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Correlation of expression of Major Vault Protein with androgen receptor and immune checkpoint protein B7-H3, and with poor prognosis in prostate cancer

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ABSTRACT

Prostate cancer diagnosis and early stratification is an important aspect to avoid undertreatment of high-risk prostate cancer patients. Major Vault Protein (MVP) has been proposed as a prognostic biomarker in prostate cancer. PTEN and the immune checkpoint protein B7-H3 interact with MVP and are important in prostate cancer progression and therapy response. We evaluated the expression of MVP by immunohistochemistry of tissue microarray samples from a retrospective cohort consisting of 119 prostate cancer patients. We correlated the protein expression of MVP with clinicopathological characteristics, and protein expression of androgen receptor (AR), PTEN, immune checkpoint proteins B7-H3 and PD-L1. We found MVP to be expressed in 53 % of prostate tumors, and correlated positively with biochemical recurrence ($\rho = 0.211/p = 0.021$). Furthermore, we found positive correlation of MVP expression with expression of AR ($\rho = 0.244/p = 0.009$) and the immune checkpoint protein B7-H3 ($\rho = 0.200/p = 0.029$), but not with PD-L1 ($\rho = 0.152/p = 0.117$) or PTEN expression ($\rho = -0.034/p = 0.721$). Our findings support the notion that expression of MVP is associated with poor prognosis in prostate cancer. The correlation between MVP and immune checkpoint protein B7-H3 in prostate cancer suggests a role for MVP in immunoregulation and drug resistance.

1. Introduction

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide [1]. Prostate cancer diagnosis and early stratification is an important aspect to avoid undertreatment of high-risk prostate cancer patients. In this regard, we have previously reported Major Vault Protein (MVP) expression to correlate to fatal outcome in an advanced metastatic cancer cohort, suggesting that MVP can serve as a prognostic biomarker to improve early risk stratification [2].

MVP also known as Lung Resistance-related Protein (LRP), is associated with multidrug resistance in various cancer cells, including prostate cancer cells [3–5]. In addition, MVP plays a role in immunity [6], inflammation [7], viral infections [8], bone differentiation [9], and radiation response [10]. MVP is also found to promote cancer progression in several cancer forms, including hepatocellular carcinoma,

Abbreviations: AR, Androgen receptor; CAPRA-S, Cancer of the Prostate Risk Assessment Postsurgical Score; IHC, Immunohistochemistry; MVP, Major Vault Protein; PSA, Prostate-Specific Antigen; TMA, tissue microarray.

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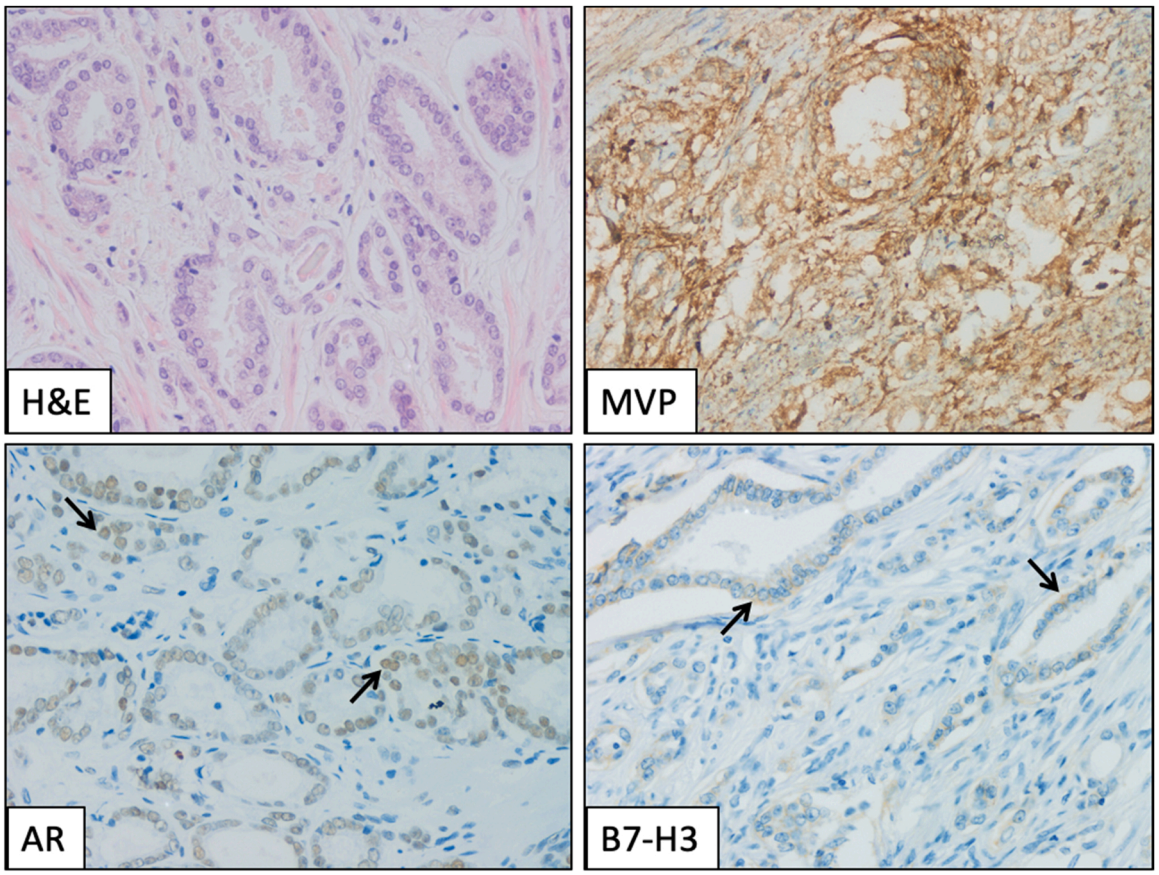

Fig. 1. Immunohistochemical profile of a prostate adenocarcinoma specimen, showing prostate cancer samples with Hematoxylin and Eosin (H&E) staining, and positive staining for MVP, positive androgen receptor (AR, nuclear), and positive B7-H3. Magnification: × 400.

thyroid, bladder, colon and prostate cancer [11–16]. Single nucleotide polymorphism in MVP gene has been associated with higher prostate cancer risk [15]. Recent studies show that MVP plays a cancer immunoediting role by binding bacterial N-Acyl homoserine lactones signaling molecules [17].

MVP is the main subunit of the multi-subunit vault ribonucleoprotein complex, that forms a cage-like structure that is involved in nucleocytoplasmic transport [18]. Vault nanocomplex may have multiple roles, including protection against cellular and DNA-damaging stresses. Several mechanisms of action have been proposed for the vaults, such as the control of the nuclear import/export of drugs and proteins, as well as alterations in gene expression and proliferative/pro-survival signaling pathways [19].

Several proteins, including tumor suppressor PTEN and immune checkpoint protein B7-H3 (*CD276*), are found to interact with MVP [20–22], and both PTEN protein and immunoregulatory B7-H3 protein expression correlate to poor prostate cancer outcome and recurrence [23–26]. In particular, B7-H3 regulates cancer stem cell enrichment and drug resistance through MVP-mediated MEK activation [21], whereas a role for MVP in PTEN nuclear import has been postulated [20]. MVP can also interact with SHP2, SRC, COP1, GLI1, and with estrogen receptor (ER) in breast cancer cells [27–31].

In this study we analyzed the association between MVP expression and prognostic variables and biochemical recurrence in a prostate cancer cohort, and analyzed co-expression with tumor suppressor protein PTEN, immune checkpoint proteins B7-H3 and PD-L1, and androgen receptor (AR).

2. Materials and methods

2.1. Immunohistochemical staining and scoring

Immunohistochemistry (IHC) was carried out using the following primary antibodies: MVP (Abcam [1032], ab14562), dilution: 1:60; PTEN (Merck Millipore, clone 6H2.1), dilution 1:100; B7-H3 (R&D, AF1027), dilution: 1:2000; and AR (SP107 ready to use, Ventana). Anti-MVP antibody was previously validated in [2]. B7-H3, PD-L1, PTEN and AR staining was described previously in [23]. Antigen retrieval was performed at pH 6 and pH 9 using PT link system (Agilent Technologies). IHC immunostainings were performed in automated immunostainers (EnVision FLEX, Dako Autostainer Plus; Dako, and BenchMark Ultra, Ventana Medical Systems). Antibodies were incubated for 30 min, followed by secondary antibody incubation for 15 min using Goat Anti Mouse and Rabbit Anti-goat Ig/HRP secondary antibodies (Dako), FLEX/HPR for 20 min, FLEX DAB/Sub Chromo for 10 min, and finally counterstaining with hematoxylin. Immunostainings of MVP were manually evaluated and scored in tumor cells or stromal cells as negative (weak/no staining) or positive (medium/high staining) by an experienced uropathologist (JIL). Immunostainings of B7-H3 and AR were evaluated in tumor cells as negative (weak/no staining) or positive (medium/high staining). The evaluation analysis was performed using a Nikon Eclipse 80i microscope (Nikon) with × 400 magnification.

2.2. Clinical data and tumor samples

The prostate cancer cohort has been previously described [23,32,33], and consisted of 119 prostate cancer patients treated with radical prostatectomy at Cruces University Hospital (Barakaldo, Spain) between

Table 1
Correlation between clinical and pathological variables and MVP expression.

		MVP negative	MVP positive
Patients – no.	N = 119	**(N = 55)**	**(N = 64)**
Median follow-up time (IQR) – year		ρ = −0.025/P = 0.235	
	10.5 (9.8–12.4)	10.9 (1–16)	10.1 (3.9–15)
Median age at surgery (IQR) – year		ρ = 0.025/P = 0.354	
	63 (59–68)	62 (50–73)	62 (48–72)
Age at surgery – no. (%)		ρ = 0.056/P = 0.541	
< 65 year	77 (65)	34 (62)	43 (67)
> 65 year	42 (35)	21 (38)	21 (33)
Preoperative PSA – no. (%)		ρ = 0.112/P = 0.260	
≤ 6 ng/ml	36 (30)	17 (31)	19 (30)
> 6 ng/ml and ≤ 10 ng/ml	43 (36)	24 (43)	19 (30)
> 10 ng/ml and ≤ 20 ng/ml	33 (28)	11 (20)	22 (34)
> 20 ng/ml	3 (2,6)	1 (2)	2 (3)
missing	4 (3.4)	2 (4)	2 (3)
Gleason score – no. (%)		ρ = 0.105/P = 0.414	
≤ 6	71 (60)	37 (67)	34 (53)
3 + 4	22 (18)	8 (14.5)	14 (22)
4 + 3	7 (6)	2 (4)	5 (8)
≥ 8	19 (16)	8 (14.5)	11 (17)
Pathological stage - no. (%)		ρ = 0.075/P = 0.411	
T2	98 (82.5)	47 (85.5)	51 (80)
T3	21 (17.5)	8 (14.5)	13 (20)
CAPRA-S risk group – no. (%)*		ρ = 0.014/P = 0.987	
Low	48 (40)	22 (40)	26 (40.5)
Intermediate	43 (36)	19 (35)	24 (37.5)
High	9 (8)	4 (7)	5 (8)
Missing	19 (16)	10 (18)	9 (14)
Biochemical recurrence – no. (%)		**ρ = 0.211/P = 0.021**	
Negative	78 (65.5)	42 (76.5)	36 (56)
Positive	41 (34.5)	13 (23.5)	28 (44)

Spearsmaṅs correlation ρ/P value.
IQR = interquartile range; PSA = prostate-specific antigen.
* The CAPRA-S scores were categorized to give the three risk groups: Low risk if score 0–2; Intermediate risk if score 3–5; High risk if score 6–12.

2000 and 2005. An experienced pathologist (JIL) selected tumor areas with well-preserved tumor tissue, representative of the whole tumor, from formalin-fixed and paraffin-embedded (FFPE) tumor tissue blocks, and tissue microarray (TMA) blocks were made from these areas. 4 mm sections were made from the TMA blocks, one of which was stained with hematoxylin and eosin (H&E) to verify the presence of tumor content. Biochemical recurrence was defined as a Prostate-Specific Antigen (PSA) measurement equal to or greater than 0.4 ng/ml after surgery. Follow-up has been recorded until October 1, 2016. Cancer of the Prostate Risk Assessment Postsurgical score (CAPRA-S) was calculated according to its definition [34], that is, by combining preoperative PSA, Gleason score, status of surgical margins, extracapsular extension, seminal vesicle invasion, and lymph node invasion. The study was performed in accordance with the Declaration of Helsinki. Ethical approvals, including informed consent from all included patients, have been obtained. Ethical approval was obtained from Comité de Ética de la Investigación con medicamentos de Euskadi (CEIm-E) no.: PI2021162.

2.3. Validation of co-expression by in silico mRNA analysis

The correlation of mRNA co-expression levels of MVP and B7-H3 (*CD276*) was analyzed using Prostate Adenocarcinoma datasets from Fred Hutchinson Cancer Research Center (FHCRC) [35], Second Military Medical University (SMMU) [36] via online web server cBioportal [37], and from The Cancer Genome Atlas Prostate Adenocarcinoma (TCGA-PRAD) and normal prostate tissue (TCGA) data via online web server GEPIA [38].

Table 2
Correlations with MVP and other markers.

			MVP negative	MVP positive
Patients – no.		N = 119	**(N = 55)**	**(N = 64)**
AR - no. (%)			**ρ = 0.244/P = 0.009**	
	Negative	25 (21)	17 (31)	8 (12.5)
	Positive	91 (76)	35 (64)	56 (87.5)
	Missing	3 (3)	3 (5)	0 (0)
PTEN - no. (%)			ρ = − 0.034/P = 0.721	
	Negative	57 (48)	24 (44)	33 (51.5)
	Positive	55 (46)	25 (45)	30 (47)
	Missing	7 (6)	6 (11)	1 (1.5)
B7-H3 - no. (%)			**ρ = 0.200/P = 0. 029**	
	Negative	100 (84)	50 (91)	50 (78)
	Positive	18 (15)	4 (7)	14 (22)
	Missing	1 (1)	1 (2)	0 (0)
PD-L1 - no. (%)			ρ = 0.152/P = 0.117	
	Negative	94 (79)	46 (84)	48 (75)
	Positive	12 (10)	3 (5)	9 (14)
	Missing	13 (11)	6 (11)	7 (11)

Spearsmaṅs correlation ρ/P value.
AR = androgen receptor.

2.4. Statistical analysis

The SPSS version 23 software (SPSS Inc., Chicago, IL, USA) was used for statistical calculations of the clinical material. Spearman rho (ρ) test was used to correlate MVP to clinicopathologic parameters, and to B7-H3, PD-L1, PTEN and AR. Pearson correlation (R) test was used to correlate mRNA co-expression of MVP and B7-H3 in Fred Hutchinson, SMMU, and TCGA prostate adenocarcinoma dataset. P value below 0.05 was considered statistically significant.

3. Results

3.1. Immunohistochemical expression of MVP in prostate cancer

MVP expression was histologically evaluated in a prostate cancer cohort consisting of TMA samples from representative well-preserved tumor areas from 119 cases (Fig. 1). Patients were followed for a median of 10.5 years (interquartile range 9.8–12.4 years), and in total 41 experienced biochemical recurrence (Table 1). The MVP staining was cytoplasmic and showed immunoreactivity in both tumor cells and tumor associated stroma.

3.2. MVP expression according to clinical and pathological variables

MVP expression correlated positively with biochemical recurrence (ρ = 0.211/p = 0.021). On the other hand, MVP immunostaining did not correlate significantly to preoperative PSA levels, Gleason score, pathological stage or to CAPRA-S risk group (p > 0.05).

3.3. MVP expression and correlations to relevant proteins and known binding partners

We investigated the correlation of the expression of MVP to binding partners, including PTEN and immune checkpoint protein B7-H3. We found a statistically significant co-expression of MVP and B7-H3 (ρ = 0.200/p = 0.029), whereas we did not find a significant correlation between MVP and PTEN expression (ρ = − 0.034/p = 0.721) (Table 2). The positive correlation in co-expression of MVP and B7-H3 in prostate cancer tissue was confirmed at mRNA level from Fred Hutchinson Cancer Research Center Prostate Adenocarcinoma (FHCRC-PRAD) data collection (R = 0.26/p = 6.786e-4), Second military Medical University Prostate Adenocarcinoma (SMMU-PRAD) data collection (R = 0.41/p = 6.394e-4), and from The Cancer Genome Atlas Prostate Adenocarcinoma (TCGA-PRAD) data collection (R = 0.1/p = 0.043), whereas no correlation was found in normal prostate tissue (R = 0.17/

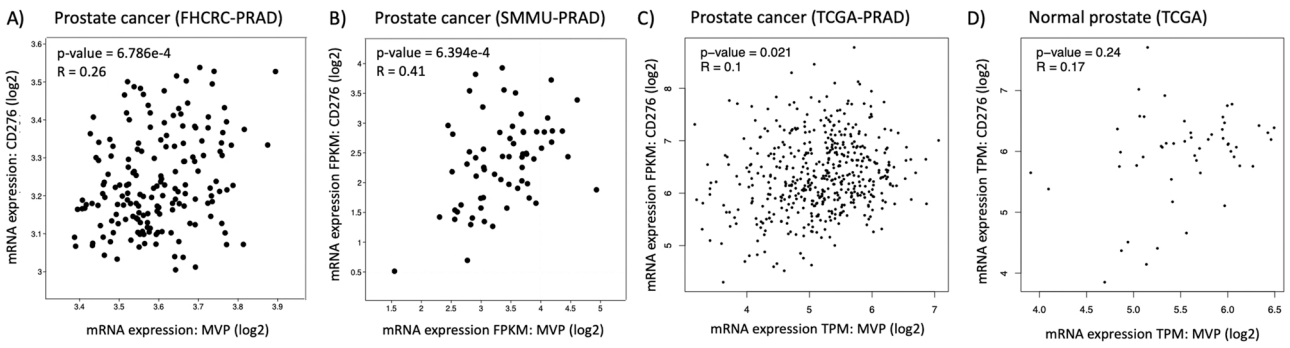

Fig. 2. Correlation between co-expression of MVP and B7-H3 (CD276) mRNA in prostate adenocarcinoma from (A) Fred Hutchinson Cancer Research Center Prostate Adenocarcinoma (FHCRC-PRAD) data collection, (B) Second Military Medical University Prostate Adenocarcinoma (SMMU-PRAD) data collection, (C) The Cancer Genome Atlas Prostate Adenocarcinoma (TCGA-PRAD) data collection, and (D) normal prostate tissue (TCGA).

$p = 0.240$) (Fig. 2). We also investigated the correlation of MVP expression with androgen receptor (AR) and immune checkpoint protein PD-L1 expression. MVP correlated positively with AR status ($\rho = 0.244$/ $p = 0.009$), but not with PD-L1 status ($\rho = 0.152$/$p = 0.117$) (Table 2).

4. Discussion

We previously reported that high levels of MVP were associated with prostate cancer specific mortality [2]. In the present study, performed on a prostate cancer cohort with mostly low pathological stage (T2) and low Gleason score (Gleason score ≤ 6), we also found correlation of MVP expression at the time of surgery with biochemical recurrence. This confirms that MVP could serve as an early prognostic marker in prostate cancer.

AR and AR-related signaling pathways are fundamental in the growth of normal and neoplastic prostate cells [39]. We observed a correlation between MVP and AR expression in prostate cancer. Co-expression of AR and MVP could be due to mutually regulatory elements; in that regard, both MVP and AR were found transcriptionally activated by the multifunctional oncoprotein Y-box binding protein-1 (YBX1) [40], a protein overexpressed in prostate cancer [41]. In breast cancer, vault particles bind estrogen receptor [29], but whether MVP binds to AR needs further investigation. Nuclear matrix protein Scaffold Attachment Factor B1 (SAFB1, SAFB) can work in prostate cancer as an AR co-repressor through epigenetic silencing of AR targets [42]. Interestingly SAFB1 silencing in prostate cancer cells was found to upregulate MVP [42]. Both immune checkpoint protein B7-H3 and MVP have been proposed to play a role in breast cancer stem cell enrichment and drug resistance [21]. The functional consequences of co-expression of MVP and B7-H3 in prostate cancer, in the context of AR signaling, resistance to antiandrogens, and immunoregulation requires further studies.

CRediT authorship contribution statement

CENX and JIL contributed to conception and design of the study, and performed experiments, collected and analyzed data. RL and JIL provided tumor samples, data acquisition and clinical details of patients. CENX, ME, IJG, HR, KAT, GMM, ØF, RL, RP and JIL contributed to manuscript writing, revision, and approved the final version.

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Data Availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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