10 Year Biochemical Failure Free Survival of Men with CD82 Positive Primary Circulating Prostate Cells Treated by Radical Prostatectomy

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Abstract

Objective: The biological characteristics of circulating prostate cells (CPCs) are probably more important than their mere presence. CD82 is a tumor suppressor, we present the outcome of radical prostatectomy (RP) in men with CD82 positive CPCs. Methods and Patients: consecutive men treated with RP were studied, age, total PSA, Gleason, stage, the presence of extra-capsular extension, positive surgical margens and infiltration of the seminal vesicles and lymph nodes were registered. Biochemical failure was defined as a PSA >0.2ng/ml. Immediately before the RP, 8ml of venous blood was taken to detect CPCs. Mononuclear cells were separated using differential gel centrifugation and CPCs identified using immunocytochemistry with anti-PSA and anti-CD82. The men were divided into three groups; 1) CPC (-), 2) CPC (+) CD82 (+) and 3) CPC (+) CD82 (-). The groups were compared with respect to clinical-pathological findings and biochemical free survival using Kaplan Meier and Cox regression models. Results: 285 men, mean age 65.9 years participated, 61 (21%) were CPC (-); 57 (20%) were CPC (+) CD82 (+) and 167 (59%) were CPC (+) CD82 (-). Group 1 had low grade small volume cancer, in Group 2, low grade but a larger volume than Group 1 and Group 3 high grade cancer. Kaplan Meier biochemical free survival curves at 36, 60 and 120 months were; Group 1 98%, 96% and 90%; for Group 2 93%, 93% and 69% and for Group 3 62%, 44% and 16% respectively. Conclusions: Kaplan Meier survival curves for Group 1 and Group 2 were similar, although Group 2 men had higher PSA values, more advanced staging but a similar Gleason score. Group 3 men had a worse prognosis. The results support that biological characteristics of CPCs are more important than their mere presence identifying men with a high risk of biochemical failure.

Keywords: Prostate cancer- circulating tumor cells- CD82- biochemical failure
et al., 1996).

In well and moderately differentiated prostate cancer the expression is above that seen in benign hyperplasia, however in poorly differentiated cancer its expression is decreased (Bouras et al., 1999; Lijovic et al., 2002). In men with low grade Gleason 4 or 5, the expression of CD82 has been detected in primary circulating prostate cells, i.e. detected before primary treatment (Murray et al., 2010). The frequency of CD82 expression in primary CPCs is inversely associated with the Gleason score, not being detected in those patients with Gleason ≥7 (Murray et al., 2010).

Expression of CD82 in the primary tumors of non-small cell lung cancer, breast cancer, bladder, pancreatic and colon cancer is associated with a better prognosis (Adachi et al., 1996; Guo et al., 1996; Huang et al., 1998; Maurer et al., 1999; Shiwu et al., 2012; Yu et al., 1997) in comparison with patients with CD82 negative tumors. It has been suggested that although CD82 positive cells can disseminate into the circulation their ability to implant is reduced, thus their presence pre-prostatectomy radical may not signify a poorer prognosis.

The objective of this study was the detection of primary CPCs, the expression of CD82 their association with clinical-pathological features, with biochemical failure after prostatectomy radical.

Materials and Methods

Patients and Methods

A single centre prospective observational study of men who underwent radical prostatectomy as the sole treatment for prostate cancer between 2005 and 2014. The study was approved by the local ethics committee and complied with the Declaration of Helsinki.

For each patient, after giving informed written consent, the following were recorded; date of prostatectomy radical, age and the following clinic-pathological information: Total serum PSA (ng/ml) at the time of diagnosis using the Siemens Advia CentaurXR® assay; percentage of biopsy cores positive for cancer; The pathological study of the surgical piece was performed by dedicated genitourinary pathologists according to the Consensus of the American Association of Pathologists (Ruben et al., 2001); as a cell expressing both PSA and P504S and detected before definitive treatment for prostate cancer. A test was considered positive for primary CPCs when at least 1 cell/8mL of blood was detected; the number of CPCs detected/8ml blood simple was registered. (Figure 1a: CPC PSA positive(red), P504S positive (brown); Figure 1b: CPC PSA positive(red), P504S negative).

In men with malignant primary CPCs detected, that is PSA (+) P504S (+), the remaining two slides were processed for PSA as previously described, positive samples underwent a second process with anti-CD82 clone 13H4 (DAKO, USA) and identified with a peroxidase based system (LSAB2, DAKO, USA) with DAB (3,3 diaminobenzidine tetrahydrochloride) as the chromogen. A primary CPC was defined according to the criteria of ISHAGE (International Society of Hemotherapy and Genetic Engineering) (Borgen et al., 1999) and the expression of P504S defined according to the Consensus of the American Association of Pathologists (Ruben et al., 2001); as a cell expressing both PSA and P504S and detected before definitive treatment for prostate cancer. A test was considered positive for primary CPCs when at least 1 cell/8mL of blood was detected; the number of CPCs detected/8ml blood simple was registered. (Figure 1a: CPC PSA positive(red), P504S positive (brown); Figure 1b: CPC PSA positive(red), P504S negative).

Statistical Analysis

The analysis was performed using the program Stata.
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CD82 and Biochemical Failure

CPC negative, 57 (20.0%) had CPCs expressing CD82 detected and 167/285 (58.6%) had CPCs negative for CD82 detected. The clinical-pathological characteristics of each group are shown in Table 1:

Comparing the clinical-pathological features, Group 1 patients had a significantly lower total serum PSA as compared to Groups 2 and 3 (p<0.01). Group 1 consisted of men with predominantly low-grade small volume

Table 1. Clinical-Pathological Features of 285 Men Treated by Radical Prostatectomy for Prostate Cancer According Presence with and without Expression CD82 of Primary CPCs and to the Absence of Primary CPCs

| Variable                  | Group 1 Negative CPC n=61 | Group 2 Positive CPC Positive CD82 n=58 | Group 3 Positive CPC negative CD82 n=166 | p-value; groups significantly different comparison |
|---------------------------|---------------------------|-----------------------------------------|------------------------------------------|--------------------------------------------------|
| Age* (years), Median; IQR | 68; 15                    | 65;10                                   | 67; 14                                   | 0.098a                                           |
| PSA*, ng/ml, Median; IQR  | 4.81; 1.99                | 6.39; 2.67                              | 6.20; 5.29                               | <0.01; 1 v/s 2 and 1 v/s 3                        |
| pGS Score ≤ 6 n (%)       | 58 (95.08%)               | 58 (100%)                               | 69 (41.57%)                              | < 0.01; 1 v/s 3 and 2 v/s 3<                     |
| ECE, n (%)                | 7 (11.48%)                | 19 (32.76%)                             | 107 (64.46%)                             | <0.01<; 1 v/s 2, 1 v/s 3 and 2 v/s 3            |
| SM, n (%)                 | 3 (4.92%)                 | 6 (10.34%)                              | 53 (31.93%)                              | <0.01<; 1 v/s 3 and 2 v/s 3<                     |
| SVI, n (%)                | 1 (1.64%)                 | 1 (1.72%)                               | 18 (10.84%)                              | 0.012<; 1 v/s 3 and 2 v/s 3<                     |
| LNI, n (%)                | 0 (0.00%)                 | 0 (0.00%)                               | 2 (1.20%)                                | p-value 1<                                       |
| Pathological stage        |                           |                                         |                                          |                                                  |
| T1                        | 53 (86.9%)                | 19 (32.8%)                              | 26 (15.7%)                               |                                                  |
| pT2                       | 5 (8.2%)                  | 34 (58.6%)                              | 84 (50.6%)                               |                                                  |
| pT3                       | 3 (4.9%)                  | 5 (8.6%)                                | 56 (33.7%)                               |                                                  |

CPC, Circulating prostate cells prior to surgery; PSA, serum total PSA at diagnosis; IQR, rango intercuartílico; pGS Score ≤ 6, pathological Gleason score = ≤ 6; ECE, extra-capsular extension; SM, positive surgical margins; SVI, Infiltration of the seminal vesicles; LNI, Infiltration of the lymph nodes a Kruskal-Wallis H test; <, Pearson’s Chi squared test; , Marascuilo Procedure (2); <, Fishers’s exact test

Results

285 men with a mean age of 65.9 ± 8.8 years underwent radical prostatectomy for prostate cancer between 2004 and 2014. Of these men 61 (21.4%) were
tumours, without local extension. Group 2 consisted of men with predominantly low-grade larger volume tumours, and Group 3 predominantly higher-grade tumours with any degree of extension.

After 3, 5 and 10 years of follow up, the Kaplan-Meier biochemical free survivals for the whole group were respectively 76.28 (95% CI: 70.53 to 81.06), 67.05% (95% CI: 60.52 to 72.75) and 47.34 (95% CI: 38.71 to 55.48). Of the whole population 103/285 (36.1%) had biochemical failure detected within the study period; 5/61 (8.2%) of men CPC negative; 7/57 (13.8%) of men CPC positive CD82 positive and 91/167 (54.4%) of men CPC positive CD82 negative (p<0.0001 Chi squared for trends).

Comparison between Groups: When comparing Groups 2 and 3, men with CPCs CD82 negative had a higher rate of biochemical failure, HR of 11.84 (95% CI 6.27-22.38 p< 0.01) as compared to men with CPCs CD82 positive, with a Harrell’s C discrimination index of 0.72, considered to be adequate.

At 10 years, the comparing predicted (according to the model of Cox) versus “Observed Survival” (model Kaplan Meier) in 285 men treated by radical prostatectomy.

**Table 2. Kaplan-Meier Survival Estimates of 285 Men Treated by Radical Prostatectomy for Prostate Cancer According Presence with and without Expression CD82 of Primary CPCs and to the Absence of Primary CPCs.**

| Time, (Months) | Group 1 Negative CPC, n=61, % survival; 95 % CI | Group 2 Positive CPC, Positive CD82, n=58, % survival; 95 % CI | Group 3 Positive CPC, negative CD82, n=166 % survival; 95 % CI |
|----------------|-----------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 36             | 98.11; 87.35 to 99.73                         | 92.69; 81.63 to 97.20*                                        | 61.57; 52.94 to 69.09                                        |
| 60             | 96.11; 85.32 to 99.01                         | 92.69; 81.63 to 97.20*                                        | 43.90; 34.58 to 52.82                                        |
| 120            | 90.35; 75.80 to 96.35                         | 68.66; 38.46 to 86.24                                        | 16.16; 8.24 to 26.41                                        |

%, percentage; CI, Confidence interval.
to the model of Cox) versus observed survival (model Kaplan-Meier) showed agreement for the comparison of men CPC (+) CD82 (+) versus men CPC (+) CD82 (-) (Figure 3). Likewise, the confidence intervals for Kaplan-Meier survival curves for the predictors contain the survivals predicted by their respective models cox. The cumulative hazard of Cox-Snell residuals for both models built, showed adequate a goodness of fit. This is summarized in Table 2.

Discussion

There are a number of techniques that have been developed for the detection of circulating tumour cells, which has hindered the comparison of different studies and the consensus of defining these cells. Each method has differing advantages and disadvantages and has been extensively reviewed (Harouaka et al., 2014; van der Toom et al., 2016). This may be due to several reasons; firstly the use of the CPC detection system. Studies using the CellSearch® EpCAM based system have detected the presence of CPCs in between 11-25% of men with pathologically localized prostate cancer (Davis et al., 2008; Eshwege et al., 2009; Meyer et al 2016), whereas a telomerase based method detected CPCs in 80% of cases (Fizazi et al., 2007). Using the ISET (isolation by size of epithelial tumour) system (ISET Rarecells) circulating tumour cells were detected in all cancer patients and in 50% of patients with a normal prostate specific antigen and a positive CTC had cancer detected using PMSA PET scans (Ried et al., 2017). Using a PSA immunocytochemical based method, with double immune-marcation, CPCs were detected in 80% of men with prostate cancer (Murray et al., 2016a).

We used double immune-marcation in our study, firstly to identify patients with malignant CPCs, that is expressing both PSA and P504S, PSA expressing cells can be detected in patients with benign prostate disease, but these cells do not express P504S (Murray et al., 2013). Men positive for this test then underwent testing for cells expressing PSA and CD82. Immunofluorescence is used in some methods to detect positive cells, though there are no studies comparing detection methods.

For a cancer to be able to produce metastasis, the cancer cells have to disseminate from the primary tumour, survive in the circulation and to be able to adhere to the vascular endothelium at a distant site before invading the distant tissue. If not all CPCs are able to adhere and invade distant sites, then complete tumour removal at the time of surgery would imply curative therapy and in the clinical would be seen as better survival rates. Recent studies have shown that the mere presence of primary CPCs is not a good prognostic factor for biochemical failure free survival (Meyer et al., 2016; Murray et al., 2016; Murray et al., 2016b). The detection of circulating tumour cells using combined nested reverse transcriptase polymerase chain reaction pre-radical prostatectomy also failed to predict biochemical failure (Thomas et al, 2002).

It has been suggested that the mere enumeration of CPCs may not be ideal and that the phenotypic characteristics of these cells is more important. We chose the co-expression of CD82 as a potential marker as it has been reported to be inversely associated with survival in differing cancers. Low expression of CD82 was negatively correlated with overall survival in colorectal cancer (Wu et al., 2015) and breast cancer (Singh R et al., 2016). However in non-metastatic prostate cancer there is little reported data.

We report that men primary CPC negative had a 10-year biochemical failure free survival of 90%. These men had, in the majority of cases, low-grade (95% having a Gleason score of ≤ 6) small volume tumours (87% T1 tumours) and only 7% having positive surgical margins or seminal vesicle infiltration. This group for the clinical-pathological findings would be expected to have the best survival rates.

Men in Group 3, CPC (+) CD82 (-), had the worst biochemical failure free survival rate, 16% at 10 years, which is consistent with the clinical-pathological findings. That is higher-grade tumours (58% Gleason score ≥ 7), larger tumours 84% pT2 or pT3 and extension outside of the prostate as evidenced by 43% having positive margins, infiltration of the seminal vesicles or lymph nodes.

Group 2 men with CD82 (+) CPCs have a much better biochemical failure free survival similar to CPC (-) men at 5 years (93% versus 96% respectively, and 69% at 10 years. The clinical-pathological features were similar to those found in Group 1 except for a higher frequency of pT2 tumours.

This results support the hypothesis that not all primary CPCs and by inference circulating tumour cells imply a worse prognosis. Those men with CD82 expressing primary CPCs had a prognosis similar to that of men CPC negative.

CD82 is a tumour suppressor gene product; this group of suppressor gene products are primarily operationally defined and rarely mechanistically understood (Zijlstra et al., 2006). CD82 acts by various mechanisms; it has been proposed that CD82 acts with other trans-membrane proteins, especially EW12/PGRL a cell adhesion molecule, to inhibit cell motility Zhang et al., (2003) and also may regulate the intra-cellular signalling pathways that are linked to its associated trans-membrane proteins to suppress cancer dissemination. CD82-Epithelial Growth Factor (EGF) receptor coupling down-regulates EGF receptor mediated signalling by accelerating EGF receptor endocytosis and subsequently inhibits cell migration (Odintsova et al, 2000). More recently it has been reported that CD82 regulates cell migration and invasion by inhibiting the Tumour Growth Factor-B1/Smad signalling pathway (Zhu et al., 2017) and by down-regulating matrix metalloproteinase 2 expression, important in tumour cell dissemination (Zhu et al., 2017).

If this were the only mechanism, it would not explain the presence of CPCs CD82 (+) in the circulation. The fact that these patients had larger tumours may in part explain why these CPCs had entered the circulation. P504S negative CPCs, defined as benign CPCs may be found in patients with prostatic hyperplasia or chronic prostatitis (Murray et al., 2013), it has been suggested that distortion of the normal architecture or inflammatory cytokines are responsible for this dissemination of...
"normal" cells (Coussens and Werb, 2002). Thus these CD82 (+) CPCs may enter the circulation as a result of the distorted architecture of a larger primary tumour or associated inflammatory changes. One limitation of this study was that CD82 expression was not determined in the primary tumour.

Once in the circulation the CPCs have to adhere to the vascular endothelial in order to implant in distant tissues. The trans-membrane protein DARC is a specific CD82 interacting cytokine decoy receptor, which is limited to select cell types, notably endothelial cells. There is a direct interaction between CD82 expressing prostate tumour cells and DARC expressing endothelial cells which leads to suppression of proliferation and induction of senescence in CD82 expressing cells (Bandyopadhay et al., 2006). In a mouse model tumour cells that lacked CD82 expression metastasized equally well in wild type and DARC +/- mice. However tumour cell CD82 expression dramatically suppressed spontaneous and experimental metastasis in wild type but not DARC +/- mice (27). CD82 expression did not lead to reduced primary tumour size, possibly because of limited direct contact between CD82 positive tumour cells and DARC positive vascular cells. The metastasis senescence appears to be due to CD82-DARC interactions occurring in the circulation, that direct physical contact between endothelial cells and circulating tumour cells can control the survival of these disseminating tumour cells (Bandyopadhay et al., 2006). This would also explain why CD82 positive bone marrow micrometastasis are rarely found (Murray et al., 2012). With time and progression CD82 expression may be lost permitting systemic rather than local metastasis.

Conclusions, the expression of CD82 on primary CPCs is associated with a good prognosis, similar to that of men CPC negative. Although CD82 expression does not affect dissemination of primary CPCs to the circulation, possibly as a result of distorted architecture, its expression decreases tumour cell-endothelial cell binding and thus prevents metastatic implantation. Thus the biological characteristics of primary CPCs appears to be more important than their mere enumeration, and would explain would as a prognostic factor the presence of primary CPCs has limited importance. The expression of CD82 in primary CPCs is a good prognostic factor and thus should not impede curative treatment or warrant adjuvant therapy, whereas patients CPC positive CD82 (negative) may require additional treatment to prevent future therapy failure.

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Conflict of Interests
Dr. Murray has received consultancy fees from Viatar CTC Solutions, Boston, USA.

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References

Adachi M, Taki T, Leki Y, et al (1996). Correlation of KA11/CD82 gene expression with good prognosis in patients with non-small cell lung cancer. Cancer Res, 56, 1751-5.

Bandyopadhay S, Zhen R, Chaudhuri A, et al (2006). Interaction of KA11 on tumor cells with DARC on vascular endothelium leads to metastasis suppression. Nat Med, 12, 933-8.

Borgen E, Naume B, Nesland JM, et al (1999). Standardization of the immuno cytotoxic detection of cancer cells in bone marrow and blood. Establishment of objective criteria for the evaluation of immunostained cells. Cytotherapy, 5, 377-88.

Bouras T, Frauman AG (1999). Expression of the prostate cancer metastasis suppressor gene KA11 in primary prostate cancers: a biphasic relationship with tumor grade. J Pathol, 188, 382-8.

Cleves M, Gutierrez R, Gould W, Mrachenko Y (2010). An introduction to survival analysis using stata. Third edition ed. Texas: Stata Press, pp 412.

Coussens LM, Werb Z (2002). Inflammation and cancer. Nature, 420, 860-70.

Davis JW, Nakashihi H, Kumar VS, et al (2008). CTCs in peripheral blood samples from patients with increased serum PSA: initial results in early prostate cancer. J Urol, 179, 2187-91.

Dong JT, Lamb PW, Rinker-Schaeffer CW, et al (1995). KA11, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. Science (Wash DC), 268, 884-6.

Dong JT, Suzuki H, Pin SS (1996). Down regulation of the metastasis suppressor gene KAI1 in prostate cancer. Cancer Res, 56, 4387-90.

Eshwege P, Moutereau S, Droupy S, et al (2009). Prognostic value of prostate circulating tumor cell detection in prostate cancer patients. Br J Cancer, 100, 608-10.

Fidler IJ (1970). Metastasis: Quantitative analysis of distribution and fate of tumor microemboli labelled with 125-I-5-iodo 2’methoxyuridine. J Natl Cancer Inst, 45, 773-82.

Fizazi K, Morat L, Chauvениc L, et al (2007). High detection of CTCs in blood of patients with prostate cancer using telomerase activity. Ann Oncol, 18, 518-21.

Guo X, Freiss H, Graber HU, et al (1996). KA11 expression is up-regulated in early pancreatic cancer and decreased in the presence of metastasis. Cancer Res, 56, 4876-80.

Huang CI, Kohno N, Ogawa E, et al (1998). Correlation of reduction in MRP-1/CD9 and KA11/CD82 expression with recurrences in breast cancer patients. Am J Pathol, 153, 973-83.

Harouaka R, Kang Z, Zheng SY, Cao L (2014). Circulating tumor cells: advances in isolation and analysis, and challenges for clinical applications. Pharmacol Ther, 141, 209-21.

Ljovic M, Somers G, Frauman AG (2002). KA11/CD82 protein expression in primary prostate cancer and in BPH associated with cancer. Cancer Detect Prev, 26, 69-77.

Maurer CA, Graber HU, Freiss H, et al (1999). Reduced expression of the metastasis suppressor gene KA11 in advanced colon cancer and its metastasis. Surgery, 126, 869-80.

Meyer CP, Pantel K, Tennstedt P, et al (2016). Limited prognostic value of preoperating circulating tumor cells for early biochemical recurrence in patients with localized prostate cancer. Urol Oncol, 34, 11-6.

Moreno JG, Croce CM, Fischer R, et al (1992). Detection of hematogenous micrometastasis in patients with prostate cancer. Cancer, 52, 6110-12.
Murray NP, Badinez L, Badinez O, et al (2010). Expression of the tumour suppressor CD82 in primary and secondary circulating prostate cells in patients with prostate cancer. Rev Mex Urol, 70, 92-6.

Murray NP, Reyes E, Tapia P, et al (2012). Redefining micrometastasis in prostate cancer—a comparison of circulating prostate cells, bone marrow disseminated tumor cells and micrometastases: implications in determining local or systemic treatment for biochemical failure after radical prostatectomy. Int J Mol Med, 30, 896-904.

Murray NP, Reyes E, Badinez L, et al (2013). Circulating prostate cells found in men with benign prostate disease are PS04S negative: Clinical implications, J Oncol, doi: 10.1155/2013/165014. Epub 2013 Apr 17.

Murray NP, Aedo S, Fuentealba C, et al (2016). Limited improvement of incorporating primary circulating prostate cells with the CAPRA score to predict biochemical failure free outcome of radical prostatectomy for prostate cancer. Urol Oncol, doi:10.1016/urolonc.2016.05.020.

Murray NP, Reyes E, Orellana N, et al (2016b). Does the presence of primary circulating prostate cells imply the presence of aggressive prostate cancer with early biochemical failure: a comparison with the Walz Nomogram. Asian Pac J Cancer Prev, 17, 2941-6.

Odintsova E, Sugita T, Berditchevski F (2000). Attenuation of EGF receptor signalling by a metastasis suppressor, the tetratraspanin CD82/KAI1. Curr Biol, 10, 1009-12.

Ried K, Eng P, Sali A (2017). Screening for circulating tumour cells allows early detection of cancer and monitoring of treatment effectiveness: an observational study. Asian Pac J Cancer Prev, 18, 2275-85.

Rinker-Schaeffer CW, O’Keefe JP, Welch DR, et al (2006). Metastasis suppressor proteins: discovery, molecular mechanisms, and clinical application. Clin Cancer Res, 12, 3882-9.

Rubin MA, Zhou M, Dhanasekaran SM, et al (2001). a-methylacyl Coenzyme-A racemase as a tissue biomarker for prostate cancer. JAMA, 287, 1662–70.

Shiwu WU, Lan Y, Wenqing S, et al (2012). Expression and clinical significance of CD82/KAI1 and E-cadherin in non-small cell lung cancer. Arch Iranian Med, 11, 707-12.

Singh R, Bhatt ML, Singh SP, et al (2016). Expression levels of tetratraspanin KAI1/CD82 in breast cancers in North Indian females. Asian Pac J Cancer Prev, 17, 3431-6.

Thomas J, Gupta M, Grasso Y, et al (2002). Preoperative combined nested RT-PCR for PSA and PMSA does not correlate with pathologic stage or biochemical failure in patients with localized prostate cancer undergoing radical prostatectomy. J Clin Oncol, 20, 3213-18.

Udea T, Ichikawa T, Tamura J, et al (1996). Expression of KAI1 protein in benign prostatic hyperplasia and prostate cancer. Am J Pathol, 149, 1435-40.

van der Toom EE, Verdone JE, Gorin MA, Pienta KJ (2016). Technical challenges in the isolation and analysis of circulating tumor cells. Oncotarget, 7, 62754-6.

Wu Q, Yang Y, wu S, et al (2015). Evaluation of the correlation of KAI1/CD82, CD44, MMP7 and ß-atenin in the prediction of prognosis and metastasis in colorectal carcinoma. Diagn Pathol, 10, 176.

Yu Y, Yang JL, Markovic B, et al (1997). Loss of KAI1 mRNA expression in both high grade and invasive human bladder cancers. Clin Cancer Res, 3, 1045-9.

Zhang XA, Lane WS, Charrin S, et al (2003). EW12/PGRL associates with the metastasis suppressor KAI1/CD82 and inhibits the migration of prostate cells. Cancer Res, 61, 2665-74.

Zhu J, Liang C, Hua Y, et al (2017) The metastasis suppressor CD82/KAI1 regulates cell migration and invasion via inhibiting TGF-ß1/Smad signaling in renal cell carcinoma. Oncotarget, 8, 51559-68.

Zijlstra A, Quigley JP (2006). The DARC side of metastasis: shining a light on KAI1-mediated metastasis suppression in the vascular tunnel. Cancer Cell, 10, 177-8.

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