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Original Article

Expressions of glucose transporter genes are diversely attenuated and significantly associated with prostate cancer progression

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Abstract: Prostate cancer is a health-threaten disease in men worldwide, however, lacking is the reliable biomarkers for patient management. Aberrant metabolic events including glucose metabolism are involved in prostate cancer progression. To examine the involvement of glucose metabolic pathways in prostate cancer, we analyzed the expression profiles of glucose transporter family genes using multiple RNA-seq datasets. Our results showed that three SLC2A family genes (SLC2A4/5/9) were significantly downregulated in primary prostate cancers compared to their benign compartments. These down-regulated expressions were inversely correlated with their gene promoter methylation and genome abnormalities. Among these three SLC2A genes, only SLC2A4 showed a significantly reverse correlation with all clinicopathological parameters, including TNM stage, disease relapse, Gleason score, disease-specific survival, and progression-free interval. In addition, the expression levels of these three genes were strongly correlated with anti-cancer immune cell filtration in primary prostate cancers. In a group of patients with early-onset prostate cancers, SLC2A4 also showed a strong negative correlation with multiple clinicopathological parameters, such as tumor mutation burden, biochemical relapse, pre-surgical PSA levels, and Gleason score but a positive correlation with progression-free interval after surgery. In metastatic castration-resistant prostate cancers (CRPC), SLC2A9 gene expression but not SLC2A4 or SLC2A5 genes showed a significant correlation with androgen receptor (AR) activity score and neuroendocrinal (NE) activity score. Meanwhile, SLC2A2/9/13 expression was significantly elevated in CRPC tumors with neuroendocrinal features compared to those without NE features. On the other hand, SLC2A10 and SlC2A12 gene expression were significantly reduced in NEPC tumors compared to CRPC tumors. Consistently, SLC2A10/12 expression levels were significantly reduced in castrated animals carrying the LuCaP35 xenograft models. Survival outcome analysis revealed that SLC2A4 expression in primary tumors is a favorable prognostic factor and SLC2A6 is a worse prognostic factor for disease-specific survival and progression-free survival in prostate cancer patients. In conclusion, our results suggest that SLC2A4/6 expressions are strong prognostic factors for prostate cancer progression and survival. The significance of SLC2A2/9/13 over-expression during NEPC progression needs more investigation.

Keywords: Prostate cancer, glucose transporter, prognosis, gene expression, castration-resistant

Introduction

Prostate cancer is one of the major health-threatening cancers around the world [1, 2]. In the last five years, the mortality rates due to prostate cancer have increased in three countries, remained stable in 59 countries, but decreased only in 14 countries [2]. In the U.S., the incidence of distant metastatic prostate cancer significantly increased during 2010-2017. Although the 10-year relative survival for localized prostate cancer was 100%, the 5-year survival for metastatic prostate cancer remained only 32.3% during 2011-2016 [3]. As

regards the ethnic groups, the 5-year survival rate for Asian/Pacific Islanders was the highest at 42.0%, followed by Hispanics at 37.2%, native Americans at 32.2%, African Americans at 31.6%, and White men only at 29.1%. Despite the commonly used PSA screening, its specificity and dependency remain a critical issue [4]. Therefore, identifying novel and reliable prognostic factors is a key issue in patient management.

Glucose is a critical ingredient for living organisms including cancer cells. Due to uncontrolled proliferation, cancer cells consume much more glucose compared to benign cells, which is one of the cancer hallmarks [5]. In the prostate organ, the differentiated gland tissue is glycolytic instead of oxidative due to the enhanced demand of citric acid to sustain physiological citrate secretion in the seminal fluid [6]. However, cancer transformation switched the metabolic properties to oxidative phosphorylation, which later, switched back to glycolytic during castration-resistant and neuroendocrinal progression of prostate cancer [6-9].

In living organisms, glucose uptake is facilitated by the trans-membrane glucose transporter protein family encoded by solute carrier family 2 (SLC2A) genes. These transporters are also responsive to other nutrient compounds such as dehydroascorbic acid or uric acid [10]. The expressions of this family of genes are tissue-specific with diverse biochemical properties and physiologic functions, contributing to the regulation of serum glucose levels and their distribution. Despite the broad relevance of enhanced glucose consumption in prostate cancer cells, there is a paucity of understanding of the mechanisms of how these transporters promote glucose uptake during prostate cancer development and progression [10].

In this study, we conducted a gene expression survey of all SLC2A family genes in prostate cancer tissues, including primary tumors, early-onset tumors, and late-stage lethal-type tumors. Our survey revealed that SLC2A family genes were diversly dis-regulated in primary prostate cancers without a significant overexpression at the mRNA levels. Among these 14 family genes, SLC2A4 downregulation was significantly correlated with most clinicopathological parameters. SLC2A10/12 genes were significantly overexpressed in late-stage lethal cancers, while SLC2A2/9/13 gene expressions were associated with neuroendocrinal progression. However, only SLC2A4/6 genes were significantly associated with both progression-free interval and disease-specific survival outcomes.

Materials and methods

Analysis of SLC2A family gene expression in primary prostate cancers

The publicly accessible RNA-seq TCGA-PRAD dataset [11] was used for the survey of SLC2A family gene expression profiles in primary prostate cancer tissues on the XIANTAO platform (https://www.xiantaozi.com/). Briefly, the RNAseq data were downloaded from the TCGA-PRAD database portal (https://portal.gdc.cancer.gov) in the format of fragments per kilobase per million (FPKM). The data were then converted to the log2 value of Transcript Per Million reads (TPM) before statistical analysis. The comparisons among different groups with various clinicopathological parameters were conducted using the R language package (version 4.2.1). Currently, there are 51 case-matched pairs of benign and malignant tissues, plus 449 cases of unmatched malignant specimens.

Analysis of SLC2A family gene expression in early-onset prostate cancers

DKFZ RNAseq dataset was generated with 292 cases (324 specimens) of primary prostate cancer diagnosed at an age less than 55 years old [12]. The diagnoses were confirmed by two independent pathologists. High-quality mRNA samples were submitted to the RNAseq analysis for the mRNA expression. The original data were downloaded for statistical analysis using GraphPad Prism (version 9.1.0). The figures were generated online on the cBioportal platform.

Analysis of SLC2A family gene expression in CRPC and NEPC cancers

SU2C/PCF RNAseq data [13] were comprehensive genomic and transcriptomic profiles from 429 patients with metastatic castration-resistant prostate cancer (CRPC) linked with neuroendocrinal features and clinical outcomes. RNA-seq data were generated on 332 tumors from 323 patients. Transcript-based NE and AR scores were used to determine the correlation

of SLC2A gene expression with NE feature or AR signaling activity [14].

Gene expression analysis in benign prostate cells and LuCAP35 xenografts

Expression profiles of the SLC2A family genes in prostate organs were extracted from the NCBI GEO dataset GDS1973 [15]. This dataset was generated using monoclonal antibody-based cell sorting of different prostate cells, including basal, luminal secretory, stromal fibromuscular, and endothelial cells. Benign prostate tissues were excised from cancer-free areas of the prostates obtained from radical prostatectomy surgeries. The antibodies used for these cell types were anti-integrin beta-4, anti-dipeptidyl peptidase IV, anti-integrin alpha-1, and anti-PECAM-1, respectively. Gene expression of antibody-sorted cell populations was assessed with Affymetrix Human Genome U133 Plus 2.0 GeneChips [15].

Gene expression changes induced by castration in prostate cancer LuCaP35 xenograft model was extracted from the NCBI GEO dataset GDS4120 [16]. After xenograft tumors were established in athymic nude mice, animals were castrated for 4 weeks before xenograft tumors were harvested for RNA extraction. The human genome U133 Plus 2.0 GeneChip array (Affymetrix) was used to examine the mRNA expression.

Data presentation and statistical analysis

All quantitative data were presented as the MEAN and the SEM (standard error of the mean) and analyzed using the R-package (version 4.2.1) and GraphPad Prism software (version 9.1.0). Comparisons for case-matched pairs were conducted with the Wilcoxon signed rank test. Group comparisons were performed using the test specified in the figure legend. Patient survival outcomes were analyzed and visualized using the survival (version 3.3.1), survminer, and ggplot2 (version 3.3.6) in the R-package. The hazard ratio (H.R.) was evaluated using the Log-rank test.

Results

SLC2A3 gene expression is predominant in benign prostate tissue

To understand the prostate tissue-specific expression profiles of SLC2A family genes, we analyzed the NCBI GEO dataset GDS1973 that contains gene expression profiles in four major cell types of basal, luminal, endothelial, and stromal. As shown in Figure S1, SLC2A3 gene expression was the predominant isoform in all four types of prostatic cells with a modest lower level in luminal cells compared to others (Figure S1A and S1C). SLC2A1/5/10/12 gene expression showed a moderate level, of which SLC2A1 was expressed mainly in basal cells (Figure S1B) while SLC2A5/10/12 genes were mainly expressed in luminal cells (Figure S1D-F). Other SLC2A genes were expressed in a very low level.

Multiple SLC2A family genes were aberrantly expressed in primary prostate cancers

To examine the expression profiles of SLC2A family genes in primary prostate cancer tissues, we utilized the TCGA-PRAD RNA-seq dataset and compared the differences of each SLC2A gene using two approaches, case-matched paired comparison, and group comparison. As shown in **Figure 1A**, **1B**, SLC2A1/8/10/12 genes were highly expressed in both benign and malignant tissues, while SLC2A2/14 gene expression was extremely low. SLC2A3/4/5/9 genes were broadly expressed with much more variation. SLC2A6/7/11/13 genes were expressed at a relatively low level. In the paired comparison (**Figure 1A**), SLC2A4/5/8/9/11 gene expression was significantly reduced in malignant tissues compared to the benign compartments, while only SLC2A1/4/5/9 genes showed a significant down-regulation in the group comparison (**Figure 1B**). We then analyzed the differences in SLC2A gene expression between patients with or without distal metastasis. As shown in **Figure 1C**, SLC2A4/5/10/12 genes were significantly down-regulated while SLC2A6/8 genes were up-regulated in patients with metastasis compared to those without metastasis. These data suggested that SLC2A4/5/9 were constantly downregulated in primary prostate cancers with or without metastasis.

SLC2A4/5/9 gene expression was associated with promoter methylation and genomic alteration

To understand the global mechanism for the downregulation of SLC2A4/5/9 gene expression, we analyzed the gene promoter methylation using the TCGA-PRAD Firehose legacy dataset. As shown in **Figure 2A-C**, the expres-

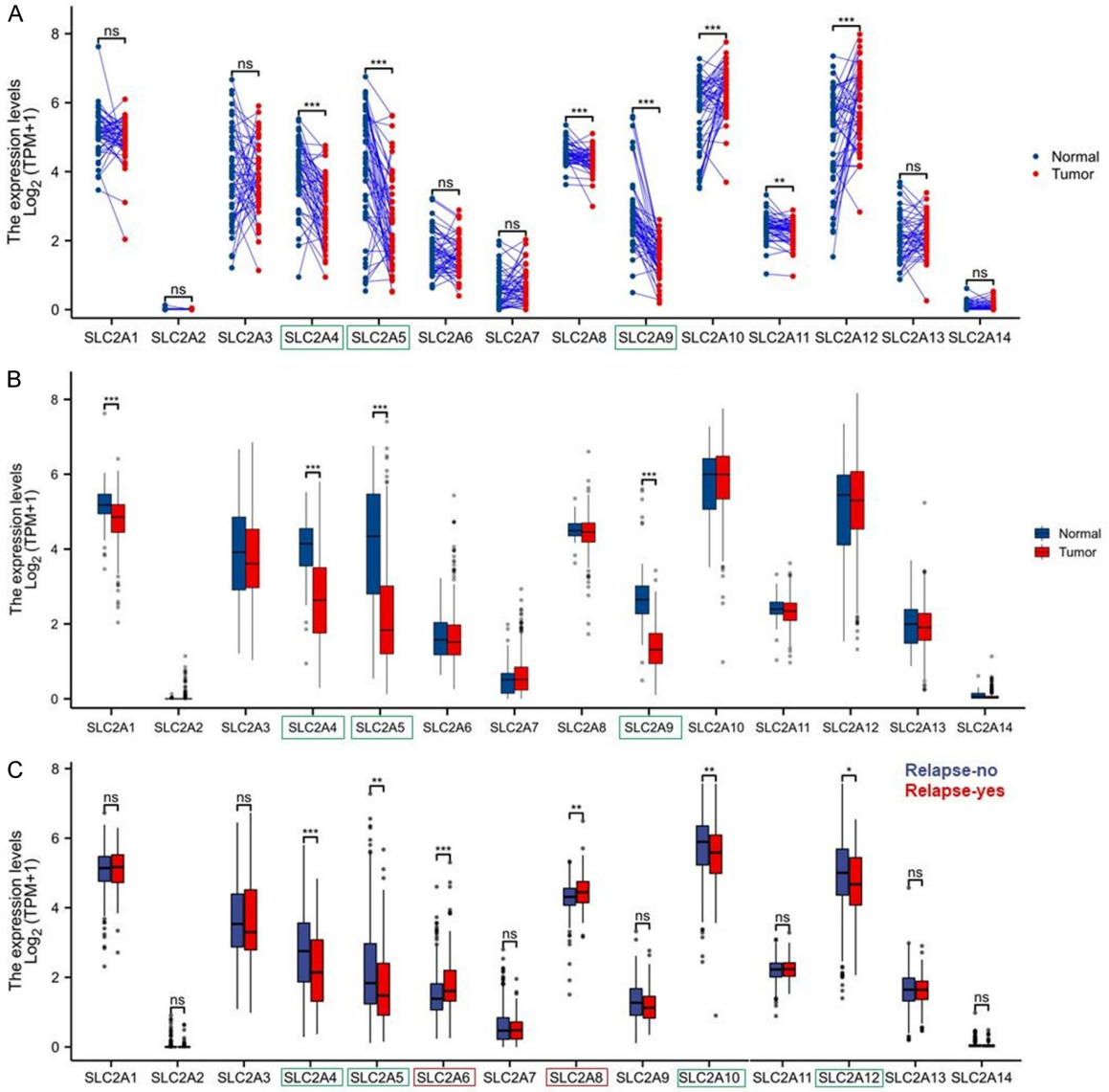

Figure 1. Multiple SLC2A family genes were aberrantly expressed in primary prostate cancers. Gene expression was compared among the 51 cases of case-matched benign and malignant prostate tissue pairs (A) and between benign (n = 51) and malignant prostate (n = 499) tissues (B). A group comparison of gene expression was conducted for patients with or without relapse (C). The *p*-values were derived from the Wilcoxon signed rank test (paired comparison) and the Wilcoxon rank sum test (group comparison). *P < 0.05; **P < 0.01; ***P < 0.001.

sion levels of SLC2A4/5/9 genes were inversely correlated with promoter methylation (Spearman correlation: -0.369/-0.745/-0.632, respectively), indicating that promoter DNA methylation played a major role in gene down-regulation. Further analysis revealed that these three genes were also negatively correlated with the factions of genomic alteration in the malignant tissues (Spearman correlation: -0.50/-0.52/-0.43, **Figure 2D-F**). These data suggested that genomic instability was also involved in the down-regulation of the SLC2A genes.

SLC2A4 gene down-regulation was significantly associated with clinicopathological parameters

We then analyzed the correlation of SLC2A4/5/9 gene expression with clinicopathological parameters to determine their potential association with disease progression. Our analysis found that the expression levels of SLC2A4/5 but not SLC2A9 genes were significantly lower in patients with late pathological stages (**Figure 3A**), lymph node invasion (**Figure 3B**), distal metastasis (**Figure 3C**), higher Gleason score

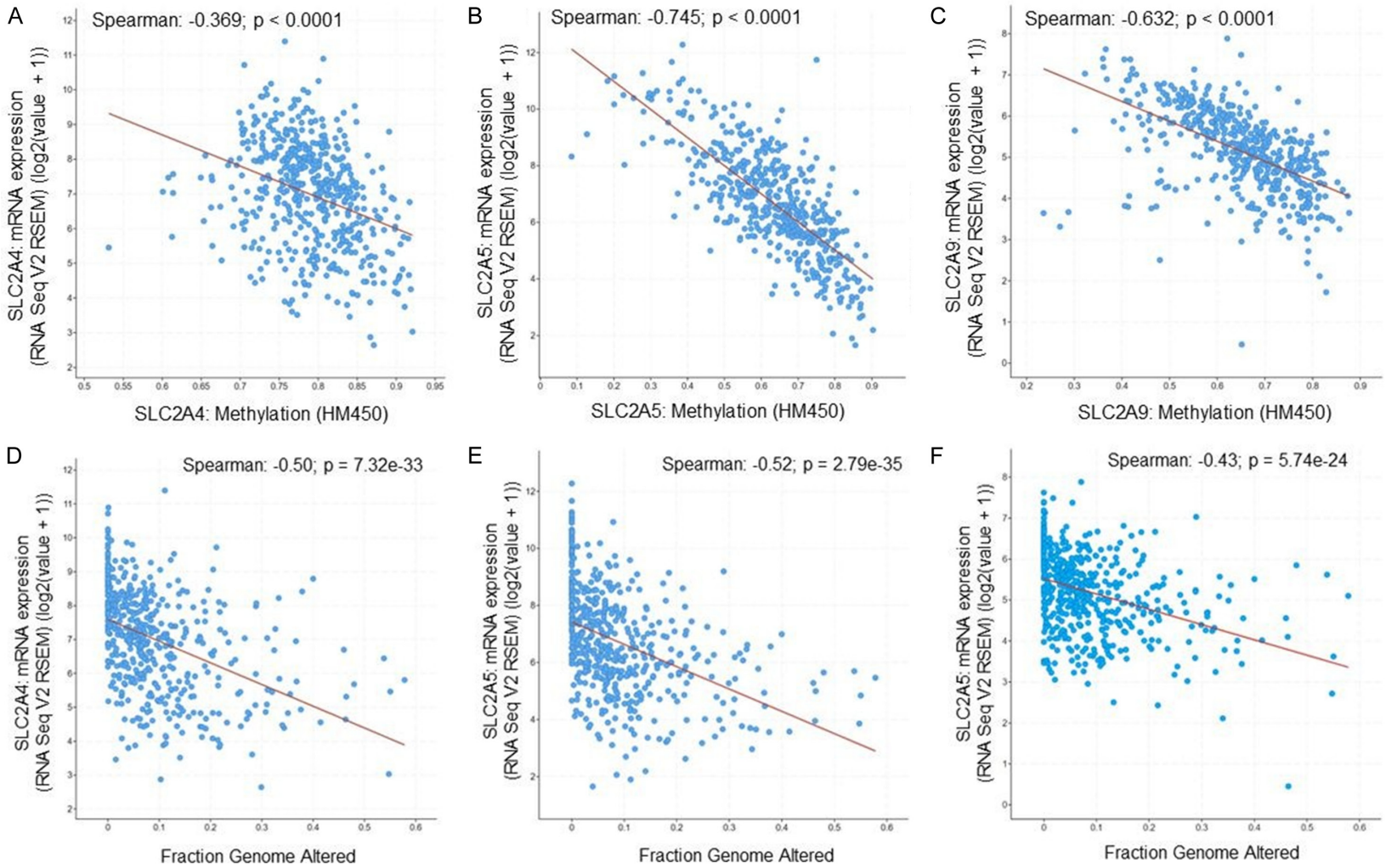

Figure 2. SLC2A4/5/9 gene expression was associated with promoter methylation and genomic alteration. Spearman correlation analysis was conducted between SLC2A gene expression and promoter methylation and genome alteration in primary prostate cancers (n = 501).

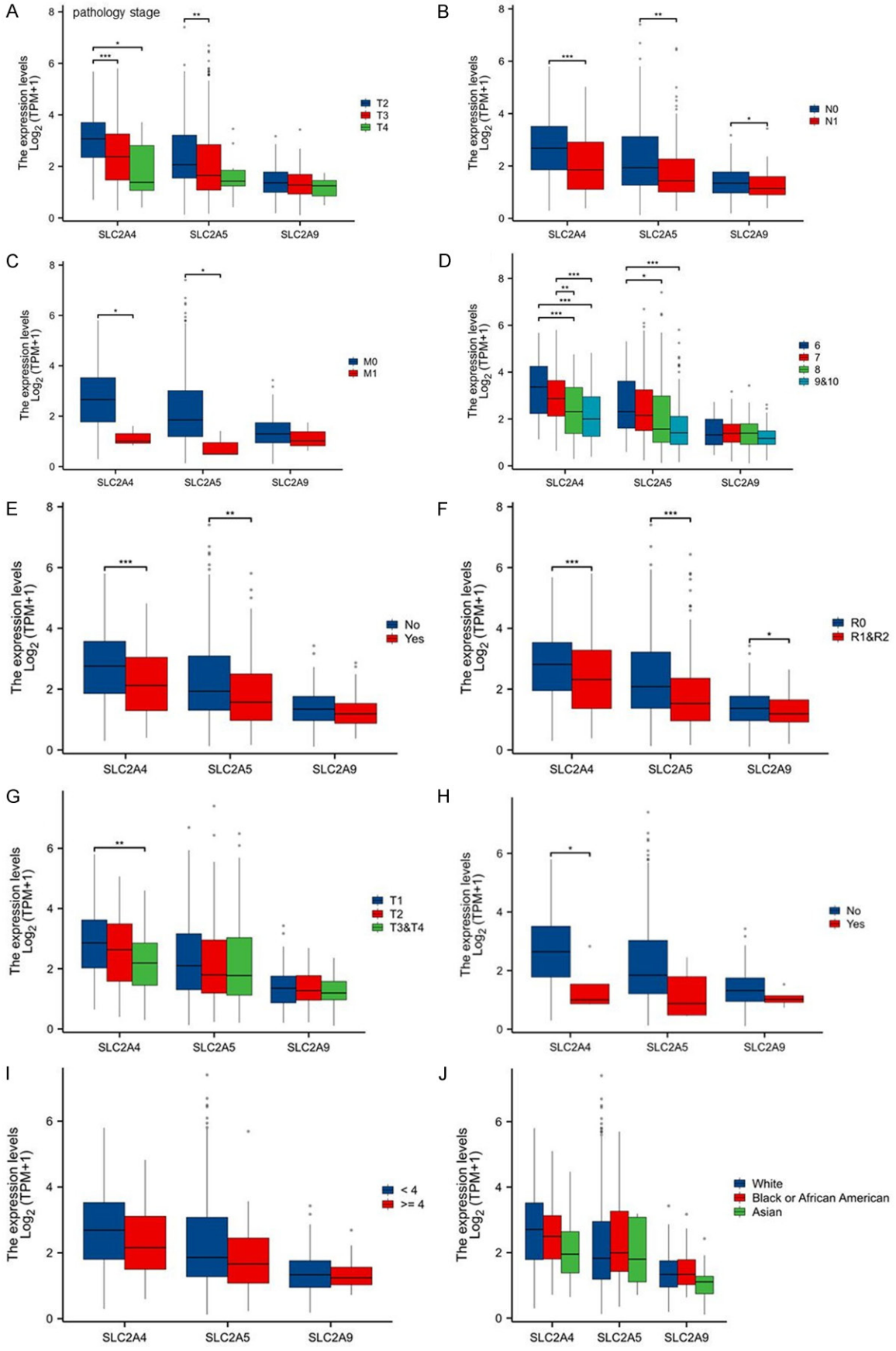
A
pathology stage
T2
T3
T4
B
N0
N1
C
M0
M1
D
6
7
8
9&10
E
No
Yes
F
R0
R1&R2
G
T1
T2
T3&T4
H
No
Yes
I
< 4
>= 4
J
White
Black or African American
Asian
The expression levels Log2 (TPM+1)
SLC2A4
SLC2A5
SLC2A9

Figure 3. SLC2A4 gene down-regulation was significantly associated with clinicopathological parameters. Expression levels of SLC2A genes as indicated were compared among various clinicopathological parameters, including pathological stage (A), lymph node invasion (B), distal metastasis (C), Gleason scores (D), disease relapse (E), residual tumors after surgery (F), clinical stage (G), cancer death (H), serum PSA levels (I), and ethnic group (J). The *p*-values were derived from the ANOVA test. *P < 0.05; **P < 0.01; ***P < 0.001.

(**Figure 3D**), and disease relapse (**Figure 3E**). All these three genes were downregulated in patients with residual tumors (positive surgical margin) (**Figure 3F**) but only SLC2A4 gene expression was significantly reduced in patients with late clinical stages (**Figure 3G**) and patient death due to prostate cancer (**Figure 3H**). However, there was no significant difference between patients with PSA levels at < 4 or > 4 (**Figure 3I**). In addition, there were no significant differences among various races (white, black, or Asian) (**Figure 3J**).

SLC2A4/5/9 gene expression was positively associated with tumor immune infiltration

To determine the correlation of SLC2A gene expression with tumor immune response, we analyzed the immune infiltration profiles related to SLC2A4/5/9 gene expression. As shown in **Figure 4A**, SLC2A4 expression was highly associated with anti-tumor immune cells, including NK cells, Mast cells, Neutrophils, Th1 cells, Eosinophils, and inducible DC with Spearman r > 0.3. Similarly, SLC2A5 expression was also significantly associated with Neutrophils, NK cells, Mast cells, and Th1 cells with Spearman r > 0.3 (**Figure 4B**). SLC2A9 expression was positively associated with Neutrophils, inducible DC cells, eosinophils, effector memory T-cells, Th1 cells, mast cells, NK cells, T-cells, B-cells, central memory T-cells, and macrophages (**Figure 4C**). Interestingly, all SLC2A4/5/9 expression was negatively associated with tumor-promoting immune regulatory T-cells (**Figure 4A-C**). These data strongly suggested that SLC2A4/5/9 gene expression in primary prostate cancer tissues is a potential biomarker for tumor immune infiltration.

SLC2A4/5 down-regulation was associated with disease progression in early-onset patients

We next analyzed SLC2A4/5/9 gene expression in early-onset prostate cancers that often harbor severe genetic alterations. As shown in **Figure 5A-I**, SLC2A4/5 but not SLC2A9 expression was negatively correlated with non-synonymous tumor mutation burden (Pearson r -0.4 and -0.32, respectively), pre-operation PSA levels (Spearman r -0.59 and -0.41, respectively), and time from surgery to biochemical relapse (BCR) (Pearson r 0.45 and 0.26, respectively). In patients with biochemical relapse (BCR), SLC2A4/5 but not SLC2A9 expression was significantly down-regulated compared to those without the BCR (**Figure 5J-L**). However, only SLC2A4 but not SLC2A5/9 expression was significantly reduced in patients with higher Gleason scores (**Figure 5M-O**). These data suggest that SLC2A4 is more significantly associated with disease progression in early-onset prostate cancers.

SLC2A2/9/13 expression was positively associated with NEPC progression

Castration-resistant prostate cancer (CRPC) is a lethal condition in the late stage of patient history without means to cure, especially when CRPC patients develop neuroendocrinal features. About 15-20% of CRPC patients progress into the neuroendocrinal prostate cancer (NEPC) stage in the clinic. We analyzed the expression levels of SLC2A family genes in 232 CRPC patients, of which 22 developed NE features (SU2C/PCF Dream-Team dataset). Our analysis revealed that SLC2A12 expression was strongly correlated to the AR activity score (Pearson r = 0.56) (**Figure 6A**, **6B**), while SLC2A10/12 expression was negatively correlated with NEPC score (Pearson r = -0.51/-0.34) (**Figure 6C**, **6D**). In addition, SLC2A2/9/13 expression was negatively correlated with AR activity score (**Figure 7A-C**), although the correlation between SLC2A13 and AR activity score was only moderate (Pearson r = -0.21). However, SLC2A2/9/13 were strongly (Pearson r > 0.30) correlated with NEPC score (**Figure 7D-F**). Consistently, SLC2A2/9/13 expression levels were significantly higher in CRPC tissues with NE features compared to those without NE features (**Figure 8A-C**). In contrast, SLC2A10/12 expression levels were drastically reduced in CRPC tissues with NE

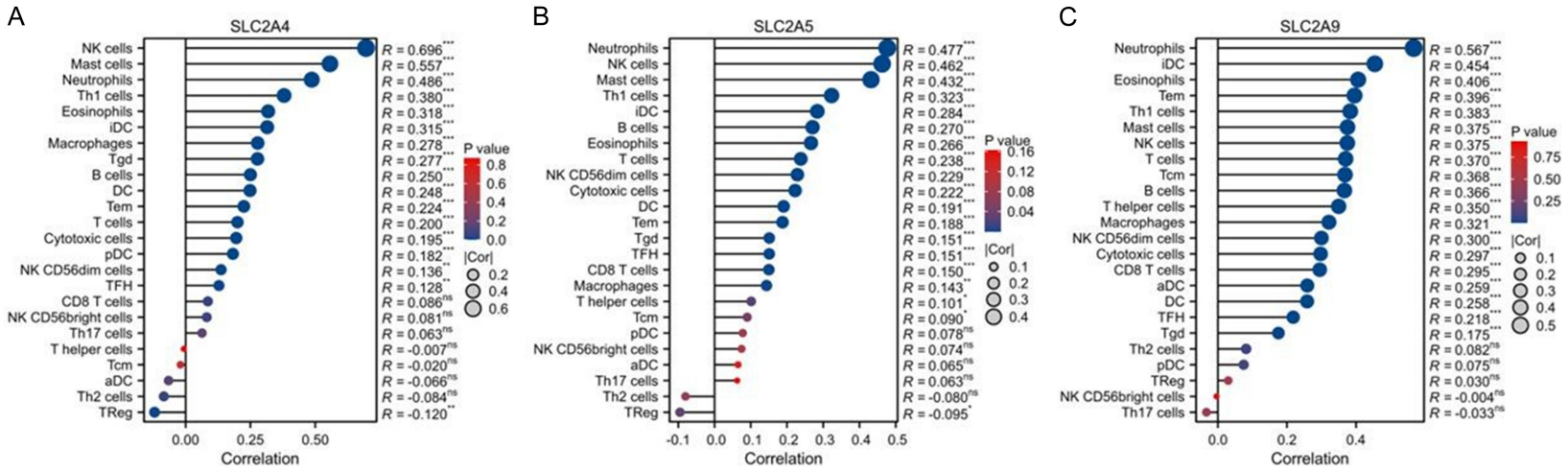

Figure 4. SLC2A4/5/9 gene expression was positively associated with tumor immune infiltration. Spearman correlation coefficient was analyzed between SLC2A gene expression (as indicated) and tumor immune infiltrations in primary prostate cancers. *P < 0.05; **P < 0.01; ***P < 0.001.

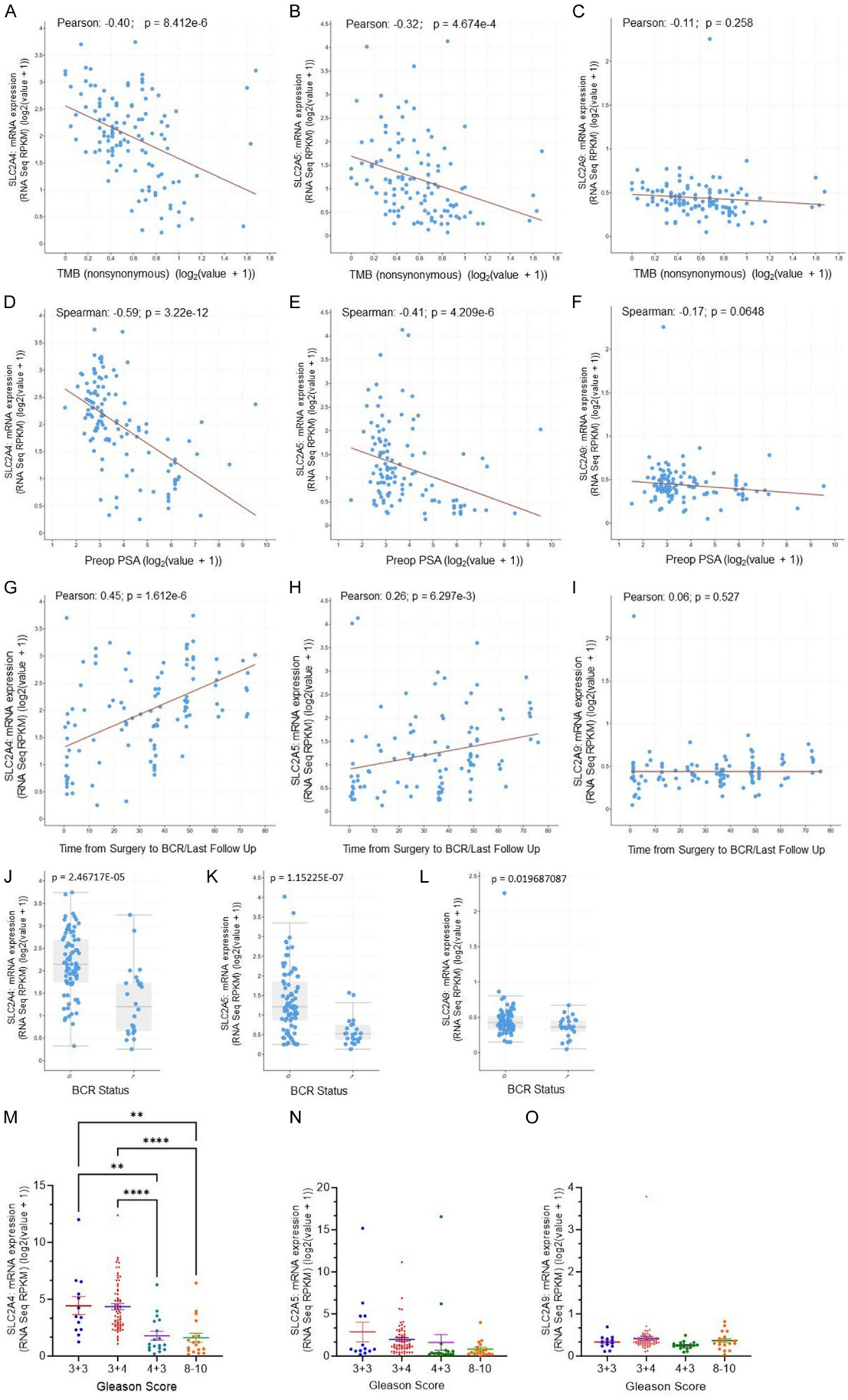
A
Pearson: -0.40; p = 8.412e-6
SLC2A4: mRNA expression (RNA Seq RPKM) (log2(value + 1))
TMB (nonsynonymous) (log2(value + 1))
B
Pearson: -0.32; p = 4.674e-4
SLC2A5: mRNA expression (RNA Seq RPKM) (log2(value + 1))
TMB (nonsynonymous) (log2(value + 1))
C
Pearson: -0.11; p = 0.258
SLC2A9: mRNA expression (RNA Seq RPKM) (log2(value + 1))
TMB (nonsynonymous) (log2(value + 1))
D
Spearman: -0.59; p = 3.22e-12
SLC2A4: mRNA expression (RNA Seq RPKM) (log2(value + 1))
Preop PSA (log2(value + 1))
E
Spearman: -0.41; p = 4.209e-6
SLC2A5: mRNA expression (RNA Seq RPKM) (log2(value + 1))
Preop PSA (log2(value + 1))
F
Spearman: -0.17; p = 0.0648
SLC2A9: mRNA expression (RNA Seq RPKM) (log2(value + 1))
Preop PSA (log2(value + 1))
G
Pearson: 0.45; p = 1.612e-6
SLC2A4: mRNA expression (RNA Seq RPKM) (log2(value + 1))
Time from Surgery to BCR/Last Follow Up
H
Pearson: 0.26; p = 6.297e-3)
SLC2A5: mRNA expression (RNA Seq RPKM) (log2(value + 1))
Time from Surgery to BCR/Last Follow Up
I
Pearson: 0.06; p = 0.527
SLC2A9: mRNA expression (RNA Seq RPKM) (log2(value + 1))
Time from Surgery to BCR/Last Follow Up
J
p = 2.46717E-05
SLC2A4: mRNA expression (RNA Seq RPKM) (log2(value + 1))
BCR Status
K
p = 1.15225E-07
SLC2A5: mRNA expression (RNA Seq RPKM) (log2(value + 1))
BCR Status
L
p = 0.019687087
SLC2A9: mRNA expression (RNA Seq RPKM) (log2(value + 1))
BCR Status
M
**
****
**
****
SLC2A4: mRNA expression (RNA Seq RPKM) (log2(value + 1))
3+3
3+4
4+3
8-10
Gleason Score
N
SLC2A5: mRNA expression (RNA Seq RPKM) (log2(value + 1))
3+3
3+4
4+3
8-10
Gleason Score
O
SLC2A9: mRNA expression (RNA Seq RPKM) (log2(value + 1))
3+3
3+4
4+3
8-10
Gleason Score

Figure 5. SLC2A4/5 down-regulation was associated with disease progression in early-onset patients. Pearson correlation (A-C, G-I) and Spearman correlation (D-F) were analyzed between SLC2A gene expression and tumor mutation burden (A-C), Pre-operation PSA levels (D-F), and biochemical relapse (G-I) in early-onset patients. The expression levels of SLC2A genes as indicated were compared between patients with or without biochemical relapse (J-L) or among various Gleason score groups. The *p*-values were derived from the Student t-test (J-L) or the ANOVA test (M-O). **P < 0.01; ****P < 0.0001.

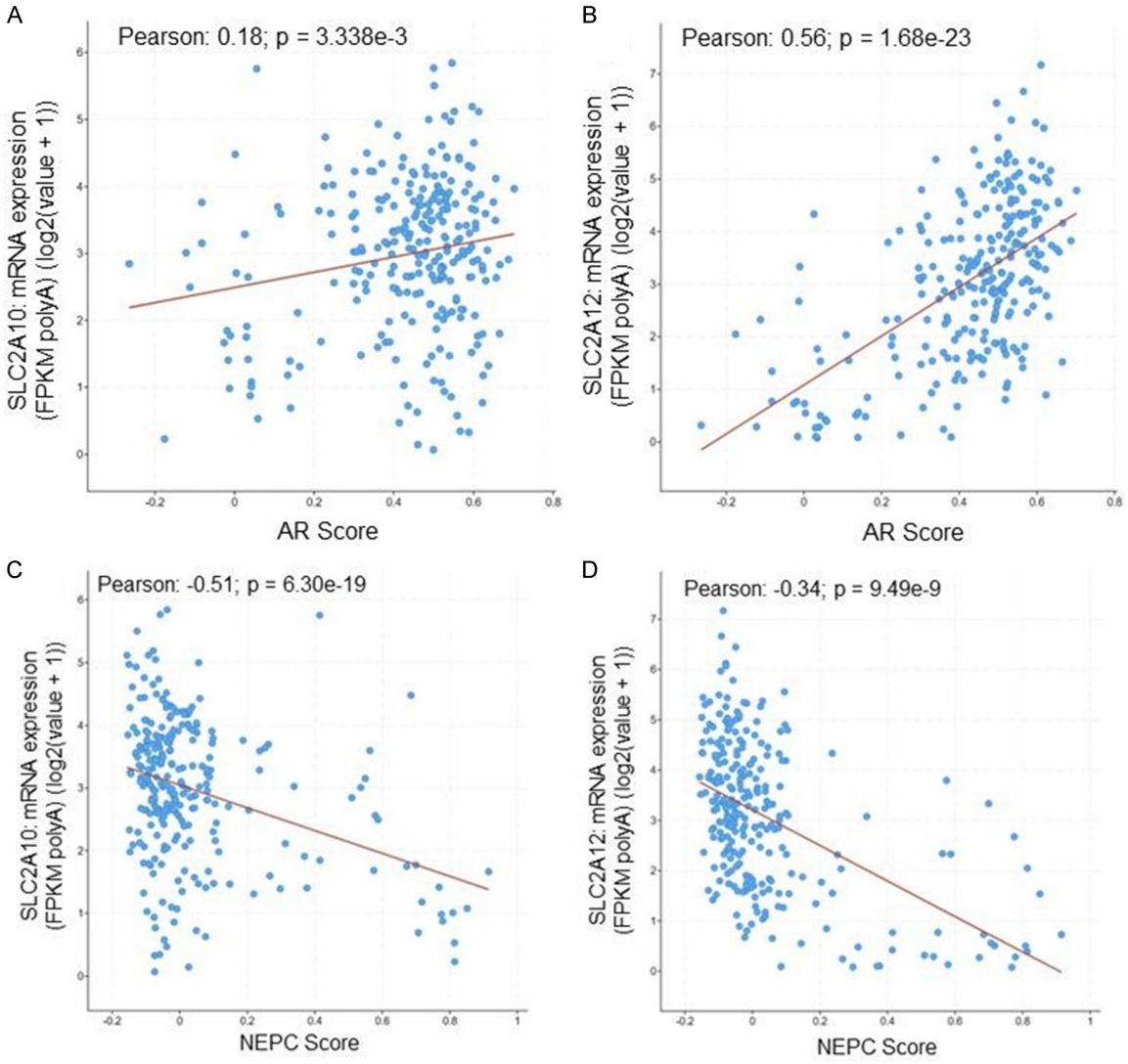

Figure 6. SLC2A10/12 expression was positively associated with AR activity. Pearson correlation was analyzed between SLC2A10/12 gene expressions and AR score (A and B) or NEPC score (C and D). n = 429.

features compared to those without NE features (**Figure 8D**, **8E**). To verify the dependence of SLC2A10/12 expression on AR activity, we analyzed SLC2A10/12 expression in LuCaP35 PDX xenografts [16]. Compared to a sham control group, SLC2A10/12 expression was significantly reduced in castrated animals (**Figure 8F**, **8G**), which was in line with previous reports [17]. These data suggested that SLC2A2/9/13 genes are involved in neuroendocrinal progression from the CRPC stage.

SLC2A4/6 expression was associated with patient survival outcomes in primary prostate cancers

Finally, we analyzed patient survival outcomes in connection to these SLC2A family gene expressions. As shown in **Figure 9**, higher expression levels of SLC2A4/5/9/10/12 genes were significantly associated with a favorite outcome in the progression-free interval (PFI) (**Figure 9A-E**), while SLC2A6/8 expression was

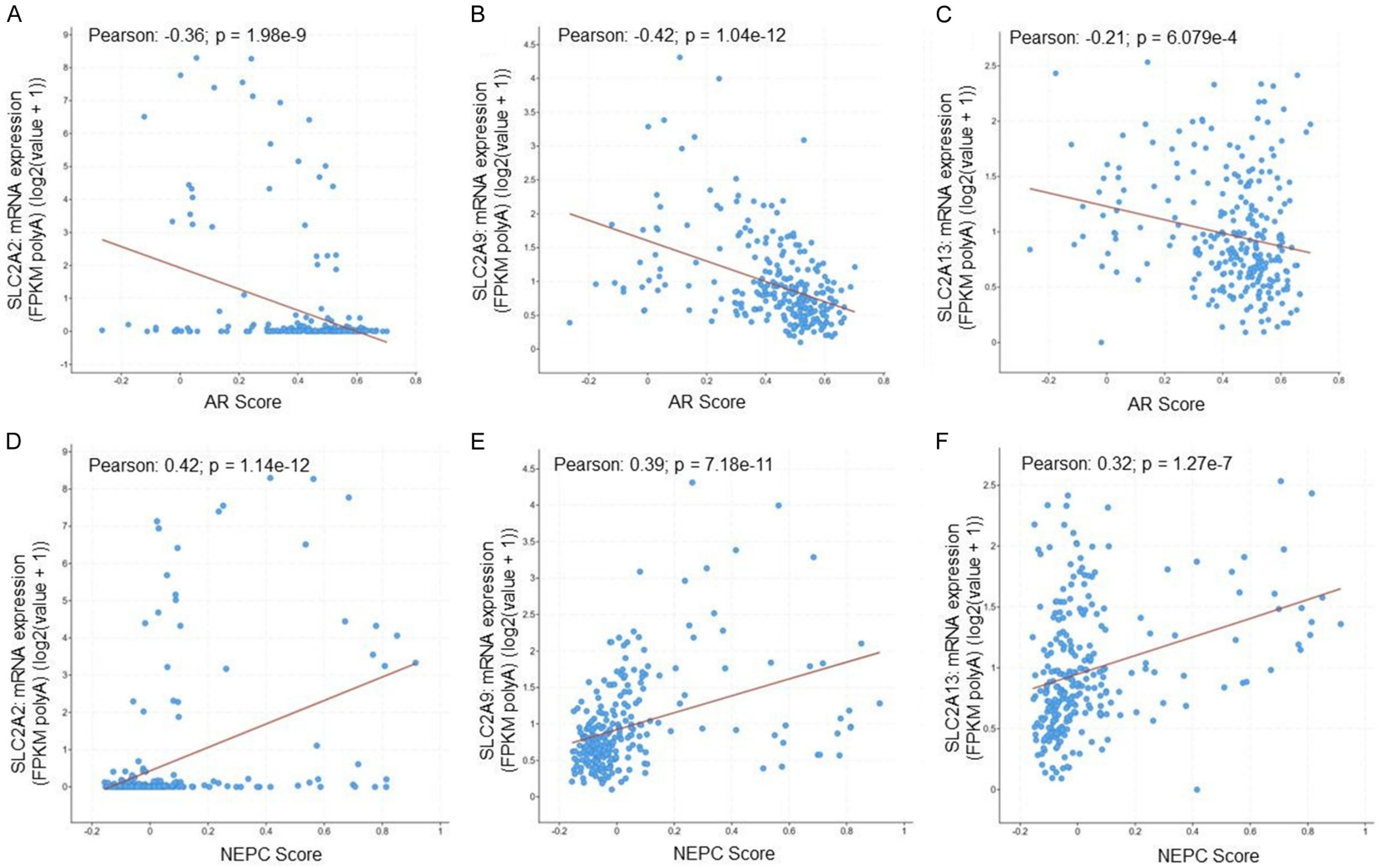

Figure 7. SLC2A2/9/13 expression was positively associated with NEPC progression. Pearson correlation was analyzed between SLC2A2/9/13 gene expressions and AR score (A-C) or NEPC score (D-F). n = 429.

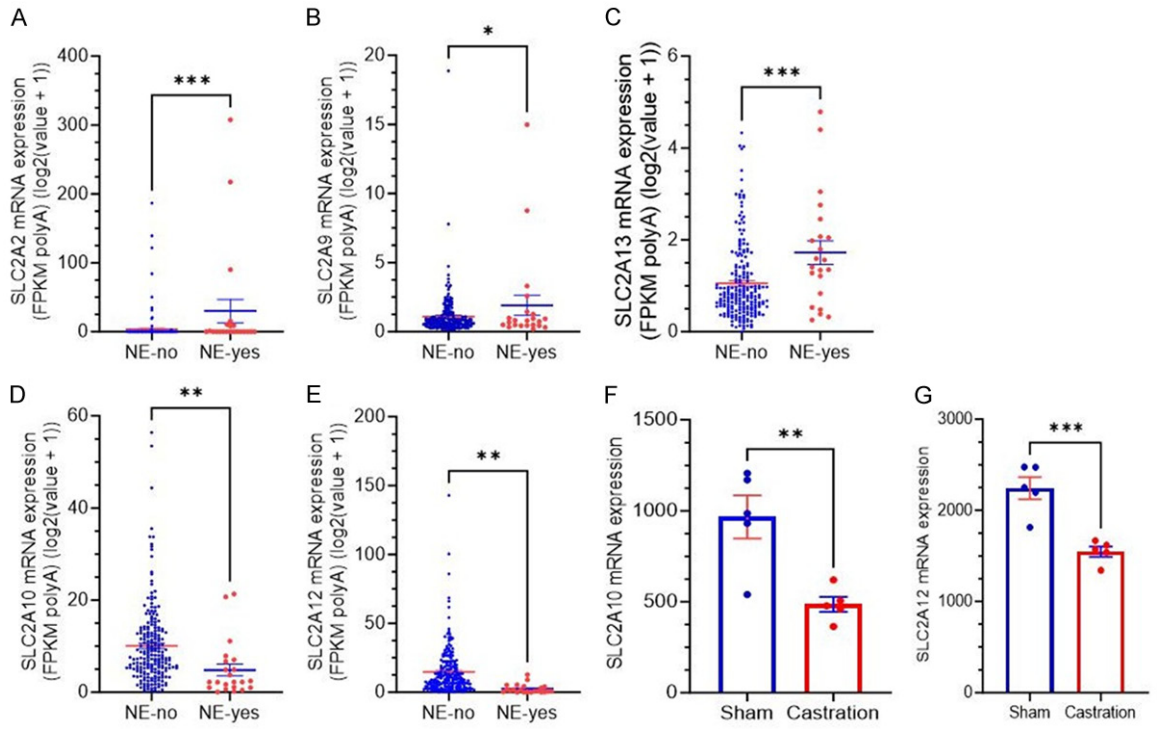

Figure 8. SLC2A gene expression was altered during NEPC progression. Expression levels of SLC2A genes as indicated were compared between patients with or without NE features (A-E). SLC2A10/12 expressions in LuCaP35 xenografts were compared between animals after sham or castration surgery (F, G). The *p*-values were derived from the Student t-test. *P < 0.05; **P < 0.01; ****P < 0.0001.

associated with a worse PFI outcome (**Figure 9F**, **9G**). Interestingly, only SLC2A4 expression was associated with a favorite disease-specific survival (DSS) while SLC2A1/6 expression was associated with worse DSS outcomes (**Figure 9H-J**). These data suggest that SLC2A4 expression is a favorite prognostic factor but SLC2A6 is a worse prognostic factor for patient PFI and DSS outcomes.

Discussion

In this study, we analyzed the expression profiles of 14 glucose transporter (SLC2A genes) family members in prostate cancers. Our results showed that SLC2A4/5/9 genes were significantly downregulated in primary prostate cancer tissues compared to their benign compartments. These gene down-regulations were associated with promoter DNA methylation and genome alterations, indicating a potential mechanistic correlation. In addition, the expressions of the SLC2A4/5/9 genes were tightly associated with anti-tumor immune infiltration, suggesting a critical clue for immune escape of prostate cancer, as reported in other types of human cancers [18, 19].

Interestingly, only the expression of the SLC2A4 gene but not the SLC2A5/9 genes was constantly associated with clinicopathological parameters, indicating that SLC2A4 gene expression is a strong prognostic factor in prostate cancer development and progression.

In a cohort of early-onset prostate cancer patients [12], only SLC2A4/5 but not SLC2A9 gene expression was associated with genome alteration (tumor mutation burden), PSA levels, and biochemical relapse. Most interestingly, only SLC2A4 gene expression was significantly associated with Gleason scores in this subtype of early-onset prostate cancers. The underlying clinical significance needs more descent investigation. SLC2A4 gene expression was recently identified as one of the six-gene signatures related to metabolism-associated prostate cancer [20]. In human prostate cancer DU145 cells, CRISPR-Cas9 knock-out screening revealed that SLC2A4 knockout

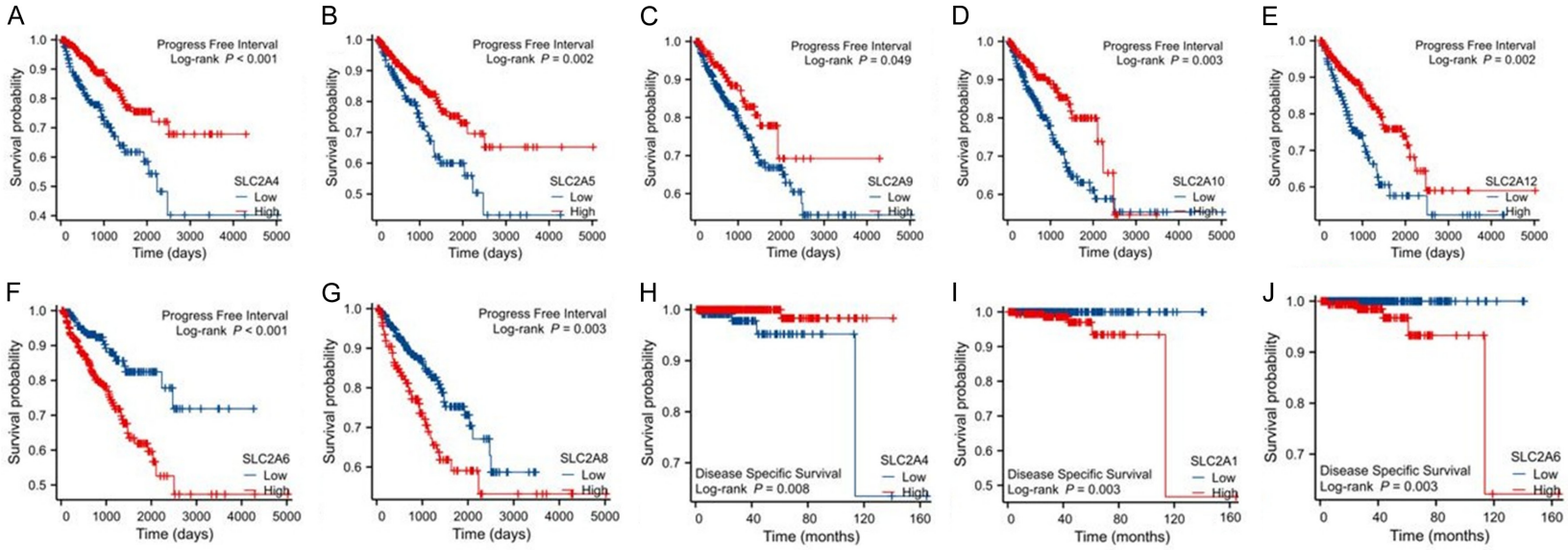

Figure 9. SLC2A4/6 expression was associated with patient survival outcomes in primary prostate cancers. Patient survival outcomes for the progression-free interval (A-G) and disease-specific survival (H-J) were analyzed based on SLC2A gene expression levels as indicated using the Kaplan-Meier curve coupled with the minimum *p*-value cut-off approach.

enhanced the potential of invasion and metastasis, indicating a tumor suppressor function of the SLC2A4 gene in prostate cancer [21].

In CRPC cancers [13], our analysis revealed that SLC2A10/12 gene expression positively correlated with AR activity score but negatively correlated with NEPC score, which is in line with a recent report that SLC2A12 gene expression is AR-modulated [17]. Conversely, SLC2A2/9/13 gene expression was negatively correlated with AR activity score but positively correlated with NEPC score, suggesting a different role in NEPC progression, the lethal type of late-stage prostate cancer.

Unfortunately, in the literature, there is a paucity of the expression profiles of SLC2A family genes in prostate cancer. Most of the studies were focused on the SLC2A1 gene, which promoted cellular glycolysis and cell proliferation in prostate cancer [22] and protected androgen-sensitive prostate cancer cells from glucose deprivation-induced cell death [10]. In CRPC patients, a higher ^{18}F-FDG PET SUVmax was reported than hormone-sensitive prostate cancer, suggesting a greater need for glucose consumption [23]. In a preclinical animal xenograft model, SLC2A1 gene expression was positively correlated with ^{18}F-FDG intake and was associated with a worse survival outcome [24]. Consistently, SLC2A1 inhibition significantly suppressed cell growth, glycolytic activities, and tumor growth in a xenograft model both in CRPC and enzalutamide-resistant prostate cancer [24]. Further analysis indicated that the AR protein directly interacted with the SLC2A1 gene promoter to modulate SLC2A1 gene expression [24]. SLC2A1 inhibiter plus Enzalutamide remarkably suppressed tumor cell proliferation and induced apoptosis in CRPC cells [24]. However, in our study, we only found a significant reduction of SLC2A1 gene expression in primary prostate cancer tissues compared to the benign prostate tissues when the comparison was conducted using the grouped data but not the case-matched pair comparison. The differences between our results and others as reported in the literature [24, 25] might be due to cell line specificity and patient specimens.

In this study, we also conducted a survival analysis of patient outcomes using the expression profiles of SLC2A family genes. Our analysis showed that SLC2A4/6 gene expressions in primary prostate cancers were associated with both progression-free interval (PFI) and disease-specific survival (DSS) [26]. SLC2A1 gene expression was positively correlated with a worse DSS outcome, which was in line with a previous report [24]. SLC2A5/9/10/12 gene expressions showed a favorite PFI outcome in primary prostate cancer patients but SLC2A8 exhibited a worse PFI outcome. The significance of this outcome analysis needs more investigation at the molecular level using cell culture and animal xenograft models.

In conclusion, our studies revealed that SLC2A4 gene expression was significantly reduced in prostate cancers, which was associated with clinicopathological parameters. In CRPC patients, SLC2A10/12 gene expressions are associated with AR activity score while SLC2A9/13 gene expressions are associated with NEPC progression.

SLC2A4/6 gene expressions are strong prognostic factors associated with PFI and DSS outcomes in primary prostate cancer patients.

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Disclosure of conflict of interest

None.

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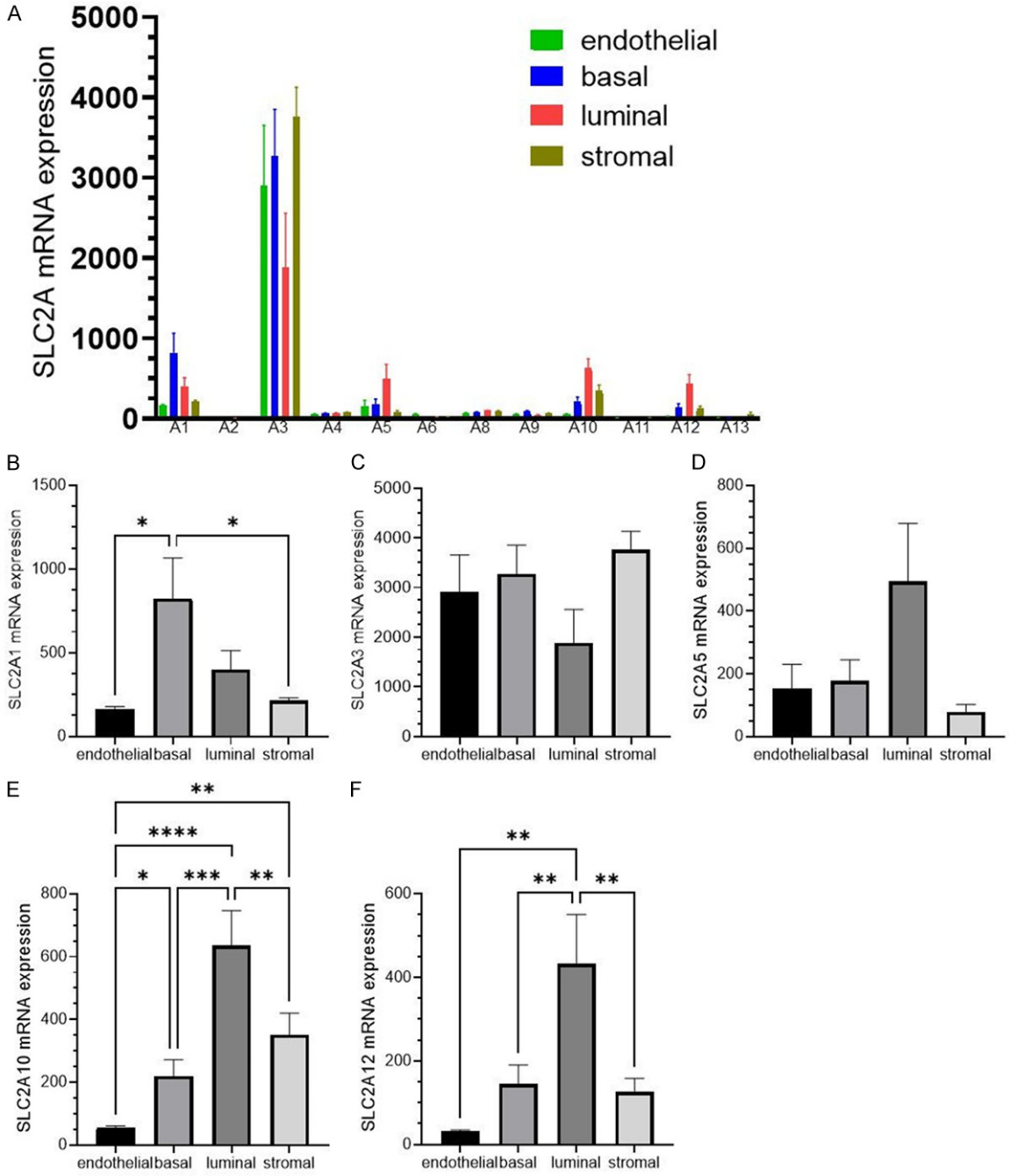

Figure S1. SLC2A gene expression patterns in various cell types of the prostate.