

Metadherin in prostate, bladder, and kidney cancer: A systematic review

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Abstract. Metadherin (MTDH) has been identified as an important oncogene in carcinogenesis, tumor progression and metastasis in numerous malignancies, through signal transduction pathways. MTDH is a potential biomarker and therapeutic target in cancers. The present systematic review was performed to search for studies regarding MTDH and prostate, bladder and kidney cancer using several databases and the eligible studies were reviewed. MTDH expression was found to significantly increase in prostate, bladder and kidney cancers, not only in clinical tissue samples, but also in cancer cell lines. Reviewing the clinical and statistical analysis revealed that MTDH may be involved in urologic cancer progression, metastasis and prognosis. MTDH may be an independent or one of the cofactors in urologic cancers for prediction of patient survival, and may be involved in potential anticancer strategies. MTDH may be associated with several signal transduction pathways in urologic cancers, indicating latent targets to develop anticancer therapeutic strategy. Further studies are required to confirm these findings.

Introduction

Metadherin (MTDH), also known as astrocyte-elevated gene (AEG)-1 and lysine-rich CEACAM-1-associated protein (LYRIC) (1-2), was first identified in human fetal astrocytes induced by human immunodeficiency virus-1 in 2002 (3). MTDH has been cloned for nearly ten years (4-6) and is considered to be an important oncogene in carcinogenesis,

tumor progression and metastasis, via a series of signaling pathways (7-9). However, as the exact functions of MTDH in cancer remain unclear, particularly in malignant tumors, future investigations are required (10).

Recent studies have shown that high expressions of MTDH are present in various tumors, involving the nervous, urogenital, respiratory and digestive systems (9,11-19). Evidence indicates that MTDH knockdown significantly inhibited the growth of gastric cancer cells (9). MTDH is an anti-apoptotic gene in glioma cells and could be used as a target of microRNA-136 in anticancer therapeutic strategy (11). A study revealed that MTDH promotes invasion and metastasis through the activation of nuclear factor- κ B (NF- κ B), interleukin-8 and matrix metalloproteinase-9 in breast cancer (12), which is consistent with studies in non-small cell lung cancer and glioma (13,14). MTDH has been shown to be associated with a poor prognosis in malignancies, including non-small cell lung cancer, invasive breast cancer, laryngeal squamous cell carcinoma, gallbladder adenocarcinoma, tongue carcinoma and bladder cancer (15-19). MTDH is also associated with the prognosis of carcinoma, possibly due to chemoresistance and radiosensitivity in cancer therapy (20,21).

Increasing evidence indicates that MTDH is an important mediator in signal transduction pathways in malignancies, a potential biomarker to predict cancer survival and provides information to develop target chemotherapies. The present systematic review aimed to investigate the expression, pathogenesis and therapeutic strategies of MTDH in prostate, bladder and kidney cancers.

Materials and methods

Literature selection. The inclusion criteria for the search are any studies regarding MTDH and prostate, bladder and kidney cancer. The exclusion criteria are as followings: i) Duplicate or series reporting, in which the most detailed results were included; ii) conference report, review or letter; and iii) study language not in English or Chinese.

Literature search. A comprehensive literature search of the English and Chinese databases was performed from the time when establishing the databases to 25 March, 2014, using Pubmed, Highwire, Springerlink, EBSCO, ProQuest, Wiley, Google Scholar, China National Knowledge Infrastructure

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and Wanfang Data Knowledge Service Platform (Wanfang data). The studies regarding MTDH and prostate, bladder and kidney cancer respectively were searched for. The following example is the search strategy of MTDH and prostate cancer in Pubmed: (metadherin or MTDH or astrocyte elevated gene-1 or AEG-1 or lysine-rich CEACAM1 or LYRIC) and (prostate or prostate neoplasm or prostate cancer). The references of the associated studies were checked manually to avoid the loss of relevant studies. Approximately 537 studies were consistent with the search strategies in these databases, and 13 were eligible for the search. Fig. 1 shows a flowchart of the search process. The detailed search results of MTDH and prostate, bladder and kidney cancers are listed in Table I.

Results and Discussion

MTDH and prostate cancer. A total of 8 eligible studies reported the association between MTDH and prostate cancer. High MTDH expression was detected in tissue specimens and prostate cancer cell lines, and was confirmed to be associated with prognosis and patient survival. Studies also investigated the possible signal transduction pathways in prostate cancer cell lines mediated by MTDH, which may be potential therapeutic targets for anticancer.

MTDH overexpression in prostate cancer. One study showed that MTDH overexpression in prostate cancer was 66.7% (22), whereas in another study, the total expression of MTDH was 100% (23). The later case-control study involved 20 prostate cancer samples from radical prostatectomy and 20 benign prostatic hyperplasia (BPH) specimens from transurethral resection. MTDH strongly positive expression in prostate cancer was 80%, whereas it was 10% in BPH. Weakly positive expression of MTDH in prostate cancer was reduced to only 20%, but 35% in BPH. The negative expression in BPH reached 55%.

A high expression of MTDH in prostate cancer cell lines was also observed in the eligible studies. Quantitative reverse transcription polymerase chain reaction (RT-PCR) and western blotting showed that the expression level of MTDH in prostate cancer cells was nearly three times higher compared to those in non-cancerous human prostatic epithelial cell line (RWPE-1 cells) at the mRNA and protein level, respectively. High MTDH expressions were found in three common prostate cancer cell lines: LNCaP, DU145 and PC-3 cell lines (23,24).

Thirkettle *et al* (10) reported the MTDH distribution in the subcellular compartments of prostate cancer and benign samples. The MTDH expression in the nucleus of luminal cells was much higher in benign cases (82.5%) compared to in tumors (26.6%). The distributions of MTDH in cytoplasm alone, cytoplasm plus nucleus and global cells in prostate cancer samples were 33.6%, 42.9% and 8.8%, respectively. The distribution of MTDH was different in subcellular compartments, which was also associated with tumor grades (10).

These results show that an association exists between the expression of MTDH and prostate cancer. MTDH overexpression not only occurs in human tissue samples, but also in prostate cancer cell lines. Studies have demonstrated that the

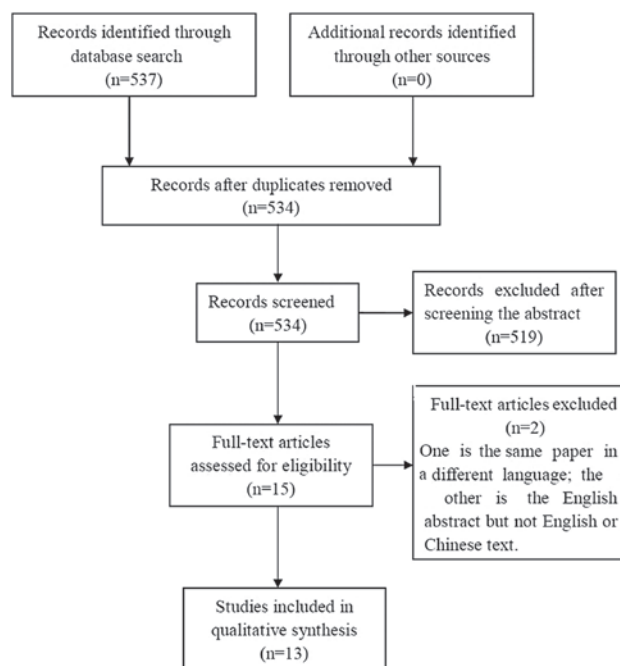


Figure 1. A flowchart of the search process regarding metadherin in prostate, bladder and kidney cancer.

high expression of MTDH is similar in prostate cancer, but is not distinctive in benign lesions (23). However, in another study, MTDH was also proved to be highly expressed in benign samples (10).

Progression and survival of MTDH in prostate cancer. A follow-up of 50 patients for <120 months indicated that mean survival times in patients with MTDH in the nucleus are longer than those losses of MTDH in the nucleus (10). In patients with bone metastasis, a high expression of MTDH was confirmed in prostate bone metastases (81.8%) and it was mainly distributed in the cytoplasm and membrane (10). Following an investigation of 97 radical prostatectomy samples, Erdem *et al* (22) showed that MTDH combined with the basic fibroblast growth factor is one of the independent prognostic parameters. These results indicate that MTDH may be a potential prognostic factor of prostate cancer.

MTDH and signal transduction in prostate cancer. The pathogenesis of MTDH in tumors may be interpreted as participating in signal transduction pathways, including NF- κ B, Ha-ras and AKT. These signaling pathways may be involved in carcinogenesis, metastasis and progression in malignancies, predicting that MTDH may be a biomarker in cancers (7,25,26).

Ash *et al* (27) used the yeast two-hybrid assay to identify that BRCA2 and CDKN1A interacting protein (BCCIP) is an associated protein of MTDH. In DU145 cells, MTDH was found to be a negative regulator of BCCIP α , which induces DU145-apparent neuroendocrine differentiation. The NF- κ B signaling pathway was considered to be involved in the interactions of MTDH and BCCIP in prostate cancer cells. Another study also verified that the knockdown of MTDH downregulated the activity of NF- κ B in PC-3 and DU145 cells (23). In

Table I. Summary of the 13 eligible studies regarding MTDH and prostate, bladder and kidney cancer.

First author	Publication year	Language	Cancer type	Contents	Specimens	Main detecting method(s)	Main conclusions	Reference
Kikuno	2007	English	Prostate	MTDH expression; signal pathway of FOXO3a	Tissue samples; PC-3, DU145 and LNCaP cells	Immunostaining; RT-PCR, western blot; MTDH knockdown	Overexpression in prostate cancer, MTDH activates AKT and suppresses FOXO3a	23
Ash	2008	English	Prostate	MTDH and its associated protein, BCCIP α	DU145 cells	Yeast two-hybrid; Western blot; IP and IIF	MTDH is a negative regulator of BCCIP α and NF- κ B may be involved	27
Thirkettle	2009	English	Prostate	MTDH is targeted to different subcellular compartment	Tissue samples;	Microarray	A significant difference among MTDH distribution, Gleason grade and survival	10
Lee	2012	English	Prostate	Molecular mechanism of anticancer drug cryptotanshinone	PC-3, DU145 and LNCaP cells	siRNA transfection, western blot, IIF array, immunohistochemistry; PC-3 xenograft model	Inhibition of MTDH is one of the molecular targets for cryptotanshinone exerting anticancer effects.	24
Zhang	2012	Chinese	Prostate	Observation of MTDH-based gene vaccine in prostate cancer models in mice	Mice models	Immunohistochemistry, flow cytometry; RM-1 xenograft model	Mice with prostate cancer <i>in situ</i> with MTDH gene vaccine exhibit prolonged tumor-bearing survival periods	30
Erdem	2013	English	Prostate	Association of the prognostic factors in prostate carcinoma	Tissue samples	Tissue microarray	bFGF and MTDH is one of the independent prognostic parameters in prostate carcinoma	22
Zhang	2013	Chinese	Prostate	Evaluation efficacy of GM-CSF adjuvant in prostate cancer models in mice	Mice models	Immunohistochemistry, flow cytometry; RM-1 xenograft model	Combining with GM-CSF adjuvant shows stronger anticancer effects, no prolonged tumor-bearing survival period	28
Hu	2013	Chinese	Prostate	Evaluation efficacy of MTDH gene vaccine on paclitaxel in prostate cancer models in mice	Mice models	Immunohistochemistry, flow cytometry; RM-1 xenograft model	Sensitivity of paclitaxel was enhanced in prostate cancer models in mice	29

MTDH, metadherin; RT-PCR, reverse transcription polymerase chain reaction; BCCIP, BRCA2 and CDKN1A interacting protein; IP, immunoprecipitation; IIF, immunofluorescence; NF- κ B, nuclear factor- κ B; siRNA, small interfering RNA; bFGF, basic fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ChIP, Chromatin immunoprecipitation; miR, microRNA.

Table I. Continued.

First author	Publication year	Language	Cancer type	Contents	Specimens	Main detecting method(s)	Main conclusions	Reference
Zhou	2012	English	Bladder	Investigating the association of MTDH expression and bladder cancer clinical stage; and MTDH as a biomarker in bladder cancer	Tissue samples	Immunohistochemistry, RT-PCR	MTDH may be a biomarker of bladder cancer progression, associated with patient survival	19
Nikpour	2014	English	Bladder	Exploring functional role of MTDH in bladder cancer cells	Tissue samples; 17 bladder cancer cell lines	RT-PCR, western blot, immunohistochemistry; RNA interference; viability and caspase assay	MTDH is overexpressed in bladder cancer. Downregulation of MTDH reduced cell viability and cell migration and increased apoptosis in bladder cancer cell lines	31
Chen	2010	English	Kidney	Detecting MTDH expression in renal cell carcinoma, revealing the association among MTDH, histopathological features and survival	Tissue samples; 786-0, OS-RC-1, Caki-2, ACHN cells	RT-PCR, western blot; immunohistochemistry	MTDH is overexpressed in kidney cancer and is associated with tumor differentiation, progression and prognosis	32
Erdem	2013	English	Kidney	Investigating the association of MTDH and p53 in renal cell carcinoma	Tissue samples	immunohistochemistry	MTDH is overexpressed in renal cell carcinoma and may be one of the prognostic parameters in renal cell cancer patients	33
Wu	2013	English	Kidney	Exploring pathways of miR-30d in renal cell cancer	Tissue samples; ACHN and 786-0 RCC cell lines	RT-PCR, western blot; flow cytometry, ChIP, RNA interference, nuclear run-on assay	Identified a novel Akt/FOXO/miR-30d/ MTDH signaling transduction pathway in kidney cancer	34

MTDH, metadherin; RT-PCR, reverse transcription polymerase chain reaction; BCCIP, BRCA2 and CDKN1A interacting protein; IP, immunoprecipitation; IIF, immunofluorescence; NF-κB, nuclear factor-κB; siRNA, small interfering RNA; bFGF, basic fibroblast growth factor; GM-CSP, granulocyte-macrophage colony-stimulating factor; ChIP, Chromatin immunoprecipitation; miR, microRNA.

addition, these results also prove that the inhibition of prostate cancer progression by MTDH knockdown may be mediated by suppression of AKT and upregulation of FOXO3a activity (23). In hypoxic PC-3 cells, MTDH may participate in the downstream of the hypoxia-inducible factor 1 α (HIF-1 α) or phosphoinositide 3-kinase pathways (24).

MTDH and prostate cancer therapies. The signaling pathways of MTDH were reviewed systematically in prostate cancer previously in this study and it was concluded that MTDH may be a target in the treatment of prostate cancer. In order to investigate the molecular mechanism of cryptotanshinone in anticancer, several genes were analyzed in the study by Lee *et al* (24), including MTDH and HIF-1 α . Inhibition of MTDH expression was found to be one of the molecular targets for cryptotanshinone exerting anticancer effects (24).

Previous studies have examined MTDH-based DNA vaccines in prostate cancer using mice models (28-30). The results have shown that a significant enhancement of humoral and cellular immune responses was detected in MTDH-immunized mice. With the MTDH gene vaccine, mice with prostate cancer *in situ* exhibited prolonged tumor-bearing survival times (28). This was considered to be due to the inhibition of the proliferation and invasion of prostate cancer. The MTDH gene vaccine combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) adjuvant shows stronger anticancer effects, except that there was no significant difference in tumor-bearing survival time (29). The MTDH gene vaccine combined with paclitaxel exhibits significant inhibition of prostate cancer growth and prolonged tumor-bearing survival times (30).

MTDH and bladder cancer. The first study of MTDH expression in bladder cancer was in 2012 by Zho *et al* (19). The study involved 15 benign cases and 60 cancer samples. The results showed a significant difference of MTDH expression between bladder benign specimens and cancers (19). This result was also proved by another study by detection of MTDH mRNA expression in bladder benign and cancer samples (31), and MTDH expression has also been verified in 17 bladder cancer cell lines (31). RT112 cell lines have the highest expression, which is higher than that of DU145 and LNCaP as the controls, whereas HT1376 showed the lowest expression in the 17 cell lines (31).

Another study indicated that MTDH is a potential prognostic factor of bladder cancer, as a significant association was demonstrated between the expression of MTDH and clinicopathological stage, tumor classification, tumor multiplicity and survival time (19). However, no significant correlations were reported in the study by Nikpour *et al* (31) between the expression of MTDH mRNA and bladder cancer grade, tumor category and lymph node metastasis.

As a positive correlation between MTDH and Ki67 has been demonstrated, MTDH may promote bladder cancer tissue growth (19). The study by Nikpour *et al* (31) also confirmed that MTDH promoted bladder cancer cell survival, clonogenicity and migration, which were verified by downregulation of MTDH via small interfering RNA. In addition to increased apoptosis, reductions of cell viability and migration have also been observed in bladder cancer (31).

MTDH and kidney cancer. MTDH overexpression in primary kidney cancer has been confirmed by immunohistochemistry, RT-PCR and western blot. Two studies found that the expression of MTDH in kidney carcinoma specimens was high compared to normal tissues (32,33). An *in vitro* study by Chen *et al* (32) investigated the expression of MTDH in four kidney cancer cell lines; 786-0, OS-RC-1, Caki-2 and ACHN. A significantly higher level of MTDH was expressed in these four cell lines in the cytoplasm compared to the HK-2 cells as the control (32).

The results of Chen *et al* (32) indicated that the MTDH expression level is associated with the differentiation degree of renal cell carcinoma and clinical stage, with tumor and metastasis classifications, but not node classifications. Survival analysis confirmed a shorter survival time when the MTDH level was higher (32). The conclusion was also verified by another study showing that MTDH may be one of the prognostic parameters in renal cell cancer patients (33). A novel signal transduction pathway Akt/FOXO/miR-30d/MTDH in renal cell carcinoma was reported by the study by Wu *et al* (34), providing a new insight into the anticancer strategy of kidney cancer.

Limitations of the present studies and prospects. MTDH, as one of numerous oncogenes, has been studied in urogenital cancers for <10 years. Limitations of the current studies may exist in this area and are as follows.

Firstly, a larger tissue sample size should be analyzed to measure the association between MTDH expression and urogenital cancers in progression, metastasis and prognosis. Regarding MTDH and progression of bladder cancer, conflicting conclusions were reported in two studies (19,31) possibly due to their limited samples. Secondly, follow-up times and repeated studies are required to investigate the higher expression of MTDH as an influence of prognostic factors. Only one study performed a 120-month follow-up of prostate cancer, which may not be enough (10). Follow-up information is not available in bladder and kidney cancers. Thirdly, increasing detection methods and more comprehensive sources of specimen should be tested in further studies. To confirm MTDH as a potential biomarker in urogenital cancers, except for body organs or tissues, samples of blood, plasma, urine, prostatic and seminal fluid may also be taken into consideration to detect the MTDH expression. Fourthly, *in vitro* and animal models are required to reveal the function of MTDH as an oncogene and its signaling transduction pathways. Signaling transduction pathways of MTDH in prostate and kidney cancers is limited in the current studies. An increase in the detailed signaling pathways should be further investigated to define the role of MTDH in tumor pathogenesis. Further studies in signaling may provide novel targets for anticancer therapies.

MTDH is overexpressed in a number of urologic cancers, including prostate, bladder and kidney cancers. MTDH may be involved in urologic cancer progression, metastasis and prognosis and may be associated with several signaling transduction pathways in urologic cancers, indicating latent targets to develop anticancer therapeutic strategies. Further studies are required to confirm the aforementioned conclusions.

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