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Association of CD44 Gene Polymorphism with Survival of NSCLC and Risk of Bone Metastasis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Previous studies have reported CD44 expression influenced the development and progression of tumors. The aim of this study was to investigate whether single-nucleotide polymorphisms (SNPs) of the CD44 gene are associated with survival of non-small cell lung cancer (NSCLC) and occurrence rate of bone metastasis.

Material/Methods: A total of 234 patients with NSCLC between 2003 and 2010 were enrolled in this study and 468 healthy persons were used as controls. Two polymorphisms, rs13347 and rs187115, in the CD44 gene were genotyped using DNA from blood lymphocytes. For statistical analysis we used the chi-square test, Fisher's exact test, Kaplan-Meier method, and log-rank test.

Results: CD44 gene rs13347 polymorphism was not associated with NSCLC risk. For rs187115, the association with NSCLC risk was observed ($P<0.001$). Allele G carriers had significantly higher occurrence rates of bone metastasis (OR=0.4, 95%CI: 0.20–0.64, $P<0.001$) and more advanced tumor stage (OR=2.6, 95%CI: 1.50–4.45, $P=0.001$) compared to carriers of allele A. The survival rates for patients with AA genotype were significantly higher than for patients with the AG+GG genotypes ($P<0.001$). In multivariate analysis of survival in NSCLC patients, significant predictors were CD44 gene (AG+GG) (RR=0.48, 95%CI: 0.34–0.68, $P<0.001$), tumor stage (RR=0.45, 95%CI: 0. 0.31–0.65, $P<0.001$), and bone metastasis (RR=1.52, 95%CI: 1.05–2.21, $P=0.027$).

Conclusions: CD44 gene rs187115 polymorphism is a potential predictive marker of survival in NSCLC patients, and is significantly correlated with bone metastasis and tumor stage.

MeSH Keywords: Bone Diseases • Carcinoma, Non-Small-Cell Lung • Polymorphism, Single Nucleotide • Survival Analysis

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Background

Lung cancer is the most common cause of cancer-related deaths worldwide, with more than 1.6 million new cancer cases and 1.4 million deaths in the year 2008 [1]. More than 80% of patients with primary lung cancer were pathologically diagnosed with non-small cell lung cancer (NSCLC) [2,3]. Approximately 55% of patients with NSCLC suffer from distant metastases [4], including to bone, liver, lung, and brain. Bone is the most common site for distant metastasis in NSCLC patients [5]. It has been reported that 30–65% of patients with NSCLC will develop bone metastases [6], with a median survival of less than 8 months [7,8]. Bone metastases can result in significant morbidity and severely decreased quality of life [9–11] due to various skeletal complications such as pathological fractures, serious bone pain, spinal cord compression, and hypercalcemia [6,12,13].

To date, the exact molecular and cellular mechanisms of the development of NSCLC and bone metastasis in NSCLC are still unclear. Many studies [14–17] have recently reported that genes, including osteopontin, CCR2-64I, XRCC1, and IL-1β gene, may play roles in the emergence and progression of NSCLC.

The CD44 gene, located on chromosome 11p13 [18], encodes a cell surface glycoprotein – CD44 [19–21]. As a cell-surface glycoprotein, CD44 is widely known as a cell-surface receptor for osteopontin and hyaluronate and it mediates cellular adhesion to the cell-extracellular matrix (ECM), which is correlated with tumor cell migration [22,23]. Besides its roles in many cellular processes, CD44 plays a crucial role in tumor cell differentiation, invasion, and metastasis [24,25]. Overexpression of CD44 reportedly leads to poor clinical outcomes and poor prognosis for human tumors [26–28]. Recent studies have shown that the CD44 gene interacts with proliferation, migration, and invasion of tumor cells [29,30], and that genetic variants of CD44 are associated with the survival, risk prediction, and prognosis of patient with NSCLC [22,26,31,32].

As the most common type of DNA sequence variation, single-nucleotide polymorphisms (SNPs), may affect the expression of certain genes [33,34]. Previous studies have reported that SNPs rs13347 and rs187115 in CD44 gene were significantly associated with the risk of human tumors [32,35–37]. However, few studies have investigated the association of CD44 polymorphisms with survival of NSCLC and risk of bone metastasis. Therefore, we conducted the present study to investigate whether the 2 SNPs (rs13347 and rs187115) in the CD44 gene have roles on the survival of patients with NSCLC and to explore whether they are associated with incidence of bone metastasis development.

Material and Methods

This study was approved by the ethics committee of the 307th PLA Hospital. Written informed consent was obtained from all enrolled participants. In this study, we recruited a total of 234 patients (156 males and 78 females) diagnosed with NSCLC between July 2003 and September 2010, 65 of which had bone metastasis and the remaining 169 were without bone metastasis. Matched-control subjects were 468 unrelated healthy individuals (308 males and 160 females) during the same period, based on sex and age. The TNM stage of the patients and differentiation system were determined according to International Association of Lung Cancer [38]. The characteristics of the patients from medical records, including age, sex, pathological tumor stage, histopathological diagnosis, and the follow-up, are displayed in Table 1. Individuals with abnormal test results were excluded from the matched-control group. All patients in this study were assessed for bone metastasis according to methods described in a previous study [14]. Blood samples were collected for genomic DNA extraction from patients and healthy controls in Vacutainer tubes containing heparin as an anticoagulant.

DNA extraction and SNP genotyping analysis

Genomic DNA was prepared using the QIAamp DNA mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. DNA samples were stored at –20°C until genotypic analysis was performed. SNP rs13347 and rs187115 in CD44 gene were genotyped using the Taqman allelic discrimination method (Applied Biosystems, Foster City, CA, USA) [39]. The PRIMER sequences were previously described [36]. The TaqMan assays were conducted in a final reaction volume of 5 ml containing 0.25 ml primer, 0.125 ml probe, 2 ml PCR mixture reagent, and 25 ng DNA. The polymerase chain reaction (PCR) consisted of an initial step at 95°C for 10 min followed by 55 cycles of denaturing at 95°C for 15 s and annealing at 60°C for 1 min [36,40]. Allelic discrimination software was used to analyze the PCR genotyping results.

Statistical analysis

All statistical analyses were performed using SPSS19.0 software (SPSS Company, Chicago, IL). Hardy-Weinberg equilibrium (HWE) was evaluated using a χ^2-test. The differences in distributions of the variables between patients and healthy controls were evaluated by Mann-Whitney U test and Fisher's exact test. The comparison of allele type and genotype distributions in the patients and healthy controls was assessed by computing the odds ratio (OR) and 95% confidence intervals (95% CI) from logistic regression analyses. Survival was calculated from the date of surgery to the time of death using the Kaplan-Meier method. *P* values less than 0.05 were considered significant for all statistical analyses.

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Table 1. Demographics of patients with NSCLC and healthy controls.

Variables	Cases (n=234)	Controls (n=468)	*P*-value
Age, y			
≥60/<60	132/102	267/201	0.872
Gender			
Male/female	156/78	308/160	0.822
Pathological type		–	–
Squamous/non-squamous	147/87	–	–
Tumor stage		–	–
I + II	102	–	–
III + IV	132	–	–
Lymph node		–	–
Positive/negative	144/90	–	–
Bone metastasis		–	–
Yes/no	65/169	–	–
KPS		–	–
≥80/<80	176/58	–	–

Results

Patient clinical characteristics

Among a total of 702 subjects of this study, the mean age was 62.21±9.8 years in cases and 61.87±10.75 in matched-pair controls. There were no significant differences in mean age and sex distributions between cases and controls. Distribution of genotypes of the 2 polymorphisms in healthy control group was in accordance with Hardy-Weinberg equilibrium in our study. Of the 234 NSCLC patients, 65 (28%) were diagnosed with bone metastasis. The follow-up period ranged from 23 to 117 months (median, 60 months; mean, 71 months). Among the 234 patients, 171 patients survived less than 5 years and 63 patients survived over 5 years (5-year survival rate of 27%). Characteristics of NSCLC patients and age- and sex-matched controls are shown in Table 1.

CD44 gene Polymorphisms with NSCLC

Table 2 shows the association of each of the SNPs in CD44 gene with the risk of NSCLC. There were no significant differences in the genotypic and allelic distributions of rs13347 polymorphisms between NSCLC patients and healthy controls. However, significant differences were observed in the relationship between frequency distributions of rs187115 and the NSCLC risk. Allele G of rs187115 SNP significantly increased NSCLC risk.

As shown in Table 3, further analysis based on stratification of clinicopathological features revealed significant correlations of frequency distributions of rs187115 SNP with NSCLC risk in tumor stage (OR=2.6, 95%CI: 1.50–4.45, *P*=0.001) and bone metastasis (OR=0.4, 95%CI: 0.20–0.64, *P*<0.001). By comparing with AA genotype, the results indicated that genotype of AG plus GG at rs187115 might significantly increase presence of advanced stage and the risk of development of bone metastasis.

CD44 gene polymorphisms with NSCLC prognosis

Patient survival analysis showed a clear positive correlation between different genotypes at rs187115 in CD44 gene (P<0.001, log-rank=25.999) (Figure 1). The survival rates for patients with the AA genotype were significantly higher than for patients with the AG+GG genotypes (*P*<0.001). Then, we carried out Cox regression analysis. After the univariate analysis, we found that the genotype of rs187115 and 2 clinicopathological parameters – tumor stage and bone metastasis – might be associated with the prognosis of NSCLC (Table 4). Further analyses of all variables in multivariate analysis subsequently revealed that CD44 gene (AG+GG) (RR=0.48, 95%CI: 0.34–0.68, *P*<0.001), tumor stage (RR=0.45, 95%CI: 0. 0.31–0.65, *P*<0.001), and bone metastasis (RR=1.52, 95%CI: 1.05–2.21, *P*=0.027) might also be independent prognostic factors for NSCLC (Table 4).

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Table 2. Distribution frequency of CD44 genotypes and alleles in 348 healthy controls and 174 NSCLC patients.

Variable	Cases (n=234)	Controls (n=468)	OR (95% CI)	*P*-value
rs13347				
CC	179	337	1 (Reference)	–
CT	51	121	1.3 (0.87–1.83)	0.225
TT	4	10	1.3 (0.41–4.29)	0.635
CT+TT	55	131	1.3 (0.88–1.82)	0.204
C	409	795	1 (Reference)	–
T	59	141	1.2 (0.89–1.70)	0.214
rs187115				
AA	133	336	1 (Reference)	–
AG	86	119	0.5 (0.39–0.77)	0.001
GG	15	13	0.3 (0.16–0.74)	0.005
AG+GG	101	132	0.5 (0.37–0.72)	<0.001
A	352	791	1 (Reference)	–
G	116	145	0.6 (0.42–0.73)	<0.001

* *P*-value<0.05 as statistically significant.

Table 3. Distribution frequency of clinicopathological features and CD44 rs187115 genotype frequencies in 234 patients with NSCLC.

Variables	Genotypic frequencies		OR (95% CI)
	AA (n =133)	AG+GG (n=101)	
Age, y			
≥60/<60	74/59	58/43	0.9 (0.55–1.57)
Gender			
Male/female	89/44	67/34	1.0 (0.59–1.78)
Pathological type			
Squamous/non-squamous	82/51	65/36	0.9 (0.52–1.52)
Tumor stage			
I + II	71	31	0.001
III + IV	62	70	2.6 (1.50–4.45)*
Lymph node			
Positive/negative	76/57	68/33	0.6 (0.38–1.11)
Bone metastasis			<0.001
Yes/no	25/108	40/61	0.4 (0.20–0.64)*
KPS			
≥80/<80	96/37	80/21	0.7 (0.37–1.26)

* *P*-value<0.05 as statistically significant.

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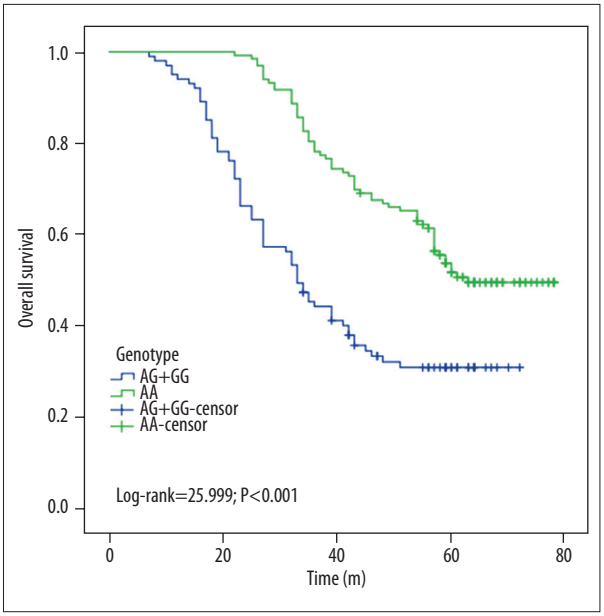

Figure 1. Kaplan-Meier survival curve for patterns of patients with cervical cancer and CD44 rs187115 genotypes.

Discussion

In the present study, we showed the effects of CD44 on prognosis of NSCLC and the risk of development of bone metastasis. To the best of our knowledge, this is the first investigation to report an association between CD44 polymorphisms and bone metastasis among NSCLC patients. The results in this study revealed that CD44 gene rs187115 polymorphism is a potential predictive marker of survival in NSCLC patients, and is significantly associated with bone metastasis and tumor stage.

NSCLC is a common tumor with poor prognosis. Many studies [12,41,42] have investigated the role of genetic factors in the progression and prognosis of NSCLC. A large body of evidence [25–28] suggests that CD44 gene participates in the regulation of tumor metastasis and that overexpression of CD44 is particularly observed in metastatic tumors, especially in those cancers that have a high propensity for the development of bone metastases [37,43,44]. Moreover, the overexpression of CD44 in the primary tumor is reportedly associated with early metastasis and poor prognosis in human cancers [26,37,43–45].

Table 4. Prognostic factors in Cox proportional hazards model.

Variables	Univariate analysis			Multivariate analysis		
	Risk ratio	95% CI	*P*-value	Risk ratio	95% CI	*P*-value
Age, y						
≥60/<60	1.024	0.712–1.579	0.703	1.035	0.686–1.561	0.871
Gender						
Male/female	1.603	0.894–2.797	0.136	1.591	0.902–2.806	0.108
Pathological type	0.619	0.327–1.198	0.172	0.639	0.339–1.204	0.166
Squamous						
Non-squamous						
Tumor stage	0.405	0.268–0.611	<0.001*	0.450	0.311–0.651	<0.001*
I + II						
III + IV						
Lymph node						
Positive/negative	0.876	0.487–1.564	0.648	0.885	0.498–1.575	0.679
Bone metastasis						
Yes/no	1.633	1.064–2.504	0.025*	1.521	1.048–2.206	0.027*
KPS						
≥80/<80	1.202	0.591–2.392	0.531	1.241	0.618–2.489	0.544
Genotype	0.459	0.322–0.655	<0.001*	0.479	0.337–0.680	<0.001*
AA						
AG+GG						

* *P*-value<0.05 as statistically significant.

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It has been reported that CD44 is a cofactor with tumor promotion and tumor suppression [46,47]. It can enhance the affinity of growth factors to their authentic receptors; therefore, CD44 might play roles in proliferation and invasiveness of cells. In contrast, in other situations CD44 acts as tumor suppressor by binding to alternative ligands, resulting in growth arrest due to contact inhibition [43]. The roles of CD44 in a given cell will depend on the subtype of CD44, cellular nature of the ECM, and other unknown conditions [46].

In the current study, we found that the distribution of genotype in the CD44 gene showed significant differences between patients with and without bone metastasis, but we found no significant difference between positive and negative lymph node metastasis (Table 3). A study by Ramasami et al. [48] also showed CD44 had no significant association with lymph node metastases or tumor stage. However, Ko et al. [22] found a strong association between CD44 gene and advanced lymph node metastasis. CD44 has unconfirmed roles in metastases in patients with tumors, and further study is needed to investigate this.

Previous studies have reported varied relationships of CD44 in cancer susceptibility and prognosis. Vazquez et al. [49] reported that allele G of CD44 (rs187115) was associated with increased risk for tumor-related death and lower drug sensitivity. Jiang et al. [50] CD44rs13347 C>T found that polymorphism may affect breast cancer development and prognosis by increasing CD44 expression. Xiao et al. [44] also found that CT and TT genotypes of rs13347 in CD44 gene were associated with increased risk of nasopharyngeal carcinoma. However, Tulsyan et al. [37] did not observe any significant differences in the frequency distribution of the genetic variants CD44 rs13347 between cases and healthy controls. In our study, we found that rs187115 was associated with NSCLC; however, the relationship between rs13347 and NSCLC was not observed. Allelic G carrier has an increased risk of NSCLC and achieves a poor prognosis. Moreover, rs187115 polymorphism is significantly correlated with bone metastasis and tumor stage. SNP rs187115 might become a potential prognostic marker for NSCLC patients.

Some limitations in this study design must be noted. First, selection bias may have occurred because the cases were enrolled from hospital but the healthy controls were chosen from the community. Second, the small sample size may cause significant fluctuations in statistics. Finally, replication in another group was not carried out.

Conclusions

In summary, our study indicated that CD44 rs187115 variant genotypes (AG + GG) could increase the risk of NSCLC and decrease survival time compared with AA genotype, and rs187115 was correlated with bone metastasis and tumor stage. However, well-designed, population-based, case-control studies with lager sample sizes are required to confirm these results.

Competing interests

The authors declare that they have no competing interests.

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