Clinical Research

Association of prostate cancer SLCO gene expression with Gleason grade and alterations following androgen deprivation therapy

Mazen Alsinnawi1 · Ailin Zhang2 · Daniella Bianchi-Frias2 · John Burns1 · Eunpi Cho3 · Xiaotun Zhang4 · Adam Sowalsky5,6 · Huihui Ye7 · April E. Slev1 · Lawrence True4 · Christopher Porter1 · Mary-Ellen Taplin8 · Steven Balk5 · Peter S. Nelson2 · R. Bruce Montgomery9 · Elahe A. Mostaghel3,9,10

Received: 28 November 2018 / Revised: 3 January 2019 / Accepted: 23 January 2019 / Published online: 19 March 2019
© Springer Nature America, Inc. 2019

Abstract

Background SLCO-encoded transporters have been associated with progression to castration-resistant prostate cancer (CRPC) after initiation of androgen deprivation therapy (ADT). Although expressed at lower levels than in CRPC tissues, SLCO-encoded transporters may also play a role in response of primary prostate cancer (PCa) to ADT and biochemical recurrence.

Methods We systematically explored expression of the 11 human SLCO genes in a large sample of untreated and ADT-treated normal prostate (NP) and primary PCa tissues, including tumors treated with neoadjuvant abiraterone.

Results Transporters with the most recognized role in steroid uptake in PCa, including SLCO2B1 (DHEAS) and 1B3 (testosterone), were consistently detected in primary PCa. SLCO1B3 was nearly 5-fold higher in PCa vs NP with no difference in Gleason 3 vs 4 and no change with ADT. SLCO2B1 was detected at 3-fold lower levels in PCa than NP but was nearly 7-fold higher in Gleason 4 vs Gleason 3 and increased 3-fold following ADT (p < 0.05 for all).

Conclusions We observed clear differences in SLCO expression in PCa vs NP samples, in Gleason 4 vs Gleason 3 tumors, and in ADT-treated vs untreated tissues. These findings are hypothesis generating due to small sample size, but suggest that baseline and ADT-induced changes in PCa OATP expression may influence steroid uptake and response to ADT, as well as uptake and response to drugs such as abiraterone and docetaxel which are also subject to OATP-mediated transport and are now being routinely combined with ADT in the metastatic castration sensitive setting.

Introduction

Androgen deprivation therapy (ADT) is standard of care for men with advanced prostate cancer (PCa) but is inevitably followed by castration-resistant prostate cancer (CRPC). Despite suppression of circulating androgens, prostatic androgens following castration remain well above levels...
capable of engaging AR, and CRPC metastases contain testosterone levels four times higher than prostate tissue of eugonadal men [1–3].

The organic anion transporting polypeptides (OATP) are SLCO-encoded proteins that transport bile acids, xenobiotics, steroid conjugates, and important drugs, including taxanes [4–6]. Several OATPs (e.g., OATP1A2, 1B1, 1B3, and 2B1) mediate uptake of steroids into PCa cells in vitro and in vivo [7–11], and single nucleotide polymorphisms (SNPs) of SLCO1B3 and SLCO2B1 that demonstrate enhanced androgen uptake are associated with more rapid disease progression in men with metastatic disease treated with ADT [8, 12, 13]. CRPC metastases express transcripts encoding SLCO transporters at significantly higher levels than in primary PCa [14]. These data strongly support a role for OATP-mediated steroid transport in moderating the tissue response to ADT and promoting disease progression in men with advanced disease.

In contrast, in primary PCa the extent to which SLCO genes influence disease or become altered in response to hormonal therapy is not well-explored. Pressler et al. examined SLCO1B1, SLCO1B3, and SLCO2B1 in a five normal prostate and 21 PCa samples and observed higher SLCO1B3 in primary PCa vs normal prostate, and an association of SLCO1B3 with Gleason score [15]. Wright et al. evaluated SLCO1B1, SLCO1B3, SLCO2A1, SLCO2B1, SLCO3A1, and SLCO4A1 levels in eight benign and eight PCa samples without significant differences in tumor vs normal tissue, likely due to limited number of samples [14]. They also found no association of genetic differences in SLCO1B3 or SLCO2B1 with PCa recurrence in a case-control sample of 469 men with localized PCa (no hormone therapy). However, an impact of SLCO expression on steroid transport in primary PCa may be most relevant in the setting of ADT (e.g., ADT combined with definitive radiation therapy). In particular, the extent to which expression of SLCO genes in primary PCa is altered by ADT is unknown but may provide insight into induction of SLCO transporters as a mechanism of resistance to ADT.

We evaluated the eleven human SLCO genes in microdissected benign (n = 20) and cancer (n = 35) tissues from untreated men with localized PCa, including separately microdissected foci of Gleason grade 3 vs grade 4 tumors. We profiled SLCO expression in a cohort of matched benign (n = 20) and cancer (n = 18) prostate samples from men enrolled in a trial of neoadjuvant ADT prior to radical prostatectomy (RP), and in primary PCa samples (n = 13) from men enrolled in a trial of neoadjuvant ADT plus abiraterone acetate (ABI) prior to RP [16, 17]. Finally, we evaluated the impact of 12 SNPS in 7 SLCO genes on risk of biochemical recurrence in a cohort of 147 men with localized PCa treated with radical prostatectomy (RP).

Materials and methods

Patient samples

All procedures were approved by Institutional Review Boards of University of Washington and Fred Hutchinson Cancer Research Center. Frozen prostate tissue was collected from men with Gleason grade 3 and/or grade 4 PCa under an approved protocol for use of excess tissue after RP, and from men with intermediate to high risk PCa (Gleason score ≥ 7) treated on a previously published trial of ADT prior to RP (NCT00298155) [17]. (Greater than 95% of men for whom data was available self-identified as Caucasian). Hormonal regimens included (1) goserelin with bicalutamide, (2) goserelin with dutasteride (3.5 mg), (3) goserelin with bicalutamide and dutasteride, and (4) goserelin with bicalutamide, dutasteride and ketoconazole (200 mg three times daily; with prednisone 5 mg daily). Formalin-fixed prostate tissue (FFPE) was obtained from men with intermediate to high-risk PCa (Gleason score ≥7) treated on a previously published trial of lupon plus ABI prior to RP (NCT00924469) [16]. Genomic DNA was isolated via macrodissection of benign prostate tissue from hematoxylin and eosin (H&E) stained FFPE tissue sections from 147 patients who underwent RP between 1995 and 2010 at the University of Washington for whom recurrence data was available.

Laser capture microdissection and RNA isolation

Microdissection and RNA isolation was performed from frozen prostate tissue as previously described [3]. In untreated tissues, foci of Gleason 3 and Gleason 4 cancer were separately microdissected. All areas to be micro-dissected were selected reviewed by a pathologist (X.Z., L.T., or H.Y). Microdissection and RNA isolation of FFPE samples from ABI treated samples was performed as described [18].

SLCO transcript profiling

Quantitative reverse transcription (qPCR) was performed as described [14]. The mean Ct for each gene was normalized to the housekeeping gene RPL13A (delta Ct or dCt). No consistent differences in RPL13A expression itself were observed in the normal vs prostate samples (Supplementary Fig S1). Samples with undetectable expression of a given gene were assigned dCt value of 33 for purposes of calculation. Fold change was calculated from the difference in mean dCt between sample groups (ddCt method; fold = 2^ddCt). Primer sequences are as published [14].
SLCO genotyping analysis

Genomic DNA was purified using the QIAamp® DNA FFPE Tissue Kit. Twelve single nucleotide polymorphisms (SNPs) with minor allelic frequency (MAF) >10% in 6 SLCO genes (SLCO1B1, 1B3, 2B1, 2A1, 3A1, and 5A1) were genotyped using TaqMan SNP assays as described [13]. The SNP assay numbers, minor allele frequency and potential role in PCa are shown in Supplementary Table 1.

Statistical analysis

Comparisons of SLCO gene expression in PCa vs NP, Gleason grade 3 vs 4 samples, and treated vs untreated PCa were performed with unpaired two-tailed t-tests. The variance between groups was compared using an F test and if significantly different (p < 0.05) Welch’s correction was applied. Time to recurrence was number of months from RP to the first measurement of biochemical relapse (BCR; PSA ≥0.2), death, loss to follow-up or 10 years. Binary recurrence within 10 years was compared across different genotypes using Fisher’s Exact Test. Cox proportional hazards models were used to compare time to recurrence by genotype, adjusted for tumor volume, TNM staging, pre-prostatectomy PSA, Gleason grade, and margin status. Heterozygous and rare homozygous variants were combined if total number of cases in any genotype was fewer than 10.

Results

Expression of SLCO genes in untreated prostate tissue

We evaluated SLCO expression in normal prostate (NP; n = 20) and separately microdissected foci of Gleason grade 3 and grade 4 PCa (n = 35) from men with localized PCa undergoing RP. In untreated tissues (cancer or benign), the percentage of samples that were undetectable for a given gene varied and did not represent a unique population (0–3% samples undetectable for SLCO2B1, 3A1, and 5A1; 10–20% for 1B3 and 4A1; 40% for 1C1 and 4C1; 60–80% for 1A2 and 1B1; and 93% for 6A1). Transcript data in NP vs PCa (comprising both Gleason grade 3 and 4 tumors) are shown in Fig. 1 and summarized in Table 1.

In NP, levels of SLCO2A1, 3A1 and 5A1 (Fig. 1a–c) were most abundant (average dCt vs RPL13A of −4 to −6), while SLCO2B1, 4A1 and 4C1 (Fig. 1d–f) were several orders of magnitude lower (dCt −14 to −17), but still easily detectable. Average levels of SLCO1B3, 1C1 and 1B1 were very low in NP (dCt of −19–22), and largely undetectable for SLCO1A2 (Fig. 1g–j). SLCO6A1 was only detected in a few samples (not shown) and was not analyzed further.

Multiple SLCO genes showed differential expression in PCa vs NP. PCa expressed higher SLCO1B3 (4.8 fold, p = 0.045; Fig. 1g), SLCO1C1 (21 fold, p = 0.002; Fig. 1h), and 1B1 (2.7-fold, p = 0.016; Fig. 1i), and lower SLCO4C1 (−37 fold, p < 0.0001; Fig. 1e), 3A1 (−10fold, p =< 0.0001; Fig. 1b) and 2B1 (−2.8 fold, p = 0.011; Fig. 1d). Thus, SLCO2A1, 3A1, and 5A1 remain the most highly expressed genes in tumor (dCt −4 to −8), while SLCO1B3 and 1C1 move up to join SLCO2B1 and 4A1 as the next most abundant (dCt −15 to −16), and SLCO4C1 moves down with SLCO1A2 and 1B1 as the least abundant (dCt −21 to −22). Consistent with a prior report, we detected minimal to no expression of the truncated SLCO1B3 splice variant in primary PCa (not shown) [11].

Association of Gleason grade with SLCO gene expression

Differences in tumor androgen levels have been reported in high vs low grade PCa [19]. Therefore, we sought to determine whether differential expression of SLCO genes (and thereby differences in androgen uptake) might plausibly contribute to this difference. Gleason 4 tumors (n = 18) had significantly higher SLCO1C1 (24-fold, p = 0.007, Fig. 2a), 2B1 (6.7-fold, p = 0.0001; Fig. 2b) and 3A1 (3.5-fold, p = 0.014; Fig. 2c) than Gleason 3 tumors (n = 17; Table 1 and Fig. 2). No differences were observed in the remaining SLCO genes (Supplementary Fig S2).

Impact of androgen deprivation on SLCO gene expression

To determine whether expression of SLCO genes is altered by hormonal therapy, we microdissected PCa and NP in frozen prostate tissue from 20 men with high risk localized PCa treated with various combinations of goserelin (Zoladex, Z), bicalutamide (Casodex, C), dutasteride (D) and ketoconazole (K) in a previously completed trial of neoadjuvant ADT for 3 months prior to surgery [17]. Due to morphologic changes caused by ADT, Gleason grade was not assessed. Specimen numbers in each subset do not enable a statistically rigorous assessment. Specimen numbers in each subset do not enable a statistically rigorous assessment among the different regimens (ZC, n = 2; ZD n = 4; ZCD, n = 6; and ZCDK, n = 8; Supplementary Fig S3), and samples were grouped into treated NP or treated PCa sets for subsequent analysis.

Compared to untreated tissues, ADT-induced differential expression of SLCO genes in both NP and PCa (Fig. 1 and Table 2). ADT-treated tumor samples had higher SLCO3A1 (4.4-fold, p = 0.0007; Fig. 1b), 2B1 (3.6-fold, p = 0.032;
Fig. 1d), and 1C1 (9.8-fold, \( p = 0.03 \); Fig. 1h), but lower 2A1 (−2.3-fold, \( p = 0.0004 \); Fig. 1a) and 5A1 (−4.2-fold, \( p = 0.0004 \); Fig. 1c). The direction and magnitude of change was generally similar for PCa and NP except for SLCO5A1, in which NP showed a significantly larger decrease in expression (−15-fold, \( p < 0.0001 \); Fig. 1c) than that in tumor; SLCO1B3, in which NP showed a decrease after ADT (−5-fold, \( p = 0.014 \); Fig. 1g) while tumor did not; and SLCO3A1 and 2B1, in which NP did not show the increase in expression observed in tumor (Fig. 1b, d).

To assess the impact of more potent androgen suppression we microdissected FFPE PCa samples from a trial of Lupron plus 3–6 months of ABI prior to RP [16]. While absolute transcript levels were lower than those in frozen tissue, the four SLCO genes most highly expressed in PCa in the studies above (SLCO2A1, 3A1, 5A1, and 2B1) were also detected in the FFPE samples (Fig. 3). Moreover, there was a near statistically significant decrease in SLCO2A1 (\( p = 0.07 \); Fig. 3a) and increase in SLCO2B1 (\( p = 0.09 \); Fig. 3d) in the ABI plus ADT-treated samples, similar to our findings in the ADT-treated tumor samples. While the changes in SLCO3A1 and SLCO5A1 were not statistically significant, the direction of changes in the tumor samples following treatment (increased for SLCO3A1, decreased for SLCO5A1) were also consistent with the findings above.

Association of SLCO genotype with prostate cancer recurrence after prostatectomy

Genomic DNA was obtained from 147 patients with PCa who underwent RP between 1995 and 2010. Longitudinal follow up (median 60 months) yielded 67 patients with and
80 without evidence of BCR. Demographics and clinical characteristics of patients are shown in Supplementary Table 2. PCa patients with BCR had more aggressive features on final prostate pathology; higher stage disease (30% had pT3 N0 vs only 8.8% in non-BCR group), higher Gleason scores (80.6% Gleason 7 vs 42.5% in non-BCR), more positive margins and larger tumor volumes. Samples were genotyped for 12 SNPs with MAF >10%, selected based on a published role in hormone transport/metabolism and/or significance in PCa [13]. Binary recurrence within 10 years showed no statistically significant difference across the different SNP genotypes except for SLCO2A1 SNP rs34550074 (p = 0.025). However, after adjustment for clinical variables the resultant model was no longer significant (Supplementary Table 3).

**Discussion**

Although expressed at lower levels than in CRPC, SLC0-encoded transporters may also play a role in response of primary PCa to neoadjuvant/adjuvant ADT and in driving BR following definitive therapy. We systematically explored the expression of SLC0 genes in a large sample of untreated and ADT-treated primary PCa tissues. Transporters with the most recognized role in steroid uptake in PCa, including SLC02B1 (DHEAS) and 1B3 (testosterone), were consistently detected in primary PCa tissue [8–11]. We observed clear differences in PCa vs NP samples, in Gleason 4 vs Gleason 3 tumors, and in ADT-treated vs untreated tissues.

The increased expression of SLC01B3 observed in PCa vs NP is consistent with prior reports showing higher SLC01B3 in PCa vs NP [8, 15]. While Pressler et al. noted an association of Gleason grade with SLC01B3, we observed an association of Gleason grade with SLC02B1 (this may reflect differences in sample preparation as we report microdissected foci of Gleason 3 and 4 tumors whereas Pressler et al. reported tumor grade as the Gleason sum). However, the increased expression of SLC02B1 in higher Gleason grade tumors is consistent with findings recently reported in primary PCa samples from The Cancer Genome Atlas (TCGA) [20].

SLCO-encoded genes may influence primary PCa in multiple ways. While the higher SLC01B3 expression in cancer or the higher SLC02B1 levels in Gleason 4 vs Gleason 3 tumors might associate with higher tissue androgen levels and more aggressive cancer, the association of tissue androgens and PCa risk is not well understood. In one study of 196 patients, higher tissue testosterone levels were significantly related to higher Gleason scores, but no association was noted with DHT, whereas in a different study of 81 patients, DHT levels were lower in patients with Gleason 7–10 disease vs Gleason 6 (testosterone not

| Table 1 | Expression of SLC0 genes in hormone naive primary prostate cancer |
|---------|---------------------------------------------------------------|
| Normal prostate (NP) | Prostate cancer (PCa) | PCa vs NP | Gleason 4 vs 3 |
| avg dCt | avg dCt | Fold | P-value | fold | P-value |
| SLCO1A2 | −22 | −21 | 2.0 | ns | −1.5 | ns |
| SLCO1B1 | −22 | −21 | 2.7 | 0.016 | 1.0 | ns |
| SLCO1B3 | −19 | −16 | 4.8 | 0.045 | −1.3 | ns |
| SLCO1C1 | −19 | −15 | 21 | 0.002 | 24 | 0.007 |
| SLCO2A1 | −5 | −4 | 1.7 | 0.055 | 1.8 | ns |
| SLCO2B1 | −14 | −16 | −2.8 | 0.011 | 6.7 | 0.0001 |
| SLCO3A1 | −4 | −8 | −10 | <0.0001 | 3.5 | 0.014 |
| SLCO4A1 | −17 | −15 | 2.8 | ns | 1.6 | ns |
| SLCO4C1 | −16 | −21 | −37 | <0.0001 | 2.3 | ns |
| SLCO5A1 | −6 | −7 | −1.8 | 0.09 | 1.5 | ns |

*aNormalized to RPL13A, dCt of −23 considered negative
b*p-values from two-sided t-tests, p ≤ 0.05 (bold) significant, p ≤ 0.10 (italicized) trending toward significance

**Fig. 2** SLC0 gene expression in Gleason 3 vs Gleason 4 prostate tumors. Transcript levels of the indicated SLC0 genes were evaluated in microdissected foci of Gleason 3 (Gl3, n = 18) or Gleason 4 (Gl4, n = 17) PCa in snap frozen prostate tissue from untreated men. Presentation of data as box and whisker plots and statistical analyses are as described in the legend for Fig. 1.
measured), actually suggesting an inverse association of androgen uptake with tumor aggressiveness [19, 21].

Importantly, testosterone interferes with OATP2B1-mediated transport of DHEAS, and thus OATP-mediated steroid uptake in the eugonadal setting may not follow the same paradigm as in ADT [22]. This is consistent with our data showing no association of SLCO genotype with PCa recurrence in 147 men not treated with ADT. Our recurrence data set clearly has limitations due to small cohort size, but is consistent with the larger study of Wright et al. showing no association of SLCO genotype with recurrence in 489 patients [14].

However, in a study of 494 primary PCa cases from TCGA, high SLCO2B1 was associated with worse disease-free survival (DFS) after RP (no association was noted for SLCO1B3) [20]. Notably, this study reported higher SLCO2B1 in higher Gleason grade tumors (consistent with our data), and found the association with DFS was only significant for Gleason score 8. This suggests that any impact of SLCO2B1 expression (or genotype) on recurrence or progression is most important in high-grade disease in which it is more highly expressed. In this regard, our study and that of Wright et al may have been negative because the populations were low risk (81% and 85% with Gleason score 6 or 3 + 4, respectively), whereas >40% of patients in the TCGA study had a Gleason score ≥8.

Alternatively, SLCO-encoded transporters may mediate uptake of other OATP substrates relevant to prostate carcinogenesis and/or progression, including prostaglandins (PGs), thyroid hormones, green tea catechins, taxanes, statins, cardiac glycosides, glitazones, and metformin [23–33]. In this regard, several of the transporters most abundantly expressed in the prostate do not have a recognized role in androgen transport. Of these, SLCO3A1 (estrone-sulfate, PGs), and 4C1 (estrone-sulfate, cAMP, thyroid hormones) were expressed at significantly lower levels in CP vs NP, possibly suggesting transport of a substrate with anti-tumor activity. In contrast, increased expression of the thyroid hormone transporter SLCO1C1 may represent a substrate with tumor-promoting properties as thyroid hormones have been shown to promote PCa cell proliferation in vitro, and several studies have suggested an association between increased thyroid hormone levels and PCa risk [24, 29, 34–41].

As in advanced PCa, OATP-mediated uptake of androgens in primary PCa may be most relevant in modifying response to ADT. The most substantive evidence for OATP-mediated androgen uptake in PCa is that of DHEAS by OATP2B1. DHEAS uptake is dependent on the expression of SLCO2B1 and greater expression of SLCO2B1 resulted in increased DHEAS transport into cells [9]. Thus, the increased SLCO2B1 observed with standard and ABI containing neoadjuvant ADT may adversely influence response to therapy, such as in patients with localized PCa receiving neoadjuvant/adjuvant ADT in context of definitive radiation, or patients with newly diagnosed metastatic disease being treated with ADT and ABI. This may be particularly relevant for SLCO2B1

| Table 2 Change in SLCO gene expression in normal and cancer prostate epithelium after androgen deprivation |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Normal prostate (NP) | Prostate cancer (PCa) |
|                 | Folda | p-valueb | Folda | p-valueb |
| SLCO1A2         | −1.3  | ns      | −1.9  | ns      |
| SLCO1B1         | −1.4  | ns      | −1.7  | ns      |
| SLCO1B3         | −4.9  | 0.014   | −1.2  | ns      |
| SLCO1C1         | 10.2  | 0.042   | 9.8   | 0.030   |
| SLCO2A1         | −1.3  | ns      | −1.8  | 0.07    |
| SLCO2B1         | −1.8  | 0.07    | 3.1   | 0.032   |
| SLCO3A1         | 1.7   | 0.06    | 4.4   | 0.0007  |
| SLCO4A1         | −1.2  | ns      | −1.4  | ns      |
| SLCO4C1         | −2.8  | ns      | 1.5   | ns      |
| SLCO5A1         | −15.3 | <0.0001 | −5.4  | 0.0004  |

aFold change relative to untreated tissue
b p-values calculated as in Table 1, p ≤ 0.05 (bold) significant, p ≤ 0.10 (italicized) trending toward significance

Fig. 3 Expression of SLCO genes in primary prostate cancer after neoadjuvant treatment with abiraterone. Transcript levels of the indicated SLCO genes (normalized to the housekeeping gene RPL13A) were evaluated in microdissected foci of cancer from formalin fixed paraffin embedded prostate tissue from untreated men or those treated with neoadjuvant abiraterone for 3–6 months prior to prostatectomy. Presentation of data as box and whisker plots and statistical analyses are as described in the legend for Fig. 1.
genotypes associated with increased transport efficiency or higher protein expression [9, 12]. Additionally, the 6.7-fold higher SLC02B1 in Gl4 vs Gl3 tumors may render Gl4 disease more resistant to ADT, which would be consistent with data from a small study of 28 patients which showed that the decrease in tissue DHT following 6 months of ADT was less in Gleason 7–10 disease than Gleason 6 disease [42]. As OATP2B1 transports both DHEAS and ABI, any net impact of the increase in SLC02B1 expression induced by ADT and ABI remains to be empirically determined from clinical studies [43].

OATP proteins are critical mediators of hepatic taxane uptake and primary determinants of systemic taxane exposure [29, 40]. A pharmacokinetic study reported that docetaxel clearance increased by approximately 100% in castrate compared to non-castrate men with PCa, and rat studies found that castration increased docetaxel clearance and was associated with increased hepatic expression of rOat2 (Slc22a7), a mouse Oatp shown to transport docetaxel [44]. OATPs also modify intratumoral accumulation of docetaxel and cabazitaxel, strongly influencing response of PCa xenografts to treatment [28, 45], and loss of tumor SLC01B3 expression is a mechanism of resistance in taxane-refractory prostate tumors [41]. Thus, an increase in tumor SLC0 expression following ADT could potentially influence docetaxel transport and enhance treatment response.

Regulation of OATP expression and function occurs at both the transcriptional and post-transcriptional level and is, at least in part, tissue-specific [46, 47]. While androgen regulation of rodent renal Oatp expression has been demonstrated in male and female rodents, androgen regulation of SLC0 genes in prostate tissue has not been explored [48, 49].

In summary, clear differences in SLC0 transcript expression are present in primary PCa compared to NP in Gleason 4 vs Gleason 3 tumors, and in ADT-treated vs untreated tumors. These findings are hypothesis generating due to small sample size, but suggest that baseline and ADT-induced changes in PCa OATP expression may influence steroid uptake and response to ADT, as well as uptake and response to critical PCa drugs such as ABI and docetaxel, which are subject to OATP-mediated transport and are now being routinely combined with ADT in the metastatic castration sensitive setting. Future work may identify how targeting the induction, repression or inhibition of these transporters might be exploited for the therapeutic benefit [50, 51]. Supplementary information is available at PCAN’s website.

Acknowledgements The authors wish to acknowledge technical assistance from Jennifer Noteboom and Lori Kollath who assisted with provision of clinical outcome data, as well as Drs. Daniel Lin, William Ellis, and Jonathan Wright for supporting collection of excess frozen prostate tissue at time of radical prostatectomy.

Funding This work was supported by NIH grants (Pacific Northwest Prostate Cancer SPORE P50 CA097186 to LT, PSN, RBM, EAM; FHCRC Cancer Center Support Grant 5P30 CA015704-40 (PSN, EAM); DF/HCC SPORE P50 CA090381 to AGS, HY, MET, and SPB; PO1 CA163227 to EAM, PSN, SPB); Prostate Cancer Foundation (Challenge Awards to EAM, PSN, MET, SPB; Young Investigator Awards to AGS, HE, EAM); Department of Defense Prostate Cancer Research Program (W81XWH-11-2-0154 to EAM; W81XWH-13-1-0267 and W81XWH-16-1-0433 to AGS; W81XWH-16-1-0431 to SPB and W81XWH-16-1-0432 to MET), the Intramural Research Program of the NIH, National Cancer Institute (AGS), and the Department of Veterans Affairs Puget Sound Health Care System (EAM).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 2008;68:4447–54.
2. Page ST, Lin DW, Mostaghel EA, Hess DL, True LD, Amory JK, et al. Persistent intraprostatic androgen concentrations after medical castration in healthy men. J Clin Endocrinol Metab. 2006;91:3850–6.
3. Mostaghel EA, Page ST, Lin DW, Fazli L, Coleman IM, True LD, et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res. 2007;67:5033–41.
4. Hagenbuch B, Meier PJ. Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties. Pflug Arch. 2004;447:653–65.
5. Kallikokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol. 2009;158:693–705.
6. Roth M, Obaidat A, Hagenbuch B, OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol. 2012;165:1260–87.
7. Arakawa H, Nakanishi T, Yanagihara C, Nishimoto T, Wakayama T, Mizokami A, et al. Enhanced expression of organic anion transporting polypeptides (OATPs) in androgen receptor-positive prostate cancer cells: possible role of OATP1A2 in adaptive cell growth under androgen-depleted conditions. Biochem Pharmacol. 2012;84:1070–7.
8. Hamada A, Sissung T, Price DK, Danesi R, Chau CH, Sharifi N, et al. Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in caucasian patients with androgen-independent prostate cancer. Clin Cancer Res. 2008;14:3312–8.
9. Wang X, Harshman LC, Xie W, Nakabayashi M, Qu F, Pomerantz MM, et al. Association of SLCO2B1 genotypes with time to progression and overall survival in patients receiving androgen-deprivation therapy for prostate cancer. J Clin Oncol. 2016;34:352–9.
10. Green SM, Kaipainen A, Bullock K, Zhang A, Lucas JM, Matson C, et al. Role of OATP transporters in steroid uptake by prostate cancer cells in vivo. Prostate Cancer Prostatic Dis. 2017;20:20–7.
Association of prostate cancer SLCO gene expression with Gleason grade and alterations following...
47. Murray M, Zhou F. Trafficking and other regulatory mechanisms for organic anion transporting polypeptides and organic anion transporters that modulate cellular drug and xenobiotic influx and that are dysregulated in disease. Br J Pharmacol. 2017;174:1908–24.

48. Lu R, Kanai N, Bao Y, Wolkoff AW, Schuster VL. Regulation of renal oatp mRNA expression by testosterone. Am J Physiol. 1996;270(2 Pt 2):F332–7.

49. Aleksunes LM, Klaassen CD. Coordinated regulation of hepatic phase I and II drug-metabolizing genes and transporters using AhR-, CAR-, PXR-, PPARalpha-, and Nrf2-null mice. Drug Metab Dispos: Biol fate Chem. 2012;40:1366–79.

50. Thakkar N, Lockhart AC, Lee W. Role of Organic Anion-Transporting Polypeptides (OATPs) in Cancer Therapy. AAPS J. 2015;17:535–45.

51. Nyquist MD, Prasad B, Mostaghel EA. Harnessing solute carrier transporters for precision oncology. Molecules. 2017;22. pii: E539.