Original Article
Role of cancer stem cell marker CD44 in gastric cancer: a meta-analysis

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Abstract: Cluster of differentiation 44 (CD44), a principal cell surface receptor for hyaluronic acid, has been implicated in tumorigenesis and metastasis. However, the relationship between CD44 expression and the patients with gastric cancer remains controversial. A meta-analysis was performed to quantitatively review the correlation of CD44 expression with the clinicopathological data of the patients with gastric cancer. We conducted a final analysis of the patients from 18 studies. Combined odds ratios (OR) suggested that CD44 expression was related with stage, tumor size, and LN metastasis of gastric cancer, and CD44v6 was related with LN metastasis, lymphatic invasion, and venous invasion. Our results suggested that CD44 and CD44v6 expression could be used to predict the metastasis of gastric cancer.

Keywords: CD44, gastric cancer, metastasis, tumorigenesis, invasion

Introduction

Gastric cancer is one of the leading causes of cancer-related mortality worldwide. A total of 989,600 new stomach cancer cases and 738,000 deaths are estimated to have occurred in 2008 [1]. In China, gastric cancer currently ranks third among the most common cancers, and will remain a significant cancer burden during the next decade [2].

Cluster of differentiation 44 (CD44) is a principal cell surface receptor for hyaluronic acid, a major component of extracellular matrices [3]. The CD44 gene is located on chromosome 11p13 and contains 20 exons, 10 of which are expressed in the standard form (CD44s) [4]. CD44 isoforms, containing variant exon 6 (CD44v6), are generated by alternative splicing of at least 12 exons [5]. CD44 has been reported to play important roles in adherence to the extracellular matrices, motility, matrix degradation, proliferation and cell survival [6, 7]. CD44v6 also plays an important biological role in the invasion and metastasis of tumor [8]. Previous studies showed that increased expression of CD44 or CD44v6 was found in gastrointestinal tumors and was associated with tumor invasion, lymph node metastasis and patients’ survival [9-12].

The association between CD44 or CD44v6 and the clinicopathological parameters of gastric cancer patients has been studied for many years. A single study may fail to completely demonstrate this complicated relationship because of a small sample size. Therefore, we performed a meta-analysis in an attempt to resolve this issue.

Materials and methods

Search strategy

Science Direct, EMBASE, and PubMed were searched to identify potentially relevant published literature. The following criteria were used to search English language articles and abstracts: ‘CD44’ and ‘gastric carcinoma’ or ‘gastric cancer’ or ‘stomach neoplasms’. Existing systematic reviews and reference lists were also checked for any potentially relevant additional studies.

Selection criteria

The studies included in this meta-analysis could be either randomized controlled studies (RCTs)
CD44 and gastric cancer

Data extraction

Data were independently extracted from each report by two authors (Wei Wang and Ning Zhang), using a data recording form developed for this purpose. Data tables were made to extract all relevant data from texts, tables and figures of each included studies, including author, year, country, patient number, and detection method. Any discrepancies between the two investigators were resolved by discussion and consultation with a third reviewer (Cheng-Hai Zhao).

Statistical analysis

The statistical process was performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group [13]. Cochrane Review Manager, version 5.2 (Cochrane Library, Oxford, UK) was used to calculate the available data from each investigation. In addition, if sufficient studies were included, we intended to construct a funnel plot of all studies to investigate the likelihood of publication bias.

Results

Search results

Detailed search steps were described in Figure 1. Two hundred and eighty-one articles were identified initially using the search strategy above. After titles and abstracts were previewed, 53 identified studies concerning CD44 and gastric cancer were further evaluated. Thirty-five of residual 53 papers were excluded due to nonhuman experiments, review, or letter to editor. Eventually, 18 eligible studies were included in the present meta-analysis and listed in Table 1.

Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Cases</th>
<th>Ages (mean)</th>
<th>Type</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>da Cunha</td>
<td>2010</td>
<td>Portugal</td>
<td>43</td>
<td>not shown</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Okayama</td>
<td>2013</td>
<td>Japan</td>
<td>135</td>
<td>63.4 y</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Horikawa</td>
<td>2013</td>
<td>Japan</td>
<td>147</td>
<td>66 ± 11 y</td>
<td>CD44</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Chen</td>
<td>2013</td>
<td>China</td>
<td>152</td>
<td>55 y</td>
<td>CD44</td>
<td>IHC</td>
</tr>
<tr>
<td>Mayer</td>
<td>1993</td>
<td>Germany</td>
<td>60</td>
<td>not shown</td>
<td>CD44</td>
<td>IHC</td>
</tr>
<tr>
<td>Müller</td>
<td>1997</td>
<td>Germany</td>
<td>529</td>
<td>64.9 y</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Wakamatsu</td>
<td>2012</td>
<td>Japan</td>
<td>190</td>
<td>not shown</td>
<td>CD44</td>
<td>IHC</td>
</tr>
<tr>
<td>Kurozumi</td>
<td>1998</td>
<td>Japan</td>
<td>572</td>
<td>61 ± 11 y</td>
<td>CD44</td>
<td>IHC</td>
</tr>
<tr>
<td>Yamaguchi</td>
<td>2002</td>
<td>Japan</td>
<td>201</td>
<td>not shown</td>
<td>CD44v6</td>
<td>WB</td>
</tr>
<tr>
<td>Chen</td>
<td>2013</td>
<td>China</td>
<td>43</td>
<td>58.5 ± 13.4 y</td>
<td>CD44v6</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Liang</td>
<td>2012</td>
<td>China</td>
<td>59</td>
<td>61.8 ± 10.5 y</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Kim</td>
<td>1997</td>
<td>Korea</td>
<td>26</td>
<td>not shown</td>
<td>CD44v6</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Chen</td>
<td>2005</td>
<td>China</td>
<td>31</td>
<td>not shown</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Yoo</td>
<td>1999</td>
<td>Korea</td>
<td>261</td>
<td>56 y</td>
<td>CD44</td>
<td>JHC</td>
</tr>
<tr>
<td>Xin</td>
<td>2001</td>
<td>China</td>
<td>155</td>
<td>not shown</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Chong</td>
<td>1997</td>
<td>Japan</td>
<td>104</td>
<td>62.8 y</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
<tr>
<td>Cao</td>
<td>2014</td>
<td>China</td>
<td>203</td>
<td>60.5 y</td>
<td>CD44</td>
<td>IHC</td>
</tr>
<tr>
<td>Qiu</td>
<td>2014</td>
<td>China</td>
<td>309</td>
<td>60.4 ± 10.4 y</td>
<td>CD44v6</td>
<td>IHC</td>
</tr>
</tbody>
</table>

RT-PCR, reverse transcription PCR; IHC, immunohistochemistry; WB, Western blot.

or observational studies (case-control or cohort) that evaluated the association between CD44 expression and gastric cancer. Articles were excluded from the analyses if there was insufficient published data for determining an estimate of RR and a CI, or if the full text couldn’t be found. If there were several publications from the same population, only the most recent reports were selected for analysis.
CD44 and gastric cancer

**Figure 2.** Meta-analysis of CD44 and the clinical characteristics of patients with gastric cancer. A. Sex; B. Differentiation; C. Stage; D. Tumor size; E. LN metastasis.
CD44 and gastric cancer

A

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Male</th>
<th>Female</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2004</td>
<td>21</td>
<td>26</td>
<td>12</td>
<td>17 4.4% 1.75 [0.42, 7.30]</td>
</tr>
<tr>
<td>Chong 1997</td>
<td>30</td>
<td>70</td>
<td>13</td>
<td>34 15.8% 1.21 [0.52, 2.80]</td>
</tr>
<tr>
<td>Kim 1997</td>
<td>7</td>
<td>8</td>
<td>16</td>
<td>18 1.9% 0.88 [0.07, 11.31]</td>
</tr>
<tr>
<td>Kurozumi 1998</td>
<td>24</td>
<td>45</td>
<td>13</td>
<td>22 12.9% 0.79 [0.28, 2.22]</td>
</tr>
<tr>
<td>Liang 2012</td>
<td>23</td>
<td>36</td>
<td>15</td>
<td>21 12.1% 0.61 [0.19, 1.93]</td>
</tr>
<tr>
<td>Okayama 2009</td>
<td>46</td>
<td>81</td>
<td>28</td>
<td>44 24.8% 0.75 [0.35, 1.60]</td>
</tr>
<tr>
<td>Yoo 1999</td>
<td>63</td>
<td>192</td>
<td>18</td>
<td>69 28.1% 1.30 [0.75, 2.56]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>460</td>
<td>225</td>
<td></td>
<td>1.04 [0.73, 1.46]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.27, df = 6 (P = 0.77), I² = 0%
Test for overall effect: Z = 0.20 (P = 0.894)

Favours experimental Favours control

B

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Differentiation</th>
<th>undifferentiation</th>
<th>Differentiation</th>
<th>Odds Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2004</td>
<td>23</td>
<td>29</td>
<td>10</td>
<td>14 24.6% 1.52 [0.35, 6.65]</td>
<td></td>
</tr>
<tr>
<td>Liang 2012</td>
<td>30</td>
<td>38</td>
<td>8</td>
<td>21 31.0% 6.09 [1.88, 19.76]</td>
<td></td>
</tr>
<tr>
<td>Okayama 2009</td>
<td>46</td>
<td>70</td>
<td>38</td>
<td>65 44.4% 1.36 [0.68, 2.74]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>137</td>
<td>100</td>
<td></td>
<td>2.23 [0.85, 5.83]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.41; Chi² = 7.42, df = 2 (P = 0.09); I² = 48%
Test for overall effect: Z = 1.64 (P = 0.10)

Favours experimental Favours control

C

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>T I/II</th>
<th>T III/IV</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2009</td>
<td>10</td>
<td>18</td>
<td>10</td>
<td>18 3.8% 0.04 [0.00, 0.83]</td>
</tr>
<tr>
<td>Kurozumi 1998</td>
<td>9</td>
<td>14</td>
<td>7</td>
<td>14 14.3% 1.30 [0.40, 4.25]</td>
</tr>
<tr>
<td>Müller 1997</td>
<td>181</td>
<td>287</td>
<td>92</td>
<td>133 26.7% 0.76 [0.49, 1.18]</td>
</tr>
<tr>
<td>Okuyama 2009</td>
<td>57</td>
<td>47</td>
<td>27</td>
<td>38 20.4% 0.58 [0.26, 1.30]</td>
</tr>
<tr>
<td>Yamaguchi 2002</td>
<td>45</td>
<td>91</td>
<td>40</td>
<td>100 24.5% 1.47 [0.83, 2.60]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>547</td>
<td>353</td>
<td></td>
<td>0.68 [0.36, 1.28]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.24; Chi² = 14.62, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 1.19 (P = 0.23)

Favours experimental Favours control

D

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intestinal</th>
<th>diffuse</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chong 1997</td>
<td>15</td>
<td>43</td>
<td>13</td>
<td>27 15.5% 0.58 [0.22, 1.54]</td>
</tr>
<tr>
<td>da Cunha 2010</td>
<td>7</td>
<td>14</td>
<td>10</td>
<td>13 7.7% 0.30 [0.06, 1.58]</td>
</tr>
<tr>
<td>Kurozumi 1998</td>
<td>16</td>
<td>31</td>
<td>21</td>
<td>36 14.0% 0.76 [0.29, 2.00]</td>
</tr>
<tr>
<td>Müller 1997</td>
<td>199</td>
<td>264</td>
<td>91</td>
<td>117 46.3% 0.87 [0.52, 1.47]</td>
</tr>
<tr>
<td>Xin 2001</td>
<td>44</td>
<td>101</td>
<td>15</td>
<td>54 16.4% 2.01 [0.98, 4.10]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>453</td>
<td>247</td>
<td></td>
<td>0.95 [0.68, 1.34]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 7.36, df = 4 (P = 0.12); I² = 46%
Test for overall effect: Z = 0.27 (P = 0.79)

Favours experimental Favours control

E

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LN metastasis</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2004</td>
<td>24</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>Chong 1997</td>
<td>26</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Kim 1997</td>
<td>6</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Kurozumi 1998</td>
<td>28</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td>Liang 2012</td>
<td>31</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>Müller 1997</td>
<td>159</td>
<td>229</td>
<td>114</td>
</tr>
<tr>
<td>Okuyama 2009</td>
<td>55</td>
<td>74</td>
<td>29</td>
</tr>
<tr>
<td>Yamaguchi 2002</td>
<td>78</td>
<td>160</td>
<td>17</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>637</td>
<td>416</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.23; Chi² = 16.05, df = 7 (P = 0.02); I² = 56%
Test for overall effect: Z = 3.35 (P = 0.0008)

Favours experimental Favours control

CD44 and gastric cancer

Association of cancer stem cell marker CD44 with the clinicopathological parameters of the patients with gastric cancer

There was no clear correlation between CD44 expression and sex (pooled OR = 1.14, 95% CI: 0.85-1.55, P = 0.38) (Figure 2A), and differentiation of gastric cancer (pooled OR = 1.30, 95% CI: 0.97-1.75, P = 0.08) (Figure 2B). However, CD44 expression was associated with stage (pooled OR = 2.05, 95% CI: 1.12-3.75, P = 0.02) (Figure 2C), tumor size (pooled OR = 1.42, 95% CI: 1.08-1.87, P = 0.01) (Figure 2D), and LN metastasis (pooled OR = 1.50, 95% CI: 1.14-1.98, P = 0.004) (Figure 2E). Furthermore, we found that CD44v6 was related with LN metastasis (pooled OR = 2.26, 95% CI: 1.40-3.64, P = 0.0008) (Figure 3F), lymphatic invasion (pooled OR = 1.45, 95% CI: 1.05-2.01, P = 0.02) (Figure 3F), and venous invasion (pooled OR = 1.62, 95% CI: 1.20-2.18, P = 0.001) (Figure 3G), but not with sex (pooled OR = 1.04, 95% CI: 0.73-1.46, P = 0.84) (Figure 3A), differentiation of gastric cancer (pooled OR = 2.23, 95% CI: 0.85-5.83, P = 0.10) (Figure 3B), stage (pooled OR = 0.68, 95% CI: 0.36-1.28, P = 0.23) (Figure 3C), and tumor type (pooled OR = 0.95, 95% CI: 0.68-1.34, P = 0.79) (Figure 3D). No obvious publication bias was observed in these studies (Figure 4).

Discussion

The role of CD44 expression in gastric cancer has been explored for nearly thirty years. CD44 was identified as a surface glycoprotein and a lymphocyte homing receptor found on lymphoid and epithelial cells in 1982 [31]. Its main function on lymphocytes is mediating interaction with the endothelium [32]. CD44v6, one of the major variants of CD44, could alter the conjugation of CD44s and hyaluronic acid (HA), or enhance the metastasis of tumor by conjugation with HA [23]. Despite there being many studies, the validity of CD44 and CD44v6 as a therapeutic or diagnostic target in gastric cancer has not been fully investigated and some findings are still controversial. In this meta-analysis, we found that CD44 could influence stage, tumor size, and LN metastasis. And CD44v6 was related with LN metastasis, lymphatic invasion, and venous invasion. Günther et al. [33] demonstrated a significant relationship between CD44v6 expression and lymph node metastasis, lymphatic invasion when they transfected plasmids expressing CD44 or CD44v6 into nonmetastatic rat pancreatic carcinoma cells.

Our study provided a more believable result due to a larger size sample, and provides expla-
nations for the inconsistencies observed in previous studies. However, some possible limitations of our meta-analysis should be acknowledged and taken into consideration. First, original information was not available in all of the selected studies. Second, the results may be influenced by the lack of observations regarding gene-environment interactions. Third, a meta-analysis is not able to solve problems with confounding factors that could be inherent in the included studies.

In summary, despite the limitations listed above, this present study shows a significant correlation between CD44 expression and stage, tumor size, and LN metastasis of gastric cancer. CD44v6 was related with LN metastasis, lymphatic invasion, and venous invasion. The value of the current meta-analysis compensates for the individual lack of precision of most studies, a problem alleviated by pooling. Further studies are required to evaluate their potential use in predicting patients’ outcome.
Acknowledgements

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Disclosure of conflict of interest

None.

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References


CD44 and gastric cancer


