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STEAP1 is overexpressed in cancers: A promising therapeutic target

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ABSTRACT

The six-transmembrane epithelial antigen of prostate (STEAP) protein was identified in advanced prostate cancer and is up-regulated in multiple cancer cell lines, including prostate, bladder, colon, ovarian, and Ewing sarcoma. STEAP1 was described as a suitable antigen for T-cell-based or antibody-based immunotherapy.

We have investigated the expression of *STEAP1* in 40 human tumor types – brain, epithelial, lymphoid – and in their normal tissue counterparts using publicly available gene expression data, including the Oncomine Cancer Microarray database. *STEAP1* was found significantly overexpressed in 11 cancers. In addition, high *STEAP1* expression was associated with poor overall survival in colorectal cancer, diffuse large B cell lymphoma, acute myeloid leukemia and multiple myeloma.

Taken together, these data suggest that *STEAP1* is a potential therapeutic target for T-cell based immunotherapy or antibody therapy in a large panel of cancers.

1. Introduction

The six-transmembrane epithelial antigen of prostate (STEAP) protein was identified in advanced prostate cancer [1]. *STEAP1* is highly expressed in human prostate cancer and is up-regulated in various cancers, including lung, bladder, colon, ovarian, and Ewing cancers [1–3]. Immunohistochemical analysis of clinical specimens demonstrates significant STEAP1 expression at the cell–cell junctions of the secretory epithelium of prostate and prostate cancer cells [1]. Little to no staining was detected at the plasma membranes of normal non-prostate human tissues, except for bladder tissue, which expressed low levels of STEAP1 at the cell membrane. Its cell-surface localization, together with its six-transmembrane topology, suggests STEAP1 may function as a channel/transporter protein in cell–cell junctions [1]. Given its increased expression in cancer tissues, STEAP1 could be a promising target for T-cell based or antibody immunotherapy. In prostate cancers, STEAP1-specific cytotoxic T lymphocytes (CTLs) were found to inhibit the growth of transplantable prostate tumor cells in murine models [2,4,5]. An immunization with recombinant DNA or modified vaccinia virus Ankara vector delivering STEAP1 antigen inhibited prostate cancer progression in a murine subcutaneous syngeneic tumor model [6]. Targeting STEAP1 appeared also useful for T-cell based immunotherapy in renal and bladder cancers [7]. Finally, STEAP1 was also described as an attractive target for antibody therapy in multiple solid tumors including prostate, renal and bladder cancers [3].

In this report, we have investigated the expression of *STEAP1* gene in 40 human tumor types – brain, epithelial, lymphoid – as well as in their normal tissue counterparts using publicly available gene expression data, including the Oncomine Cancer Microarray database.

2. Materials and methods

2.1. Databases and gene expression data

STEAP1 gene expression in normal or malignant human tissues or cell lines was obtained from the Oncomine Cancer Microarray database (http://www.oncomine.org) [8], Amazonia database (http://amazonia.montp.inserm.fr/) [9], or ITTACA database (Integrated Tumor Transcriptome Array and Clinical data Analysis, http://bioinfo-out.curie.fr/ittaca/) [10]. Comparison of *STEAP1* expression between samples was performed only when gene expression data were from a same study, using the same methodology. Gene expression profiling (GEP) data are either two channel ratio data (from cDNA microarrays) or single channel intensity data (from Affymetrix microarrays). All data were log transformed, median centered per array, and the standard deviation was normalized to one per array [11].

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MMCs were purified from 206 patients with newly-diagnosed MM after written informed consent was given at the University hospitals of Heidelberg (Germany) or Montpellier (France). The study was approved by the ethics boards of Heidelberg and Montpellier Universities. After Ficoll-density gradient centrifugation, plasma cells were purified using anti-CD138 MACS microbeads (Miltenyi Biotech, Bergisch Gladbach, Germany). Microarray experiments were performed in DNA microarray platform of the Institute of Research in Biotherapy at the Montpellier University Hospital (France) (http://irb.montp.inserm.fr/en/index.php?page=Plateau&IdEquipe=6). The CEL files and MAS5 files have been deposited in the ArrayExpress public database (E-MTAB-372). We also used Affymetrix data of a cohort of 345 purified MMC from previously untreated MM patients from the University of Arkansas for Medical Sciences (UAMS, Little Rock, AR). These data are publicly available via the online Gene Expression Omnibus (Gene Expression Profile of Multiple Myeloma, accession number GSE2658. http://www.ncbi.nlm.nih.gov/geo/). We also used Affymetrix data of a cohort of patients with colorectal carcinoma ($N = 177$) (accession number GSE17538. http://www.ncbi.nlm.nih.gov/geo/) with diffuse large B cell lymphoma ($N = 414$) (accession number GSE10846. http://www.ncbi.nlm.nih.gov/geo/) and a cohort of patients with acute myeloid leukaemia ($N = 79$) (accession number GSE12417. http://www.ncbi.nlm.nih.gov/geo/). Affymetrix gene expression profiles of 917 cancer cell lines were also investigated for *STEAP1* expression (accession number GSE36133). Patient cohorts were described in Supplementary Appendix A.

2.2. Statistical analysis

Statistical comparisons were done with Student *t*-test. Gene expression data of MM patients were normalized with the MAS5 algorithm and analyzed with our bioinformatics platforms: RAGE (http://rage.montp.inserm.fr/) [12] and Amazonia (http://amazonia.montp.inserm.fr/) [9]. The prognostic value of *STEAP1* gene expression signal was determined using the MaxStat R function in R software (http://www.r-project.org). The statistical significance of differences in overall survival between groups of patients was calculated by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. Survival curves were plotted using the Kaplan–Meier method. All these analyses have been done with R.2.10.1 (http://www.r-project.org/) and bioconductor version 2.5.

2.3. Western blot analysis

Cells were lysed in 10 mM Tris–HCl (pH 7.05), 50 mM NaCl, 50 mM NaF, 30 mM sodium pyrophosphate (NaPPi), 1% triton X-100, 5 μM $ZnCl_2$, 100 μM Na_3VO_4, 1 mM DTT, 20 mM β-glycerophosphate, 20 mM p-nitrophenolphosphate (PNPP), 20 μg/ml aprotinin, 2.5 μg/ml leupeptin, 0.5 mM PMSF, 0.5 mM benzamidine, 5 μg/ml pepstatin, and 50 nM okadaic acid. Lysates were resolved on 12% sodium dodecyl sulfate–polyacrylamide by gel electrophoresis (SDS–PAGE) and transferred to a nitrocellulose membrane (Schleicher and Schuell, Kassel, Germany). Membranes were blocked for 2 h at room temperature in 140 mM NaCl, 3 mM KCl, 25 mM Tris–HCl (pH 7.4), 0.1% Tween 20 (TBS-T), 5% non-fat milk and human Ig (1 mg/ml), and then immunoblotted with a mouse anti-STEAP1 mAb (Sigma, St. Louis, MO, clone 4F6-1F3). As a control for protein loading, we used a mouse monoclonal anti-β-actin antibody (Sigma, St. Louis, MO). The primary antibodies were visualized with goat anti-mouse (Bio-Rad, Hercules, CA) peroxidase-conjugated antibody by an enhanced chemiluminescence detection system. Blots were quantified by densitometry using acquisition into Adobe Photo Shop (Adobe Systems, San Jose, CA), and analyzing with the NIH Image J software (National Institutes of Health, Bethesda, MD, USA).

2.4. Immunofluorescence staining

A total of 5×10^4 cells were deposited onto poly-L-lysine-coated slides, fixed in 4% paraformaldehyde and permeabilized with 0.1% Triton. Non-specific staining was blocked by incubating the slides in 5% BSA–PBS, after which the slides were subjected to labeling with the anti-STEAP1 mAb for 1 h in a moist chamber. Slides were then washed with PBS and incubated for 1 h with an Alexafluor 488-conjugated rabbit anti-mouse antibody (Molecular Probes, OR, USA) in a dark moist chamber. Slides were washed and mounted with Vectashield containing 4′-6-diamidino-2-phenilindole (DAPI) (Sigma Aldrich, St. Louis, MO, USA), and examined under an epifluorescence microscope (Leica Microsystems, Wetzlar, Germany).

3. Results and discussion

STEAP1 expression was investigated in 40 tumor types including 36 solid tumors and 4 hematological malignancies and in the corresponding normal tissues (Table 1 and Fig. 1). Overexpression of *STEAP1* was found in glioblastoma compared to normal brain ($P = 4.5E{-}5$) [13]; in esophageal cancer compared to normal esophagus in two independent studies ($P = 4.5E{-}5$, 7.4E−9) [14,15]; in pancreatic carcinoma compared to normal pancreas in three independent studies ($P = 1.6E{-}13$, 6.1E−5, .007) [16–18]; in prostate carcinoma compared to normal prostate in three independent studies ($P = 1.8E{-}6$, 2.4E−4, 9.6E−4) [19–21]; in head and neck cancer compared to normal counterpart in three independent studies ($P = 2.3E{-}18$, 1.1E−5, .001) [22–24]; in lung carcinoma compared to normal lung in six independent studies ($P = 1.5E{-}4$, $P = 2.3E{-}4$, $P = 3.9E{-}4$, $P = 5.1E{-}16$, $P = 8.8E{-}16$, $P = 4.5E{-}5$, $P = 7.8E{-}5$ and $P = .005$) [25–30]. Overexpression of STEAP1 was also found in primary effusion lymphoma compared to normal B cells ($P = 3.1E{-}5$) [31] and in various leukemia compared to normal bone marrow: T-cell acute lymphoblastic leukemia ($P = 5.6E{-}9$) [32], acute myeloid leukemia ($P = 5.6E{-}9$) [32]; B-cell acute lymphoblastic leukemia ($P = 8.3E{-}12$) [32]; and T-cell prolymphocytic leukemia ($P = 5.1E{-}7$) [33].

Table 1
Expression of *STEAP1* gene in human tumors and in normal tissue counterparts using publicly available gene expression data, including the Oncomine Cancer Microarray database.

		Gene overexpression compared to normal tissue counterpart
Tissue	Datasets	*STEAP1*
Myeloma	28	No
Leukemia	79	Yes
Lymphoma	48	Yes
Bladder	17	No
Brain	55	Yes
Breast	116	No
Cervical	13	No
Colorectal	69	No
Kidney	32	No
Esophageal	17	Yes
Gastric	17	No
Head & Neck	27	Yes
Liver	22	No
Lung	64	Yes
Melanoma	44	No
Ovarian	37	No
Pancreas	24	Yes
Prostate	52	Yes
Sarcoma	40	No

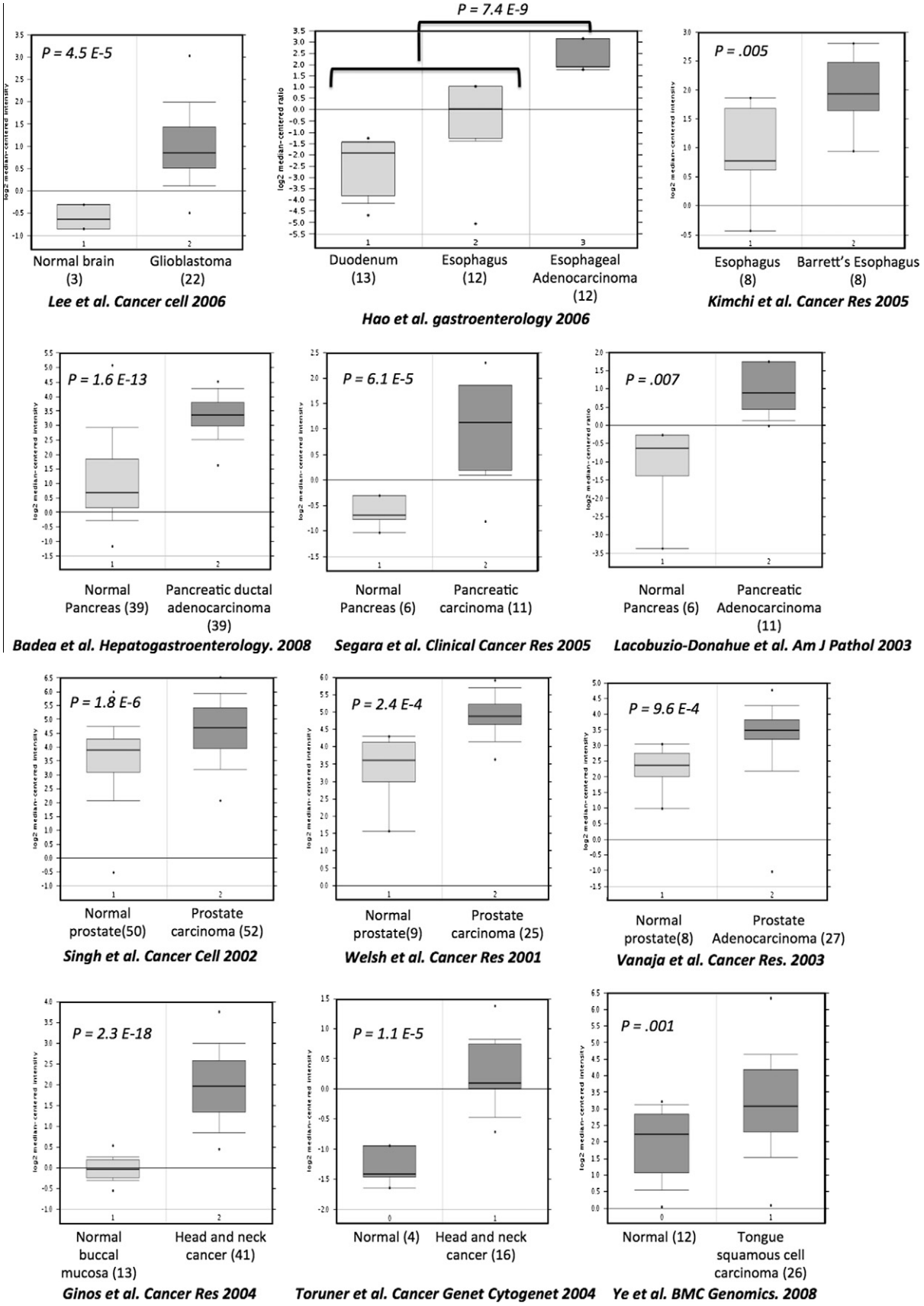

Fig. 1. Increased *STEAP1* gene expression in cancer tissue compared to normal counterparts. *STEAP1* gene expression in glioblastoma, esophageal adenocarcinoma, pancreatic carcinoma, prostate cancer, head and neck cancer, lung adenocarcinoma, primary effusion lymphoma, T-cell acute lymphoblastic leukemia, acute myeloid leukemia, B-cell acute lymphoblastic leukemia, T-cell prolymphocytic leukemia and the corresponding normal tissues. Data sets in a given panel were from the same study. GEP data are log transformed and normalized as previously described [8].

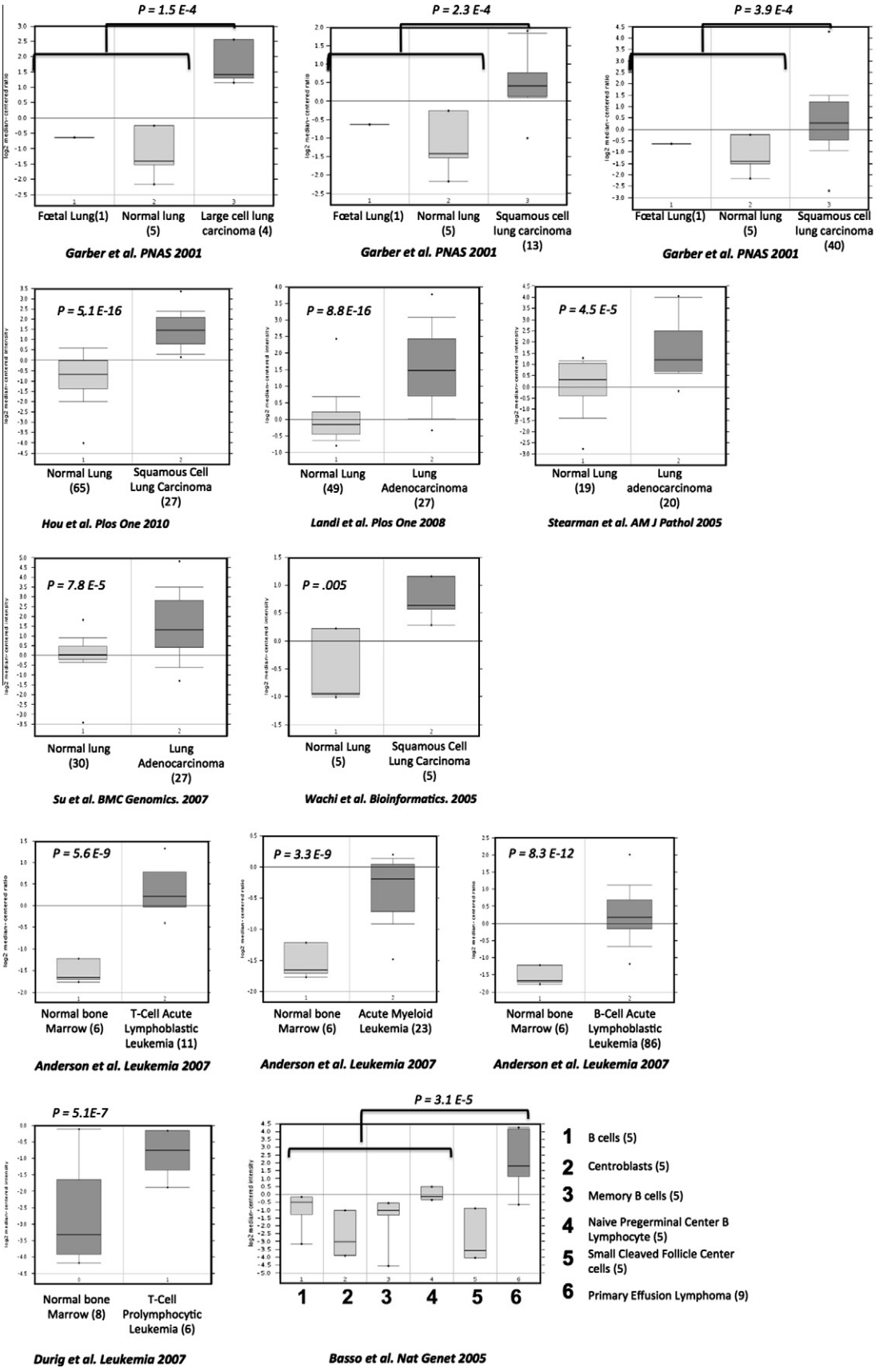

Fig. 1. (*continued*)

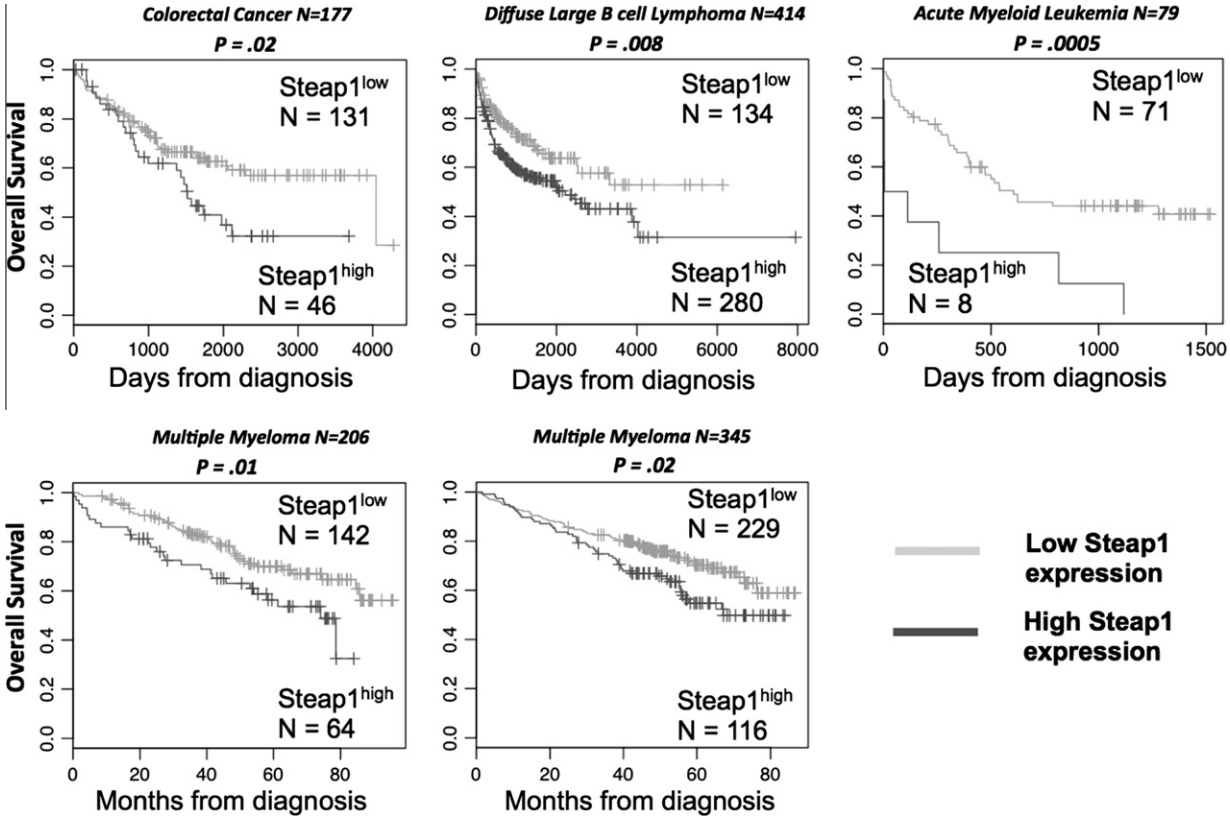

Fig. 2. Overall survival related to *STEAP1* gene expression in cancers The prognostic value of *STEAP1* gene expression was determined using the MaxStat R function in R software. The overall survival of subgroups of patients was compared with the log-rank test and survival curves computed with the Kaplan–Meier method (R software).

Given that *STEAP1* was shown to be expressed in prostate cancer metastases [3] and to be associated with invasive behaviour of Ewing tumors [34], an association between *STEAP1* expression and tumor progression and patients' survival was investigated. A high *STEAP1* expression was significantly associated with a reduced overall survival in patients with colorectal cancer ($N = 177$; $P = .02$), with diffuse large B cell lymphoma ($N = 414$; $P = .008$), with acute myeloid leukemia ($N = 79$; $P = .0005$), or with multiple myeloma (MM) ($N = 206$; $P = .01$ and $N = 345$; $P = .02$) (Fig. 2). Patients were split into two groups using Maxstat R function [35] according to *STEAP1* expression. In patients with colorectal cancer, a maximum difference in overall survival (OS) was obtained splitting patients in a high-risk group of 26% patients (STEAP1 signal >1155 (unlogged GEP data)) with a 50 months median OS and a low risk group of 74% patients (STEAP1 signal $\leqslant -1155$) with 133 months median OS (Fig. 2). In patients with DLBCL, a maximum difference in overall survival (OS) was obtained splitting patients in a high-risk group of 67.6% (STEAP1 signal >164 (unlogged GEP data)) with a 73 months median OS and a low risk group of 32.4% patients (STEAP1 signal $\leqslant 164$) with not reached median OS (Fig. 2). In patients with cytogenetically normal AML, a maximum difference in overall survival (OS) was obtained splitting patients in a high-risk group of 10.1% (STEAP1 signal >6.07 (log transformed GEP data)) with a 4 months median OS and a low risk group of 89.9% patients (STEAP1 signal $\leqslant 6.07$) with 20 months median OS (Fig. 2). In patients with MM, a maximum difference in overall survival (OS) was obtained splitting patients in a high-risk group of 31% with a 74 and 67 months median OS respectively in two independent cohorts of patients and a low risk group of 69% patients with not reached median OS (Fig. 2). Furthermore, *STEAP1* is significantly overexpressed in malignant plasma cells compared to normal bone marrow plasma cells and in tumor cells of patients with AML compared to normal hematopoietic stem cells (Supplementary Fig. S1). In MM, seven molecular groups of tumor cells have been identified in previously-untreated patients [36], and *STEAP1* was significantly overexpressed in the proliferation group and in the groups associated with Cyclin D1 or MMSET translocations (Fig. 3), two of them (proliferation and MMSET) being associated with poor survival in MM [36]. Using Cox univariate analysis in

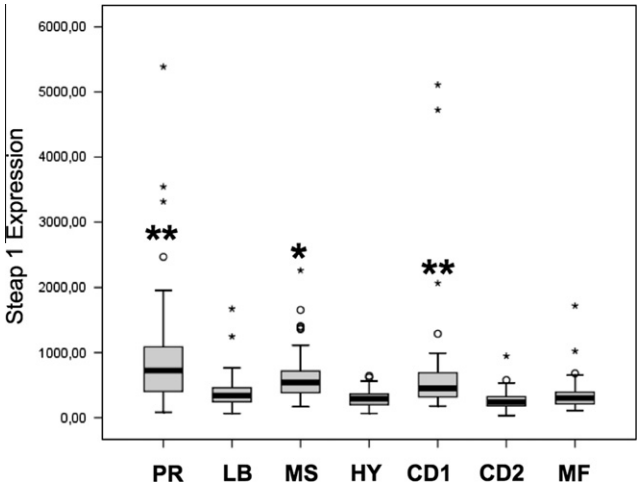

Fig. 3. *STEAP1* expression in the seven molecular groups of malignant plasma cells documented in patients with previously-untreated multiple myeloma. The expression of *STEAP1* gene was investigated in the seven molecular groups of UAMS cohort of patients treated with Total therapy two protocol. PR: proliferation, LB: low bone disease, MS: MMSET, HY: hyperdiploid, CD1: Cyclin D1, D2: Cyclin D2, MF: MAF. $^{*}P$ value < .05 and $^{**}P$ value < .01.

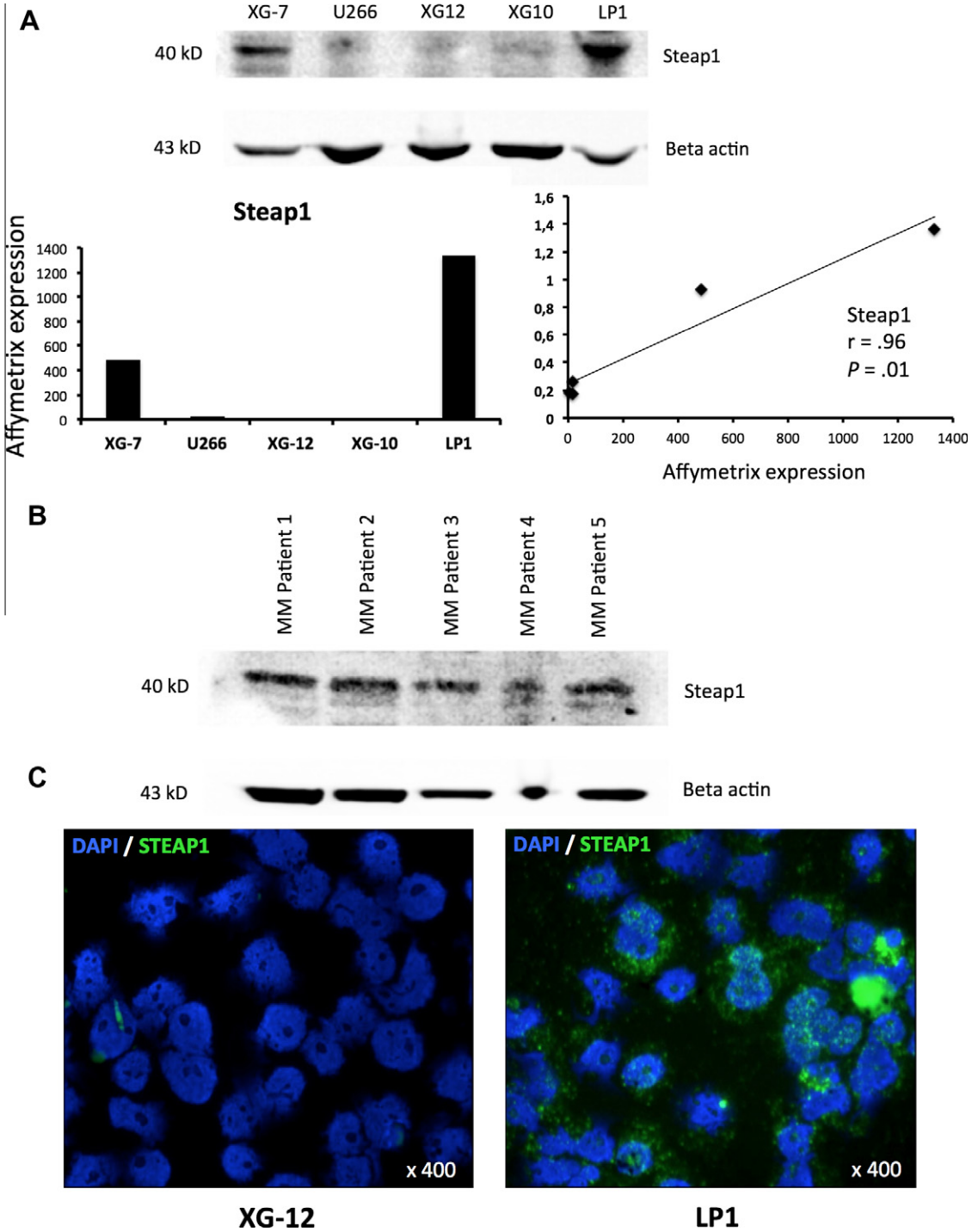

Fig. 4. Validation of *STEAP1* expression. (A) Expression level of STEAP1 protein in HMCLs using Western blot and correlation with STEAP1 gene expression Affymetrix signal value. For each cell line, the ratios of STEAP1 and β-actin proteins were determined in order to compare STEAP1 protein expression between cell lines. (B) STEAP1 protein expression in purified primary myeloma cells using Western blot analysis. (C) STEAP1 protein expression in STEAP1 negative XG-12 and STEAP1 positive LP1 HMCLs using immunofluorescence analysis.

colorectal cancer patient cohort, AJCC staging, colorectal cancer grading and *STEAP1* expression had prognostic value. Comparing these prognostic factors two by two, *STEAP1* expression remained significant compared to AJCC staging, and colorectal cancer grading (Supplementary Table. S1). When these parameters were tested together, *STEAP1* expression and AJCC staging kept prognostic value. In MM patient cohorts, UAMS-HRS, IFM-score and GPI (growth proliferation index) had prognostic value as well as t(4;14), del17p, β2m and ISS (Supplementary Table S2). Comparing these prognostic factors two by two, *STEAP1* expression remained significant compared to β2m, ISS, IFM-score and GPI (Supplementary Table S2). When these parameters were tested together, only β2m and t(4;14) kept prognostic value in the two cohorts. In cytogenetically normal AML patient cohort, *STEAP1*, *BAALC*, *ERG*, *MN1* and *EVI1* expression had prognostic value (Supplementary Table S3). Comparing these prognostic factors two by two, *STEAP1*

expression remained significant compared to *BAALC*, *ERG*, and *EVI1* expression (Supplementary Table S3). When these parameters were tested together, only *STEAP1* and *BAALC* kept prognostic value. *STEAP1* gene expression was also confirmed at protein level in five human myeloma cell lines (HMCLs) and purified primary myeloma cells of five patients using western blot (Fig. 4A and B). Normalized STEAP1 protein expression was significantly correlated with *STEAP1* Affymetrix expression ($r = .96$, $P = .01$) (Fig. 4A). STEAP1 gene expression was also validated in HMCLs at protein level by immunofluorescence (Fig. 4C). STEAP1 was first identified in advanced prostate cancer. Comparing *STEAP1* expression in all of these cancer cell lines, we identified a significant overexpression of *STEAP1* in acute lymphoblastic T cell leukemia, diffuse large B cell lymphoma, Hodgkin lymphoma, multiple myeloma, oesophagus carcinoma and lung carcinoma cell lines compared to prostate cancer cell lines (Supplementary Fig. S2). No significant difference of *STEAP1* expression was noted between acute myeloid leukemia, acute lymphoblastic B cell leukemia, Burkitt lymphoma, glioma, pancreas carcinoma and pancreatic ductal carcinoma cell lines compared to prostate cancer cell lines (Supplementary Fig. S2). Investigating genes correlated with *STEAP1* expression among various tumor samples, we identified 1313 genes, 1041 genes and 638 genes significantly correlated with *STEAP1* in colon cancer, DLBCL and MM respectively (Supplementary Table S4–S6). Crossing the gene lists, four genes appeared correlated with STEAP1 expression: dermatan sulfate epimerase (DSE), ubiquitin-conjugating enzyme E2T (UBE2T), atlastin GTPase 3 (ATL3) and CSL-type zinc finger-containing protein 2 (DPH3) (Supplementary Table S7). These genes are not linked with a specific biological pathway (Ingenuity and Reactome analyses).

Taken together, these data demonstrate that STEAP1 could be an interesting target not only in solid tumors but also in haematological malignancies. Recent study described a function of STEAP1 in mediating the transfer of small molecules between adjacent cells in culture, indicating its potential role in tumor cell intercellular communication [3]. Antibodies directed to STEAP1 inhibited STEAP1 induced intercellular communication of prostate cancer cells in a dose-dependent manner. Furthermore, anti STEAP1 antibodies significantly inhibited tumor growth of patient derived prostate and bladder cancer cells in a mouse model [3]. STEAP1 peptides have been recently demonstrated to induce antigen-specific CTLs that were able to recognize and destroy STEAP1-expressing tumor cells in vitro [2,5]. Active immunization against STEAP1 using DNA prime/modified vaccinia virus Ankara boost strategy inhibits prostate cancer progression in a murine model [6]. The immunogenicity of STEAP1 has led to the development of anti-STEAP1 antibody–drug conjugates to combine the specificity of anti-STEAP1 antibody to the cytotoxic potency of chemotherapeutic drugs [37].

Using a dye transfer assay, it was shown that STEAP1 expression in connexin deficient prostate cancer cells induces significant dye transport between cells, which is inhibited by specific STEAP1 siRNA. The predicted secondary structure of STEAP1 as a channel protein supports the possibility that STEAP1 acts as a transporter protein to directly transfer the dye between the cells [3]. More recently, Grunewald et al. demonstrated that STEAP1 is important for anchorage-independent colony-formation and invasiveness of Ewing tumor cells in vitro and for tumorigenicity and metastasis in vivo [34]. In Ewing tumors, STEAP1 expression correlates with increased cellular reactive oxygen species (ROS)-levels, which in turn induce the expression of redox-sensitive and pro-invasive genes. These results sustain previous data that STEAP1 overexpression promotes ROS-mediated hyperproliferation of thyroid epithelial cells [38]. Elevated ROS-levels activate pro-metastatic and pro-proliferative signaling in cancer cells [39,40]. STEAP1 overexpression could promote proliferation, invasiveness, tumorigenicity, and metastasis through ROS-levels upregulation in cancer. A recent study reported the interest of antibody–drug conjugates as promising therapeutic approach combining the STEAP1 antigen targeting specificity of monoclonal antibodies with the cytotoxic potency of chemotherapeutic drugs [37].

4. Conclusion

The current analysis emphasizes that STEAP1 could be a good candidate for T-cell based or antibody-based immunotherapy in a large panel of solid and hematological cancers.

5. Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

JM designed the study, supported data analysis and wrote the paper.

AK was involved in the study design and supported data analysis.

DH participated in the design of the study.

BK was involved in the study design and wrote the paper.

All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.10.123.

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