohistochemical Eli Vision method in the study of Howard *et al*., and the primary expression of FOXG1 protein positive granules in the cytoplasm was determined by immunohistochemistry S-P method in the study of Li Zhimeng *et al*..

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The cytoplasmic expression rate of FOXG1 mRNA was significantly higher in the experimental group with axillary lymph node metastasis than that without axillary lymph node metastasis group. It suggested that the overexpression of FOXG1 in the cytoplasm was not only involved in the evolution of breast cancer but also positively associated with lymph node metastasis [34]. Huo Hua et al. suggested that the localization of the FOXG1 protein mainly depended on the differentiation stages of the tumor, and its expression sites might change with different stages of tumor progression, which to some extent supported our findings in this study [20].

FOXG1 plays an essential role in inducing tumor differentiation.

Transcription factor FOXG1 is the first ARF specific transcription inhibitor found in the world [35]. Recently, it has been reported that it can be used as an essential central regulator of the tumor suppressor, ARF, which played an essential role in the negative regulation of cellular transcription and cell differentiation [1,36]. In those articles, Chen Yingchao et al. suggested that FOXG1 expression is related to the degree of differentiation of various tumor cells [5,17,18,20,22,25]. Huo Hua *et al*. also showed that the higher the degree of differentiation of cancer cells in gastric cancer, the lower the positive expression rate of FOXG1. Chen Yonglin et al. found that the expression rate of FOXG1 in cancerous cells was 18.0% (7/39), and the expression rate in gastric cancer was 64.7% (64/99), suggesting that the expression of FOXG1 closely associated with the development of gastric cancer [5]. However, Zhao Zhihong *et al*. proposed that FOXG1 be highly tissue-specific in NSCLC (Non-small-cell lung carcinoma), and its high expression does not link with the differentiation of tumor cells [4]. It was no significant difference between distinct differentiation degrees of FOXG1, and it may have little effect on the differentiation tendency of gastric cancer cells [23].

While studying the negative correlation between FOXG1 expression and tumor differentiation, the theory was put forward that FOXG1 expression in the tumor associated with lymph node metastasis [17,18,20,22,25]. For example, compared with that the FOXG1 expression rate is only 60.0% (12/20) in the group without metastasis, the expression rate of FOXG1 is 85.5% (47/55) in the lymph node metastasis group. It suggested that the overexpression of FOXG1 inhibited the differentiation and promoted lymph node metastasis of tumor cells [20].

Zhao Zhihong et al. found that the expression of FOXG1 was not related to lymph node metastasis in the tissues of non-small cell lung cancer. Meanwhile, the expression of FOXG1 did not link with tumor differentiation [4]. However in the study of gastric cancer, Li Zhimeng et al. found that the expression of FOXG1 was the positive correlation with lymph node metastasis, which was contrary to the conclusion of Chen Yonglin in gastric cancer tissues [5,23]. Thus, we could conclude that FOXG1 might be involved in different cellular signaling pathways during cell differentiation and tumor metastasis, which are related to the network regulation of multiple genes in both cell biological behaviors. Andrea Lunardi *et al*. suggested that the role of FOXG1 in inhibiting tumor mainly caused by the low expression of FOXG1, which blocked the differentiation of cells, and led to the poorly differentiated malignant tumor [37]. Multiple genes including FOXG1 might be involved in the development of the tumor. Combined with the above literatures, we suggested that the expression of FOXG1 in tissues was mainly negatively correlated with cell differentiation and was positive correlation with lymph node metastasis. It might have the function of promoting cancer in different stages of tumorigenesis.

FOXG1 could promote tumorigenesis and development through the ARF-MDM2-p53 pathway

Because of its critical role in a plethora of different lineage fate decisions and terminal cell differentiation, FOXG1 may play an even more complex and multifaceted role in tumorigenesis than has been described for other POK family members, especially in the process of cell signal transduction [37]. Gibson SL *et al*. suggested that the high expression of FOXG1 protein could inhibit the activity of ARF and weaken the carcinostatic action of ARF, while the low expression of ARF promoted the expression activity of MDM2 (Mouse double minute 2), which in turn increased the expression of mutant P53 and then affected the progression of the tumor [38]. Maeda T et al. showed that FOXG1 might specifically inhibit the activity of ARF by two pathways: For one thing, FOXG1 bound directly to the FOXG1-binding site located 50 base pairs upstream from the transcription start site of ARF, which repressed p14ARF expression levels. For another thing, FOXG1 mediated homodimer or heterodimer formation in the POZ/BTB domain and then inhibited ARF function [1].

Studies in the squamous cell carcinoma, breast cancer, colorectal cancer, and liver cancer suggest that FOXG1 up-regulated MDM2 by inhibiting ARF, and then inhibited the activity of wild-type p53, and thus affect the tumor metastasis via the above signaling pathway [9,14,16-19,26,27]. It is consistent with the conclusions of Maeda T, and Agrawal A, *et al*.. [1,29]. In particular, Xuyu Zu *et al*. mentioned in the study of breast cancer that FOXG1 gene played a crucial role in the tumorigenesis: FOXG1 functions as an oncoprotein by inhibiting the ARF/p53 pathway and then promoted tumor formation, development, and transfer [8,9].

In our previous study, we found that FOXG1 do not work on the carcinogenesis and cancer progression in CRC through FOXG1-p14ARF-MDM2-p53 pathway when it plays a role in CRC [14]. We confirmed our assumption in three ways. Firstly, there was no expression correlation between FOXG1 and p14ARF in CRC; secondly, the expression rates of p14ARF in CRC is 75.8%, indicating that most p14ARF expression in CRC was not suppressed by FOXG1, unlike other studies mentioned above; and finally, after knockdown of FOXG1 in LoVo cells, the expression

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of p14ARF was not significantly changed. It suggested that the inhibitory effect of FOXG1 on p14ARF might not play a role in CRC. The same result can be found in the study of lung cancer and breast cancer [16, 39]. It may be due to network regulation between different signaling pathways, but it may also be the result of differences in tissue types [16].

FOXG1 could also increase the stability of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) in the nucleus, which may inhibit the apoptosis by repressing transcription of the Rb gene [19]. This pathway is also mentioned by ZuX, Jeon BN, Lee DK, and Sovak MA *et al.*, in which, Jeon BN *et al*. suggested that FBI-1 may repress transcription of the Rb gene mainly by binding to FRE2 and by recruiting co-repressors [9,11,40,41]. The expression of FOXG1 and E2F3 positively correlated in laryngeal squamous cell carcinoma, and they played a synergistic role in the FOXG1-Rb-E2F pathway, which together inhibited p53 gene, promoted the disorder of cancer cell cycle, and then promoted the proliferation and metastasis of cancer cells [42].

The expression of FOXG1 is closely related to the tissue type of tumor

Studies have shown that FOXG1 was highly expressed in solid tumors such as colon cancer, breast cancer, prostate cancer, bladder cancer, and lung cancer, and played a crucial role in tumorigenesis, development, and metastasis [42-44]. The expression of FOXG1 in the eight adenocarcinomas and three squamous cell carcinomas was all associated with tumor metastasis in our study. Moreover, Choi *et al.* suggested that FOXG1 was aberrantly overexpressed in many human solid tumors, especially in adenocarcinomas and squamous carcinomas [45]. It is consistent with the conclusions of other studies, such as the studies in laryngeal squamous cell carcinoma and liver cancer [35,42,46]. However, in our study, we found in other tumors, such as lung cancer, cardiac cancer, and endometrial cancer, the expression of FOXG1 was not associated with the metastasis [16,21,24,33].

These two views indicated that the role of the FOXG1 gene in tumorigenesis and development might be specific to different tissue sources. The results of Wang Bo's study in human hepatocellular carcinoma also suggested that there was no association between the expression of FOXG1 and lymph node metastasis (5/30, P>0.05) and metastasis at extrahepatic organs (4/30, P>0.05), suggesting that the different clinical characteristics of FOXG1 expression in different tissues might be related to the difference of the samples taken [47]. Andrea Lunardi et al. suggested that the ability of FOXG1 to promote terminal differentiation by antagonizing oncogene pathways such as SOX9, NOTCH, E2F4, or Cyclin A was possible oncosuppressive functions for this protein in specific cell systems and tumor types, suggesting that FOXG1 were functionally different in different tumors [37].

Conclusion

POK prcancer isefore critical developmental regulators and essential players in the pathogenesis of human cancer that are found to act in different roles found in many studies. The results of this study suggested that the localization of FOXG1 in the nucleus do not associate with tumor metastasis, and immunohistochemistry exploration of the FOXG1 localization in tumor cells may help to evaluate the prognosis of the tumor. The ability of FOXG1 to inhibit the differentiation of tumor cells was intimately related to tumor metastasis. High expression of FOXG1 protein in tissues, combined with their degree of differentiation, may be beneficial to predict the risk of metastasis. FOXG1 up-regulated MDM2 and down-regulated by inhibiting ARF, thereby promote tumor metastasis. The quantitative detection of mRNA and protein of FOXG1 and related genes in ARF/p53 pathway may be potential molecular targets for the diagnosis and treatment of various tumors; the high expression of FOXG1 in adenosquamous carcinoma suggested that it was expressed with organ specialty and closely associated with tumor metastasis.

Author Contribution

Zhengwei Su initiated and supervised the study and revised the final manuscript. Lei Lei and Man Yang performed the study and wrote the paper. Lei Lei helped collect the published articles and contributed to the design of the study. All of the authors have read and approved the final paper.

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