Perspective

Perspective on the regulatory role of UGT2B28 as a conjugating enzyme in the progression of prostate cancer

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Abstract: The maintenance of steroid homeostasis in the prostate is critical, with perturbation of steroidogenesis contributing to the modulation of active ligands in the androgen pool. In this scenario, enzymes catalysing the biosynthesis, inactivation and conjugation of steroids are the key players, regulating active ligand levels and in so doing, the activation of the androgen receptor (AR). The glucuronidation of potent ligands renders them unable to bind the AR, allowing the secretion of conjugated steroids. Uridine diphosphate glucuronosyltransferase 2B type 28 (UGT2B28), one of the UGT enzymes catalyzing the glucuronidation of androgens, has recently been given a prominent role in the regulation of prostate steroidogenesis—one which stands in contrast to the accepted dogma that lower androgen levels resulting from increased conjugation are associated with decreased prostate cancer (PCa) risk and disease progression. Increased DHT and its precursors, T and androstenediol, were reported to be associated with increased UGT2B28 tumor expression levels, linked to lower PSA levels but higher Gleason scores and increased PCa risk. In addition, the complete deletion of UGT2B28, was associated with decreased T, DHT and glucuronide derivatives when compared to patients carrying both alleles. UGT2B28 is encoded by a single gene giving rise to UGT2B28 type I which catalyses androgen glucuronidation and, due to alternative splicing, also produces two distinct transcripts, UGT2B28 type II and III. Type II with its premature stop codon, is devoid of the cofactor binding domain while type III is devoid of the substrate binding domain, both catalytically inactive, truncated proteins. Increased UGT2B28 mRNA expression was reported in primary tumours, and while variable nuclear and strong cytoplasmic staining were distinctive of tumour cells, the expression levels and compartmentalization of the specific protein isoforms remain unknown. While increased expression of type I would contribute towards lowering androgen levels, increased expression of types II and III would not. The abundance of type III transcripts in multiple tissues may provide insight into a regulatory role with truncated isoforms possibly affecting androgen levels by regulating substrate and/or co-factor availability, dimerization or the formation of protein complexes with other UGTs, while protein-protein interaction may also impact cascade signaling pathways in PCa development and disease progression.

Keywords: 11keto-testosterone; copy-number variation; dihydrotestosterone; prostate cancer prognosis; UDP-glucuronosyltransferase

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In their article "The UGT2B28 sex-steroid inactivation pathway is a regulator of steroidogenesis and modifies the risk of prostate cancer progression" published in *Eur Urol* in April 2016, Belledant *et al*. report a regulatory role to the enzyme uridine diphosphate glucuronosyltransferase 2B type 28 (UGT2B28), modulating prostate cancer (PCa) progression. This role is separate from that of UGT2B28's function as a conjugative inactivating enzyme, with UGT2B28 influencing circulating androgen levels in PCa patients as well as clinical and pathologic factors associated with the disease (1).

Placing the work in context, we will discuss the contribution of steroidogenic enzymes towards the production and maintenance of active androgens which interact with the androgen receptor (AR) and the crucial role that these enzymes play—not only in normal prostate homeostasis but also in PCa. We will also briefly discuss genetic variability within UGT2B enzymes, focusing on B28, after which we will review the concepts highlighted by Belledant *et al*. and provide a perspective on the role of this conjugating enzyme in PCa.

Active androgen levels are maintained by both metabolic and catabolic enzymes with 5α-reductase type 1 (SRD5A1) and type 2 (SRD5A2) catalyzing the biosynthesis of dihydrotestosterone (DHT) from testosterone (T) or alternatively from androstenedione (A4) and the 5α-androstane-3,17-dione (5αDIONE) intermediate. The interconversion of A4 and T and their 5α-reduced metabolites by the reductive or oxidative 17β-hydroxysteroid dehydrogenase (17βHSD) enzymes further adds to the complexity of steroidogenesis in the prostate. The equilibrium is however perturbed in PCa and tumour development is associated with the modulation of enzyme expression. Increased expression of the reductive enzyme 17βHSD3 (31-fold) has been reported in the prostate tumour microenvironment (2) as well as increases in 17βHSD5 (AKR1C3) expression ranging 2–5-fold, favouring T biosynthesis. In conjunction with the increased expression of the reductive enzymes, a 7-fold decrease in the expression of the oxidative enzyme 17βHSD2 which catalyzes the reverse conversion of T to A4, has been reported which again diverts the flux towards T production. In addition, while SRD5A2, which is expressed in normal prostate tissue, is decreased (2–4-fold), the expression of SRD5A1 has been shown to be increased (2-fold) in castration-resistant prostate tumours thus maintaining DHT levels in the prostate [(3) and the references therein)].

Contributing to the active androgen levels in the prostate microenvironment are the inactivating and conjugating enzymes. Only androgens with a hydroxyl group at C17 or C3 are potential substrates for conjugation by UGTs and as such both T and DHT can be converted to their glucuronide derivatives, rendering them inactive to be secreted into circulation. DHT together with 5αDIONE are, however, also inactivated by 3α-hydroxysteroid dehydrogenase type 3 (AKR1C2), which catalyzes the reduction of the keto group at C3, forming 5α-androstane-3α,17β-diol (3αDIOL) and androsterone (AST), respectively, allowing the subsequent addition of the glucuronide moiety at C3. While AKR1C2 also exhibits oxidative activity, this reverse reaction is primarily catalyzed by 17βHSD6, 17βHSD10 and retinol dehydrogenase 5 expressed in the prostate (4-7). In primary PCa, AKR1C2 expression levels have been reported to be significantly decreased compared to benign tissues (7-9), which contributes to significantly higher DHT levels in primary PCa tumours (10). In malignant epithelial cells, increased expression (3-fold) of 17βHSD10, which mediates the conversion of 3αDIOL to DHT, increased DHT tumour production (11). Furthermore, androgen deprivation therapy led to a 2-fold increase in 17βHSD6 expression levels, also associated with the biochemical progression of PCa (11). It is therefore apparent that the intricate homeostasis in the prostate is modulated by the perturbed expression of the steroidogenic enzymes catalyzing DHT production and those catalyzing the inactivation of androgens.

The expression of the UGT2B enzymes are tissue and substrate specific. UGT2B7, B15 and B17 are the three major UGT2Bs primarily responsible for androgen conjugation in humans and of these only B15 and B17 are actively expressed in the prostate (12). The UGT2B enzymes conjugate androgens in a regiospecific manner, either catalyzing the addition of the glucuronide moiety at C17 and/or at C3. UGT2B7 conjugates 3αDIOL and AST at C3 and T, DHT and 3αDIOL at C17; UGT2B15 only at C17 of T and 5α-reduced androgens, DHT and 3αDIOL; UGT2B17 at C3 and C17 of T, DHT, 3αDIOL and AST and UGT2B28 conjugates 3αDIOL at both C3 and C17 (low efficiency), as well as AST and T. Although UGT2B28 conjugates 3αDIOL, its capacity to conjugate 3αDIOL is much lower than that of B15 and B17 (12,13). In addition, UGT2B28 also conjugates estradiol (E2), etiocholanolone and 5β-androstane-3α,17β-diol. The latter is the product of androstenediol (5-diol) catalyzed by AKR1C2 and SRD5A (13,14). Interestingly, 5-diol was shown by Belledant *et al*. to be increased and associated with increased UGT2B28 levels in prostate tumour tissue.

In contrast to the steroidogenic enzymes catalyzing biosynthesis pathways, the genes encoding the UGT enzymes are characterized by substantial genetic variability brought about by polymorphisms, the production of alternative transcripts through alternative splicing/last exon/internal exon use and exon skipping, together with copy number variation (CNV) and alternative promoters. These factors all contribute to the complexity of the role of the UGT enzymes in steroid inactivation, impacting protein expression levels and enzymatic activities which in turn impact circulating androgen levels and PCa outcomes (15).

While comparative studies relating to circulating hormone levels are complicated by interindividual variations, biochemical studies inevitably yield tangible data regarding enzyme kinetics as, for example, in the case of the Asp85Tyr polymorphism of UGT2B15. This functional polymorphism encodes a protein with the Asp85Tyr mutation and has been shown to be expressed either homozygously for one or the other as well as heterozygously in patients with both alleles. Similar Km values for DHT and 3αDIOL are reported but the enzyme containing Tyr residue catalyzes the inactivation more efficiently with a 2-fold higher Vmax value (16,17). UGT2B15, B17 and B28 are encoded by a single gene (15), with polymorphisms in the former two genes having been shown to significantly impact circulating levels of free unconjugated T and AST (18-20), and the intra-prostatic levels of 3αDIOL-3G and 3αDIOL-17G (21). Whole gene deletions were reported for UGT2B28 in this paper and previously by Nadeau *et al*. (18), in which they also showed that in UGT2B17 (–/–) PCa patients circulating 3αDIOL-17G levels were significantly reduced. Although T and DHT levels were not significantly lower, AST levels were increased, indicative of increased flux in these metabolic pathways and if unconjugated, would allow the reactivation of AST and a concomitant increase in AR signaling. This study also showed that in UGT2B28 (+/–) patients, circulating androgen levels were not affected. However, patients with a single copy in conjunction with the UGT2B17 (–/–) deletion not only had significantly increased AST levels but also significantly decreased AST-G and 3αDIOL-17G levels (15,18).

Investigations into complete UGT2B28 deficiency by Belledant *et al*. (1) reported significantly decreased circulating T, DHT AST-G, and 3αDIOL (both C3 and C17 derivatives) in patients when compared to UGT2B28 (+/+) patients. In addition, their study also reported that high tumour expression levels of UGT2B28 were associated with lower protein specific antigen (PSA), smaller tumour volume, but with higher Gleason score and positive nodal status. Patients with increased nuclear and cytosolic UGT2B28 expression in tumours together with significantly increased circulating T and DHT levels suggested an association with progression to a more aggressive disease.

It should be noted that three UGT2B28 isoforms are expressed in humans—type I, II and III characterized in 2001 by Lévesque *et al*. (13). RT-PCR data identified the three transcripts in mammary gland tissue and in LNCaP prostate cancer cells with only type III expressed in prostate and benign prostatic hyperplasia tissue. The active UGT2B28 type I was shown to catalyze the conjugation of E2, T, AST and 3αDIOL efficiently. UGT2B28 type II contained a 308 bp deletion, amino acid residues 335 to 437 in the cofactor binding domain and contained a premature stop codon, and UGT2B28 type III lacked residues 105 to 221 in the putative substrate binding domain. Both truncated isoforms yielded a non-functional protein. Western blot analyses, using the polyclonal EL-93 anti-UGT2B17 antiserum, specific to the UGT2B enzymes, showed the three isoforms to have apparent molecular masses of 52, 35 and 42 kDa, respectively. While UGT2B protein was also shown to be present in liver preparations together with RT-PCR identifying UGT2B28 type II and III transcripts (13), the present study by Belledant *et al*. showed the polyclonal EL-93 antibody yielding a positive signal for all the UGT2B proteins. In contrast, the UGT2B28 antibody was shown to specifically bind UGT2B28 protein only and since it was raised against a peptide sequence spanning residues 113–124 the antibody only recognizes the type I and type II isoforms. Since only type III mRNA transcripts were shown in normal prostate (a single prostate tissue sample purchased from Clontech) (13), it is therefore interesting that immunohistochemistry (IHC) analyses showed the presence of UGT2B28 in normal prostate tissue, in the nucleus of basal and some secretory cells, pointing to the presence of both the type I and II isoforms. Cancer tumour cells from UGT2B28 (+/+), on the other hand, showed strong nuclear and cytoplasmic staining (1) and while it is very possible that type III is also present, the data cannot distinguish between type I and II. Interestingly comparative analyses of UGT2B28 expression and gene copy number showed, in both the nuclei and cytoplasm, that expression levels were similar between +/+ and +/– patients. Strong nuclear staining was associated with significantly lower PSA levels and patients presented with smaller tumours, while strong cytoplasmic staining was associated with higher Gleason scores and positive nodal status. Considering circulating androgens, significantly

increased T and DHT levels were also associated with increased nuclear UGT2B28 expression. Although these androgens also increased with increased cytosolic expression, their levels were not significant. 5-diol, the product of dehydroepiandrosterone catalyzed by AKR1C3/17βHSD3, also increased with increased nuclear (P=0.079) and cytoplasmic (P=0.026) expression of UGT2B28 (1), and would as such contribute towards T levels due to the presence of 3β-hydroxysteroid dehydrogenase type 2 catalyzing the conversion of 5-diol to T.

Analyses of circulating androgens in UGT2B28 (–/–) PCa patients showed significantly reduced T, DHT as well as downstream conjugated metabolites, AST-G and 3αDIOL-3G and 3αDIOL-17G levels in comparison to UGT2B28 (+/+) patients. Circulating A4 was significantly increased in the UGT2B28 (–/–) cohort (1) which would contribute to the production of DHT via the 5αDIONE pathway in prostate steroidogenesis (22). Although all downstream intermediate steroid metabolites were not reported in this study, analyses of the ratio of A4, T and DHT to their conjugated metabolites, 8.59 [UGT2B28 (+/+)] and 8.97 [UGT2B28 (–/–)] offers some perspective into the metabolic flux. However, these steroids cannot be regarded in isolation as we have also shown the hydroxylation of A4 by cytochrome P450 11β-hydroxylase leads to the production of 11β-hydroxyandrostenedione (11OHA4) in the adrenal, which would also be increased in UGT2B28 (–/–) patients with higher A4 levels, and would certainly contribute to the androgen pool via the 11OHA4-derived pathway (23,24).

The data presented is certainly open to interpretation and the manner in which the enzyme isoforms would impact PCa complex. Inactive androgens in circulation are also products of other UGT enzymes. When considering increased circulating T, DHT and 5-diol being associated with increased tumour expression of UGT2B28, it is prudent to note that androgens in the prostate and in circulation would be conjugated by UGT enzymes expressed either in the prostate itself or in other target tissue and therefore circulating levels cannot be regarded in isolation. In addition, the expression levels of UGT2B28 isoforms in the prostate and prostate tumours are unclear, since the expression can be that of type I or type II. It is furthermore possible that type III is also present. In the translation of UGT2B28 transcripts encoding type II, the deletion of exon 4 and 5 excises the UDPGA binding site and disrupts the open reading frame with the ensuing premature stop codon yielding a protein fold different to that of type I. Despite not having a transmembrane domain, the truncated type II was reported to nevertheless be present in the endoplasmic reticulum and in the perinuclear membrane as in the case of type I. Type III on the other hand contains all the relevant structural domains but not the substrate binding domain. Although the data was not shown Lévesque *et al*. also reported that type III was capable of homodimerization (13). It is interesting to note that in their study in which the three isoforms were expressed in HEK293 cells, Western blotting showed type I and III to be represented by single bands while only type II showed additional bands of greater apparent masses indicting possible protein aggregation, either type II with itself or with the other two isoforms. Although one would normally not expect protein aggregation under denaturing electrophoretic conditions, it is fairly common that proteins form stable aggregates as for example in the case of cytochrome b_5, which electrophoreses as dimer and tetramer aggregates even under stringent denaturing conditions (25). Besides the IHC data not distinguishing between type I and II, it is unclear if isoform expression would be compartmentalized as in the case of UGT2B15 and 17 with the former being expressed in the luminal cells and the latter in the basal cells (26), further contributing towards the fine regulation brought about by compartmentalized conjugation and ligand availability to the AR. An interesting aspect brought to the fore by the Belledant *et al*. study is indeed a novel tier of regulation other than that of the inactivation of androgens. Increased T and DHT levels associated with increased UGT2B28 protein expression and more aggressive PCa could perhaps also be indicative of decreased UGT2B15 and B17 expression since androgens have been shown to negatively regulate their conjugation by these enzymes (27).

While an increase in the active isoform may contribute towards high levels of circulating conjugated androgens, the expression of the inactive forms would not contribute towards conjugated androgen levels. Linking UGT2B28 (+/+) to an increase in biochemical recurrence (BCR) and overexpression to increased PCa risk and potent androgens, would possibly implicate the expression of the inactive isoforms and an impaired ability to conjugate androgens. On the other hand, the isoforms may aggregate as has been shown for the UGT1 and UGT2 enzymes (28,29)—not only forming dimer-dimer complexes but also aggregates with other UGT2B enzymes thus rendering them unable to catalyze the conjugation of androgens.

Whether UGT2B28 is the active androgen-inactivating

UGT isoform under high-androgen exposure as the authors suggested is unclear as the expression of UGT2B28 in the prostate remains to be fully characterized. While type I would certainly contribute towards androgen inactivation in the prostate, the expression of the isoform types in normal and PCa tissue and the expression level of the three isoforms as well as possible compartmentalization remain unknown. Since data thus far indicate tissue-specific processing of mRNA transcripts, investigations into the regulation of post-transcriptional activities in the expression of UGT enzymes will shed light on the role of the UGT2B28 isoforms. It is possible that type III may be involved in regulating co-factor availability while type II may sequester androgens, rendering them unavailable for AR activation, depending on the level of expression. In addition, the role of UGT2B28 type I in the inactivation of estrogens rendering these steroids incapable of activating the estrogen receptor, AR or mutated AR may be one of critical importance. Furthermore, UGT2B28 has been considered only in terms of T and DHT—C_{18}, C_{21} and C11-oxy steroids would certainly also impact PCa and possibly find associations with BCR. Previously published data suggests a regulatory role for UGT2B28 in terms of estrogen conjugation as AST and E2 were efficiently conjugated while more than 50% estrone (E1) remained in the free form in breast cyst fluid (13). Lévesque *et al.* (13) showed the presence of all three isoforms of UGT2B28 in mammary gland tissue, however, when transiently expressed, E1 was not conjugated by UGT2B28 type I—suggesting that other UGT2B enzymes are involved in the conjugation of E1. However, since the conjugation of E2 has been shown, a role for UGT2B28 in breast cancer is highlighted. Furthermore, with perturbed UGT2B28 expression and E2 conjugation decreased, promiscuous binding of E2 to the mutated AR in PCa may also occur (30). Interestingly while the three UGT2B28 transcripts were detected in breast tissue none were detected in the ovary or placenta and thus the presence of UGT2B28 type III in the testis, prostate and BPH tissue (13) suggests a prominent role for UGT2B28 in male steroid homeostasis. It was previously reported that the C11-oxy C_{19} steroids were poor substrates for conjugation and that UGT2B17 exhibits lower catalytic activity towards C_{19} steroids containing a C11-hydroxyl group, even though it has been shown that 5α-androstane-3α,11α/β-17β triol and T are conjugated at similar rates (15,31). We recently reported that 11OHA4 is metabolized to 11keto-dihydrotestosterone in PCa cells and have shown that it is as potent as DHT in activating the AR (32). We have since shown that 11keto-testosterone is not glucuronidated efficiently in LNCaP cells and as such would readily activate the AR as T and DHT are fully conjugated. Furthermore, we reported that the C11-oxy C_{19} steroids are present at significantly higher levels than the C_{19} steroids in circulation, in PCa tissue (33) and in BPH tissue (unpublished data), drawing attention to C11-oxy metabolites in PCa.

In summary, the contribution of UGT2B enzymes to active ligand availability can only be fully assessed in the context of all steroids which may contribute to PCa and its aggressive progression. This will certainly lead to a better understanding of the complex regulation by these inactivating enzymes, modulating receptor signaling, not only in terms of C_{19} steroids but also in terms of the C_{18} and C_{21} steroids as well as the C11-oxy steroids. As has been demonstrated by this study, genetic variations together with tissue-specific mRNA processing and the biosynthesis of different isoforms, as well as CNVs, contribute to the complexities of the UGT enzymes and their impact on PCa development and disease progression. Both UGT2B15 and B17 have also been reported to conjugate pharmacological compounds while the contribution of UGT2B28 to drug inactivation remains unknown. UGT2B17 and B28 are also among the UGT genes of the human genome which are the most commonly deleted genes and as such may impact drug metabolism and therapeutic strategies. While the usage of an alternative promoter may modulate the expression and/or activity of UGTs, it may also contribute to variability in the glucuronidation pathway and steroid hormone levels observed in patients. In the case of UGT2B17, gene deletions and CNVs have been shown to affect steroid inactivation, altering tissue and circulating androgen levels, supporting the general hypothesis of reduced inactivation by UGT enzymes resulting in increased active ligands, risk of PCa and its recurrence (34). The current report by Belledant *et al.* (1) showing increased UGT2B28 expression linked with increased T, DHT and 5-diol and a more aggressive disease, together with CNV associating gene deletion with decreased active AR ligands and conjugated downstream derivatives, points to other mechanisms at play involving pathways other than steroid inactivation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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