The role of insulin-like growth factor axis in bladder cancer: a systemic review and meta analysis

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Abstract: Background: The role of the IGF axis in bladder cancer has been extensively studied in recent years, but the results are controversial. Methods: Pubmed, Embase, China national knowledge infrastructure and Wanfang databases were searched to identify eligible studies to evaluate the association among IGF-1, IGFBP-3, IGF-1R and IMP-3 expression and bladder cancer risk, depth of invasion and recurrence. Results: 15 studies were involved in the analysis, 5 of them reported the relation between serum concentration of IGF-1 or IGFBP-3 and bladder cancer risk. The difference in serum IGF-1 concentration was not significant between patients with bladder cancer and health controls (P=0.57). The serum IGFBP-3 concentration was lower in patients with bladder cancer (SMD: -0.78, 95% CI: -1.40, -0.15). 10 studies were involved in the analysis of the relation between IGF-1R or IMP-3 expression and bladder cancer. The expressions of IGF-1R and IMP-3 were elevated in MIBC compared with NMIBC (OR: 0.30, 95% CI: 0.19, 0.48 and OR: 0.30, 95% CI: 0.19, 0.46). The expressions of IGF-1R and IMP-3 were also found to be elevated in recurrent bladder cancer compared with primary bladder cancer (OR: 5.05, 95% CI: 2.43, 10.51 and OR: 2.47, 95% CI: 1.48, 4.13). Conclusion: The IGF axis plays an important role in tumor proliferation and invasion, recurrence and metastasis. IGFBP-3 may be a potential serum biomarker for the screening of bladder cancer. The elevated expressions of IGF-1R and IMP3 in tissue are symbols of a highly malignant bladder cancer, and they could be utilized in the molecular classification of bladder. IGF-1R may be a promising therapeutic target for bladder cancer, but further studies are needed to evaluate the sensitivity of bladder cancer to the new targeted drugs and the predictive effect of serum IGFs in the targeted therapy.

Keywords: Bladder cancer, invasion, recurrence, IGF-1, IGFBP-3, IMP-3

Introduction

Bladder cancer is the most common urinary tract cancer and the ninth common cancer worldwide [1]. The TNM stage system is currently the most effective risk stratifying system. However, its utilization in the assessment of the malignancy and prognosis is limited due to the heterogeneity of bladder cancer. Patients with Ta-1 bladder cancer were mostly treated with bladder preservation approach because it is theoretically likely to be cured by transurethral resection of bladder tumor (TURBT). However, according to the result of a meta analysis of 19 trials and 3088 patients, 21% of the patients with NMIBC showed progression to MIBC after TURBT [2]. In patients with T2-4 bladder cancer (known as muscle-invasive bladder cancer), although radical cystectomy was performed routinely, cancer relapsed in about 50% of them and finally leads to cancer related death [3]. A better stratifying system is required to distinguish the bladder cancer with highly progressive and recurrent capacity from the low risk ones.

Recently, a large number of studies have reported possible biomarkers for the screening of potential patients and prediction of disease progression in patients with bladder cancer. Insulin-like growth factor (IGF) axis was an extensively studied system and several proteins in this axis were reported to be promising biomarkers for cancers. In our previous proteomic study, abnormally altered expressions of IGF related biomarkers were also identified in patients with bladder cancer. Thus we performed this study to verify the role of IGFs and IGF relat-
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Materials and methods

Literature search and study selection

A comprehensive literature search was performed in March 2013 using Pubmed, Embase, China national knowledge infrastructure and Wanfang databases to identify possible data resources. The reference list of included studies and related reviews were also examined to identify articles not captured by the primary search.

Studies published before May 2014 discussing expression of IGF-1, IGF-1R, IGFBP-3 and IMP-3 in bladder cancer were examined. Studies reporting on circulating concentration or expression of these proteins in tissue in patients with bladder cancer were included for further screening. This process was completed by two independent reviewers. Disagreements were resolved through discussion.

Eligible studies had to fulfill the following criteria: 1) Testing of IGF-1, IGF-1R, IGFBP-3 or IMP-3 in serum or tumor tissue of bladder cancer patients. 2) All patients diagnosed with bladder cancer were confirmed by histopathological examinations. 3) Studies reported sufficient data to calculate the mean with standard deviation (SD) or odds ratio (OR) with 95% confidence interval (CI).

Articles were excluded for the following reasons: 1) Reviews and case reports. 2) Studies without valid data or with improper data. 3) Duplicated reports.

Study quality assessment

The level of evidence was evaluated according to the criteria of Oxford Center for Evidence-Based Medicine. The methodological quality of each study was assessed with the Newcastle-Ottawa Scale (NOS).

Data extraction

Two reviewers examined the full texts of the included studies separately. For the included studies, data on characteristics of the tumor, expression of IGF-1, IGF-1R, IGFBPs and IMP3 in blood or bladder tissue, and data on survival were extracted.

Statistical analysis

The serum concentrations of IGF-1 and IGFBP-3 were assessed by mean and standard deviation (SD). For the studies reporting on serum concentrations of IGF-1 and IGFBP-3 in mean and range, the SMD were calculated with the method described by Hozo et al. [4]. Meta analyses were carried out using the “metan” command of STATA 12.0 (Stata Corporation, Collage Station, Texas, USA). The relation between depth of tumor invasion, recurrence and expression of IGF-1R and IMP-3 in cancer tissue was evaluated by OR and 95% CI. I-squared test was used to evaluate the heterogeneity among studies. If the heterogeneity was not significant, pooled estimates would be calculated with the fixed-effect model (Mantel-Haenszel method [5]); otherwise the random-effect model (DerSimonian-Laird method [6]) would be used.

The pooled effect was determined by Z test. The result was considered statistically significant when \( P < 0.05 \). Leave-one-out sensitivity analysis was performed to access the impact of the individual data set to the pooled results [7].

Results

After removing duplicates, a total of 2880 articles (109 in English, 2761 in Chinese) were...
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2831 articles were excluded by review of titles and abstracts. The full texts of the remaining 49 articles were examined. 6 studies reported on serum concentration of IGF-1 and IGFBP3. 5 studies were included for the analysis of IGF1R, and 5 studies for the analysis of IMP3. The quality of the included studies was showed in Table 1.

Five studies reported the serum concentration of IGF-1 and IGFBP3 in patients with bladder cancer and healthy controls [8-12]. The $I^2$ values of the two datasets are 95.8% and 94.1%, respectively, so the random effect model was used. The pooled mean difference for IGF-1 was -0.95, 95% CI (-45.82, 27.72) ($P=0.63$) (Figure 1). The pooled mean difference for IGFBP-3 was -0.6, 95% CI (-11.1, -0.09) ($P=0.02$) (Figure 2).

A total of 5 studies (one in English, and four in Chinese), including 349 patients with bladder cancer and 54 controls, reported expression of IGF1R in tissue [13, 14]. The expression of IGF1R in tissue was found to be significantly associated with bladder cancer ($I^2=0$, fixed
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effect, OR=17.09 95% CI [6.70, 43.62], Figure 3). For depth of invasion, the $I^2$ value of the dataset is 49% ($P=0.541$), therefore fixed effect model was used. The pooled odd was lower in NMIBC group (fixed effect, OR=0.30 95% CI [0.19, 0.48]) (Figure 4). The major heterogeneity comes from the study of Rochester et al. In this study, the expression of IGF-1R was detected by immunochemical staining of whole-mount sections in 55 samples and tissue microarrays (TMA) in the other 80 samples [13]. The IGF-1R positive ratio of cases examined by TMAs is higher than whole-mount sections. When the cases examined by TMA were removed, the pooled OR was 0.23 (95% CI: 0.14, 0.40, $I^2=0$, fixed effect). With regards to recurrence, the expression of IGF1R was found to be strongly associated with bladder cancer recurrence.

Figure 3. Forest plot of expression of IGF-1R in bladder cancer versus normal urothelial tissue.

Figure 4. Forest plot of expression of IGF-1R in non-muscle invasive bladder cancer versus muscle invasive bladder cancer.
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(I²=0%, fixed effect, OR=5.05 95% CI [2.43, 10.51]) (Figure 5).

With respect to the expression of IMP3 in tissue, 5 studies, a total of 214 patients with NMIBC and 483 patients with MIBC were included [15-18]. With regards to depth of invasion, the pooled odd was lower in NMIBC group versus MIBC group (I²=51.1%, fixed effect, NMIBC vs. MIBC: OR=0.3095% CI [0.19, 0.46]) (Figure 6), and was lower in T1 group compared with T2 group (I²=26%, fixed effect, T1 vs. T2: OR=0.39 [0.21, 0.73]) (Figure 7). The major heterogeneity comes from the study of Özdemir et al. It can be explained by the selection bias of this study, because only patients with T0-2 bladder cancer were involved. After removal of this study, the pooled OR is 0.36 (95% CI: 0.23, 0.57). With regards to recurrence, the pooled odd was larger in recurrent bladder cancer.
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Discussion

IGFs are multi-functional peptides that regulate cell proliferation, differentiation and apoptosis. Serum concentrations of IGF-1 and IGFBP-3 were reported to be associated with several lifestyle carcinogenic factors and environmental toxicities [19]. The altered IGF axis may play a key role in the carcinogenesis.

In many cancers, such as prostate, breast, colon, and lung cancer, altered serum concentrations of IGF-1 and IGFBP-3 have been reported [20]. However, reports on concentrations of serum IGF-1 in patients with bladder cancer came to conflicted outcomes. In a case-control study of 154 patients with bladder cancer and 154 health controls reported by Zhao et al. [9], concentrations of serum IGF-1 elevated signifi-
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Significantly in patients with bladder cancer, however, in the study of Safarinejad et al. [11], concentrations of serum IGF-1 were lower in patients with bladder cancer than health controls. In the studies of Shariat et al. and Mahmoud et al. [8, 10], the difference of serum IGF-1 between patients and controls was not statistically significant. Our result of the meta analysis suggests that the serum IGF-1 is not statistically different between the bladder cancer patients and health people and therefore not an eligible biomarker for bladder cancer.

IGFBP-3 is an important regulator of IGFs. Approximately 75 percent of serum IGFs are bound to IGFBP-3 [21]. IGFBP-3 can inhibit cell proliferation and enhance cell apoptosis by attenuating the effect of IGFs or directly binding with the IGFBP-3 receptor [22]. The pooled serum concentration of IGFBP-3 was lower in patients with bladder cancer compared with healthy controls, and a lower serum level of IGFBP-3 was reported to be associated with lymph node metastasis and poor clinical outcome after radical cystectomy when adjusted for IGF-I level [8]. It may be a potential serum biomarker for bladder cancer, but further studies are needed to evaluate its efficiency.

Free of lamina muscularis infiltration can be either the symbol of bladder cancer with low malignancy or a temporal status of highly invasive bladder cancer. Better risk stratification system is desperately needed for the assessment of heterogeneity of NMIBC behavior. Several biomarkers have been studied for their potential application in the assessment of tumor invasiveness, metastasis and recurrence. However, their predictive effect is far from satisfying.

Type I insulin-like growth factor receptor (IGF-1R) is a transmembrane protein tyrosine kinase which mediates the biological effects of IGF-1 and most of the actions of IGF-2 [23]. Its expression in normal tissue is low, but high in bladder cancer (OR=17.09 95% CI [6.70, 43.62]). More importantly, our finding demonstrated that the expression of IGF-1R is significantly related to the depth of invasion (OR: 0.31 95% CI [0.19, 0.49]) and bladder cancer recurrence (OR: 5.05 95% CI [2.43, 10.51]). In a retrospective study, IGF-1R overexpression was associated with overall mortality and cancer-specific mortality [24]. Therefore the IGF-1R status could be included in the risk stratification system of bladder cancer.

Insulin-like growth factor II mRNA-binding protein 3 (IMP-3) is a member of the IMP family, which plays an important role in RNA trafficking and stabilization, cell growth, and cell migration during the early stages of embryogenesis [25]. It was rarely detected in adult normal tissues but over-expression of IMP-3 was reported in urothelial tumors [26]. IMP-3 plays a critical role in regulation of cell proliferation via an IGF-2-dependent pathway. We investigated the expression of IMP-3 in NMIBC and MIBC. The result showed that IMP3 status were significantly related to the depth of invasion (NMIBC vs. MIBC: OR 0.34 95% CI [0.21, 0.54]; T1 vs. T2: OR 0.31 [0.17, 0.57]). Relation between IMP-3 and tumor progression was also proved in a cohort, in which the patients with IMP-3 positive NMIBC were found more likely to develop a MIBC (OR: 6.5 95% CI [2.2, 19.0]) [27]. These findings suggest that IMP-3 is a potential biomarker for the evaluation of tumor invasiveness and prediction of progression. Correlation of IMP-3 and tumor recurrence were also studied, remarkable correlation was found between the IMP-3 status and recurrence (recurrent bladder cancer vs. primary bladder cancer: OR 2.47 95% CI [1.48, 4.13]). Moreover, the IMP-3 status was significantly related to disease-spe-
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cific survival and recurrence-free survival in three cohorts [15, 16, 27]. The IMP-3 status should be utilized in the assessment of invasion, recurrence, and metastasis risk of bladder cancer, especially NMIBC.

As IGF-1R and IMP-3 are rarely expressed in normal tissue, but up-regulated in cancer tissue, they may be ideal therapeutic targets. Compared with the traditional chemotherapy regimens, treatments targeting IGF axis may destroy cancer cells with better specificity and it may show better efficiency in preventing tumor progression and recurrence. Since its expression is higher in muscle invasive and recurrent bladder cancer, it may be more effective on high risk NMIBC and MIBC, and could be a reasonable option for the salvage treatment after bladder cancer recurrence.

Several IGF-1R monoclonal antibodies, such as AVE1642, AMG479, R1507 and Figitumumab, have been developed. The IGF-1R targeted drugs achieved well tolerance and durable response in several kinds of cancers [28-31]. In a recent phase I study, 48 patients with advanced solid tumors received AVE1642 (three weekly, dosed at 6 mg/kg), combined with docetaxel, gemcitabine and erlotinib, or doxorubicin. The treatment was well tolerated and durable disease control were achieved in 44% patients [28]. With respect to biomarkers for IGF targeted therapy sensitivity, the serum concentration of free or total IGF-1 or IGF-2 appear to correlate with response to IGF-1R targeted therapy [28, 32]. However, numbers of cases in these studies were small and no study has specifically studied the application of these drugs in bladder cancer. Further researches are needed to evaluate the effect of these targeted drugs and the relation between expressions of IGF related biomarkers and sensitivity to IGF1R-targeted therapy in bladder cancer.

In conclusion, IGF axis plays an important role in tumor proliferation and invasion, recurrence and metastasis. IGFBP-3 may be a potential serum biomarker for the screening of bladder cancer. The elevated expression of IGF-1R and IMP3 in tissue is a symbol of a highly malignant bladder cancer, and could be utilized in the molecular classification of bladder. Since IGF-1R is rarely expressed in normal urothelial tissue but over-expressed in bladder cancer, it may be a promising therapeutic target for bladder cancer, but further studies are needed to evaluate the sensitivity of bladder cancer to the new targeted drugs and predictive effect of serum IGFs in the targeted therapy.

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Disclosure of conflict of interest

None.

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References

[9] Zhao H, Grossman HB, Spitz MR, Lerner SP, Zhang K and Wu X. Plasma levels of insulin-like growth factor-1 and binding protein-3, and
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