Review Articles on Urothelial Carcinoma

The prognostic role of steroid hormone receptor signaling pathways in urothelial carcinoma

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Abstract: Emerging preclinical or clinical evidence suggests a vital role of nuclear receptor-mediated signals in modulating urothelial carcinogenesis and cancer growth. These include, but are not limited to, androgen receptor, estrogen receptors, glucocorticoid receptor, progesterone receptor, vitamin D receptor, retinoid receptors, and peroxisome proliferator-activated receptors, as well as orphan receptors. In particular, immunohistochemical studies in surgical specimens have demonstrated that increased or decreased expression of steroid hormone receptors, as well as alterations of their upstream or downstream signaling pathways, is often associated with oncologic outcomes in patients with bladder or upper urinary tract cancer. This review article summarizes and discusses available data indicating that steroid hormone receptors and related signals serve as biomarkers for urothelial tumors which further predict their recurrence and/or progression.

Keywords: Androgen; estrogen; glucocorticoid; progesterone

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Introduction

Urinary bladder cancer, which is mostly a urothelial carcinoma, is one of the most commonly diagnosed neoplasms, with nearly 550,000 new cases and 200,000 deaths estimated in 2018 throughout the world (1). In addition to the bladder (and the urethra), urothelial carcinoma occurs in the upper urinary tract (UUT) composed of the pyelocaliceal system and the ureter. Although urine cytology remains the most accurate non-invasive test for detecting urothelial carcinoma, no screening test has been recommended for its early detection. Meanwhile, no biomarkers that provide precise prognostic information are available. Strikingly, the prognosis in patients with urothelial carcinoma has not significantly improved after decades of therapeutic advances. Specifically, the Surveillance, Epidemiology, and End Results (SEER) database showed that the 5-year relative survival rates for those diagnosed with bladder cancer in 1975–1977 and 2009–2015 were 72.3% and 78.3%, respectively (2).

A variety of molecules, including transcription factors, as well as their upstream and downstream pathways, have been implicated in urothelial cancer outgrowth. In particular, current evidence indicates the involvement of the nuclear receptor superfamily-mediated signals in the development and progression of urothelial cancer. These receptors include, but are not limited to, androgen receptor (AR), estrogen receptor-α (ERα), ERβ, glucocorticoid receptor (GR), progesterone receptor (PR), vitamin D receptor (VDR), retinoid receptors [e.g., retinoic acid receptor

(RAR), retinoid X receptor (RXR)], and peroxisome proliferator-activated receptors (e.g., PPARγ), as well as orphan receptors. These observations have thus provided novel therapeutic targets for urothelial carcinoma. Of note, recent studies have addressed the role of nuclear receptor signals and related pathways, as diagnostic and/or prognostic biomarkers, in urothelial tumors. In this article, we review the results mainly from immunohistochemical studies in surgical specimens demonstrating the relationship between alterations of steroid hormone receptors, including sex hormone receptors (3-27) and GR (15,28), as well as other members of nuclear receptors, in urothelial tumors and long-term oncologic outcomes (online: http://cdn.amegroups.cn/static/application/4519bb9f737b56688eb5bc85f1d6fd3c/tcr.2020.01.06-1.pdf). We additionally highlight several molecules whose expression is modulated via the AR and/or ER pathways in urothelial cells.

AR

Preclinical findings have suggested that androgen-mediated AR activation is associated with the promotion of urothelial tumorigenesis [reviewed in (29)], which may clearly explain the male dominance in the incidence of bladder cancer. Accordingly, as documented in retrospective studies (30-33), androgen deprivation therapy, which has primarily been used in the treatment of advanced prostate cancer, is anticipated to prevent the recurrence of non-muscle-invasive (NMI) bladder tumors following transurethral surgery, or otherwise, the tumor development in high-risk populations. The authors' group has also demonstrated *in vitro* and *in vivo* data indicating that AR activation correlates with urothelial cancer progression which is a pathological event/process distinct from carcinogenesis or cancer initiation [reviewed in (29); more recent findings in (34,35)].

Immunohistochemistry in surgical specimens has shown that the positive rates of AR expression in bladder or UUT urothelial tumors range from 11% to 55% (3-17, 19,20). In most of the comparative studies (3-5,9,15), AR positivity in urothelial tumors was significantly lower than that in control/normal urothelial tissues. However, three of the studies demonstrated no AR expression in non-neoplastic urothelium (8,12,17). Similarly, some of the studies demonstrated down-regulation of AR expression in high-grade or muscle-invasive (MI) tumors, compared with low-grade or NMI tumors, respectively (3-5,7-10,14). Interestingly, all of the studies, except for one (19), have shown no significant differences in AR expression between urothelial tumors from male versus female patients.

The prognostic impact of immunoreactivity for AR in urothelial tumors remains controversial. In spite of the promoting properties of AR signals in urothelial tumorigenesis, three studies demonstrated a significant association (13,20) or a tendency (8) between AR expression and a lower risk for the recurrence of bladder tumor after surgery. In addition, a meta-analysis of 3 immunohistochemical studies involving 496 patients revealed a significantly lower risk of disease recurrence in those with AR-positive NMI bladder tumor, compared with AR-negative tumors [hazard ration (HR) =0.593; P=0.006] (36). By contrast, AR expression was strongly (12) or marginally (9) associated with the tumor progression in two studies, while others failed to reveal its prognostic significance in patients with bladder cancer. None of the immunohistochemical studies in patients with UUT tumor have shown significant associations of AR expression with their prognosis. Additionally, in relatively small cohorts of patients with bladder cancer, AR expression has been shown to be associated with resistance to neoadjuvant chemotherapy (37) or intravesical BCG immunotherapy (38).

The prognostic value of *AR* gene expression in bladder cancer has also been investigated in two studies using a quantitative polymerase chain reaction (PCR) method. In MI bladder cancers from patients undergoing radical cystectomy, high *AR* expression was significantly associated with worse recurrence-free survival (P=0.005) or disease-specific survival (P=0.001) (39). In the other study, *AR* expression was significantly elevated in NMI tumors, compared with MI tumors (P=0.0004), and was found to be an independent prognosticator for disease-free survival [likelihood ratio (LR) Chi^2=7.23; P=0.007] or overall survival (LR Chi^2=4.32; P=0.04) in female patients (40).

ERs

It has been documented that estrogens both induce and inhibit urothelial cancer outgrowth, and their effects appear to be cell-specific and otherwise dependent on the functional activity of ERα and ERβ as well as G protein-coupled estrogen receptor 1 (GPER)/G protein-coupled receptor 30 (GPR30) (41-49). For instance, bladder cancer was significantly more frequently detected in *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine-treated female ERα knockout mice, compared with female wild-type littermates, implying the preventive role of ERα in tumor development (48). However, estrogens were shown to promote the cell

proliferation of a urothelial cancer line predominantly via the ERα pathway as well as that of primary urothelium line predominantly via the ERβ pathway (44), while selective ER modulators, such as tamoxifen and raloxifene, suppressed the cell growth of bladder cancer lines expressing the ERβ (41,43).

ERα protein has been immunohistochemically detected only in a small subset (e.g., 1–5%) of bladder cancer samples (12,21-23). Nonetheless, a PCR-based study demonstrated that *ER*α gene was positive in all of the 10 bladder tumors examined, which was even greater (2.77-fold) than in corresponding normal tissues (44). Our immunohistochemical analyses also demonstrated relatively high rates of ERα positivity in bladder [i.e., 27% (9) or 31% (of NMI tumors) (32)] and UUT [i.e., 18% (15)] tumors. Unlike the PCR data described above (44), the levels of ERα protein expression in non-neoplastic urothelial tissues were elevated, compared with those in urothelial cancer (9,15,22,32). At least two of these immunohistochemical studies also revealed that ERα expression was down-regulated in higher grade or more invasive tumors (9,22). However, no studies have indicated the prognostic value of ERα expression in patients with urothelial cancer. Instead, the status of *ER*α expression in radical cystectomy specimens could further stratify those with low *AR* tumor into subgroups with significantly poorer outcomes (39).

In some of studies (8-10,15,21,24,25,32), 22–76% of urothelial tumors were found to be immunoreactive for ERβ, which was significantly lower than the positive rates in non-neoplastic urothelial tissues. More recently, ERβ was shown to be immunohistochemically positive in all of the 410 bladder tumors examined (23). In addition, ERβ expression was significantly up-regulated (9,13,21,24) or down-regulated (25) in higher grade/stage tumors. Elevated ERβ expression in bladder tumors was also associated with higher risks for disease recurrence and/or progression (8,9,26). In one of the studies (8), ERβ positivity was reported to be an independent predictor (HR=11.663; P=0.025) for the progression of non-invasive bladder tumors (8). The meta-analysis of 3 immunohistochemical studies further revealed associations between ERβ positivity in NMI bladder tumors and a lower recurrence-free (HR=1.573; P=0.013) or progression-free (HR=2.236; P=0.089) survival rate (36). Conversely, a strong association between ERβ overexpression and favorable prognosis was demonstrated in at least three studies (13,23,27).

GR

It remains controversial whether glucocorticoids induce versus inhibit urothelial tumorigenesis. A case-control study demonstrated that prolonged use of glucocorticoids was associated with an elevated incidence of bladder cancer (50), presumably via immunosuppression. By contrast, our recent study has revealed that a synthetic glucocorticoid prednisone prevents the malignant transformation of GR-positive urothelial cells, but not that of GR-negative cells (51). Prednisone and other natural or synthetic glucocorticoids, such as corticosterone and dexamethasone, have also shown to strongly inhibit bladder cancer cell invasion and metastasis via, for instance, inactivating NF-κB (52-54). However, treatment with dexamethasone (and most of other glucocorticoids examined) in bladder cancer lines resulted in increases in cell viability and decreases in apoptosis particularly that induced by a widely used chemotherapeutic medication, cisplatin. Apart from glucocorticoid-induced immunosuppression, glucocorticoid-mediated GR signals appear to have dual roles (i.e., inhibition of tumor development and progression versus promotion of cell proliferation) in urothelial cancer. Further studies have indicated that the action of glucocorticoids may be dependent on a balance between transactivation and transrepression of GR (51,54,55) that involve their therapeutic effects and associated adverse effects, respectively. In particular, transrepression appears to correlate with the function of GR as a tumor suppressor.

Our immunohistochemical analyses in bladder (28) and UUT (15) tumors have demonstrated that GR is expressed in most of non-neoplastic urothelial tissues, which is down-regulated in urothelial neoplasms. The levels of GR expression were also significantly lower in high-grade or MI bladder tumors than in low-grade or NMI tumors (28). However, there were no significant differences in GR positivity between low-grade versus high-grade or NMI versus MI UUT tumors (15). In addition, loss of GR expression was associated with the recurrence of NMI bladder tumors and the progression of MI bladder tumors (28). Multivariate analysis further identified low GR expression as a predictor for the recurrence of NMI tumors (HR=2.252; P=0.034) and the progression of MI tumors (HR=3.690; P=0.077) (28). The levels of GR expression in UUT tumors were not strongly associated with patient

outcomes in our study (15).

PR

A case-control study demonstrated a significantly lowered risk of developing bladder cancer in multiparous women or those using oral contraceptives (56). Using a transgenic model for bladder cancer, multiparous female mice were also found to develop significantly smaller tumors than nulliparous females (57). These findings suggested that not only estrogens but also progestogens could prevent urothelial tumorigenesis.

Using hormone-binding assay, PR was shown to be positive in 1 of 3 non-invasive and 3 of 3 advanced urothelial tumors (58). An immunohistochemical study then detected immunoreactivity for PR in 18 of 20 bladder tissues from boys aged 1–12 years (59). However, subsequent larger immunohistochemical studies failed to detect PR signals in 198 (22) and 410 (23) cases of bladder cancer. Another study, using 120 cases of surgical specimens, showed PR expression in 2% of non-neoplastic bladders and 4% of bladder cancer tissues (12). More recently, we demonstrated that PR was positive in 13% of control urothelial tissues from the UUT and 16 (16%) of 99 UUT tumors (15). Although the levels of PR expression were not significantly altered in low-grade versus high-grade or NMI versus MI UUT tumors in our study, PR positivity in pT3-4 tumors was associated with a significantly higher risk of disease-specific mortality. Moreover, patients with ERα-positive and/or PR-positive pT3-4 UUT tumor had a significantly higher risk of disease-specific mortality, and positivity of either ERα or PR, or both was an independent prognosticator (HR=2.434; P=0.037) in this subgroup of patients. In support of our data (15), the status of *ER*α and *PR* expression in MI bladder cancers was shown to help stratifying a subgroup of patients into those with significantly poorer outcomes (39).

Other members of nuclear receptors

The mRNA or protein expression of other nuclear receptors, including VDR, RARα, RARβ2, RARγ, RXRα, and PPARγ, as well as a few orphan receptors, has been investigated in urothelial cancer specimens.

Although controversial data exist (60), low serum levels of vitamin D (61), as well as *VDR* gene polymorphisms (62) associated with reduced receptor activity, have been implicated in the risk of developing bladder cancer. Using preclinical models, vitamin D was also shown to prevent the development of chemical carcinogen-induced bladder tumors and suppress the cell growth of VDR-positive bladder cancer lines (63). Thus, VDR signaling appears to function as a tumor suppressor for urothelial cancer. Immunohistochemical studies in surgical specimens demonstrated that VDR was positive in 86–100% of bladder tumors (64-66), which was significantly higher (65) *vs.* lower (66) than the VDR-positive rate in normal urothelial cells. In addition, the levels of VDR expression were higher in high-grade or MI tumors (64) *vs.* the lowest in more advanced (pT2b-4) or metastatic cases (66). The outcome analysis also showed strong associations between elevation (65) *vs.* loss (66) of VDR expression and poorer prognosis.

A meta-analysis of 25 studies assessing the preventive effects of retinoic acids on bladder cancer development demonstrated an inverse association of dietary intake of vitamin A/retinol with its risk (67). In preclinical models, retinoids have been shown to inhibit the development of carcinogen-induced bladder cancer in animals (68) and the proliferation of bladder cancer cells (69). A study using a PCR-based method showed that all of the normal bladders or NMI bladder tumors examined expressed the retinoid receptors, while some of MI bladder tumors lost RARα (60%), RARγ (20%), and RXRα (40%) (70). In addition, RARβ2 was found to be positive in 100% of normal bladder specimens, 50% of NMI tumors, and 40% of MI tumors (70). However, no studies have assessed associations of retinoid receptor expression in urothelial tumors with patient outcomes. Instead, it was shown that the frequency of RARβ promoter methylation in 36 cases of non-invasive low-grade papillary urothelial carcinoma was not statistically different between those with (16%) versus without (29%) tumor recurrence following transurethral surgery (71).

Although debatable, the use of pioglitazone, a PPAR agonist prescribed as an anti-diabetes medication, has been linked to an increased risk of developing bladder cancer (72,73). Treatment with a PPARγ agonist rosiglitazone or overexpression of PPARγ in bladder cancer lines was also found to result in significant induction of cell migration and invasion (74), whereas PPARγ agonists conversely showed inhibitory (75,76) or no stimulatory (77) effects on cell growth. These findings may indicate the presence of multiple mechanisms for the induction/suppression of urothelial tumor outgrowth by PPARγ signals and/or the effects of PPARγ agonists via the non-PPARγ pathways. Amplification of *PPARγ* gene has been documented in bladder cancer specimens (74), but there have been no studies showing PPARγ expression in urothelial tumors.

Up- or down-regulation of the expression of several

Table 1 Molecules whose expression is modulated via sex hormone receptor-mediated signaling in urothelial cells

	Associated receptor (s)	Hormone effect on the expression	Consequence for urothelial cancer outgrowth	Reference
Akt	AR/ERα	Up-regulation/down-regulation	Stimulation	(48,83)
ATF2	AR	Up-regulation	Stimulation	(35)
β-catenin	AR	Up-regulation	Stimulation	(17,84,85)
Bcl-xL	AR	Up-regulation	Stimulation	(86)
CD24	AR	Up-regulation	Stimulation	(87,88)
c-myc	AR	Up-regulation	Stimulation	(89)
cyclin D1	AR	Up-regulation	Stimulation	(86)
cyclin D3	AR	Up-regulation	Stimulation	(89)
cyclin E	AR	Up-regulation	Stimulation	(89)
EGFR	AR	Up-regulation	Stimulation	(83)
ELK1	AR	Up-regulation	Stimulation	(90,91)
ERBB2	AR	Up-regulation	Stimulation	(83)
ERK1/2	AR	Up-regulation	Stimulation	(83)
FGFR3	AR	Up-regulation	Stimulation	(89)
GATA3	AR/ERβ	Down-regulation/up-regulation	Inhibition	(89)
INPP4B	ERα	Up-regulation	Inhibition	(48)
MMP-9	AR	Up-regulation	Stimulation	(86)
NF-κB	AR	Up-regulation	Stimulation	(34)
p21	AR	Down-regulation	Inhibition	(89,92)
p53	AR	Down-regulation	Inhibition	(89,92)
PTEN	AR	Down-regulation	Inhibition	(89)
Slug	AR	Up-regulation	Stimulation	(11)
UGT1A	AR/ERβ	Down-regulation/up-regulation	Inhibition	(47,93)

orphan receptors in bladder cancer tissues, compared with paired normal bladders, has been demonstrated. Of these receptors, HNF4G expression was most frequently elevated in tumors, and its overexpression in bladder cancer cells resulted in the promotion of tumor growth (78,79). Nurr1 was also found to be often overexpressed in bladder cancers and was associated with the induction of tumor cell migration (78,80). Indeed, in an immunohistochemical study, the expression levels of Nurr1 were significantly elevated in higher grade/stage tumors, and high cytoplasmic Nurr1 expression, but not total expression, was found to be an independent predictor of cancer-specific mortality (HR=4.894; P<0.001) (80). Similarly, Nur77 was overexpressed especially in MI bladder tumors (78,81), while Nur77 activation resulted in the delay of tumor growth in cell lines and animal models (81,82).

Molecules whose expression is modulated via steroid hormone receptor signals

An increasing amount of evidence suggests the involvement of upstream pathways and downstream effectors of steroid hormone receptor-mediated signals in urothelial cancer outgrowth. *Table 1* summarizes such molecules directly or

indirectly regulated via the AR and/or ER pathway(s). The following are key molecules, including several transcription factors, whose expression has been not only shown to be up- or down-regulated via androgen-mediated AR and/or estrogen-mediated ER pathways in bladder cancer cells but also assessed their prognostic role in surgical specimens.

ATF2, a member of the leucine zipper family of DNA-binding proteins, is normally activated via its phosphorylation in response to phospho-ERK/MAPK signals. We have recently demonstrated that androgens activate ATF2 in both neoplastic and non-neoplastic urothelial cells expressing the AR and that ATF2 activation results in the promotion of urothelial tumorigenesis and tumor progression (35). In our immunohistochemistry in a set of bladder tissue microarray, the levels of ATF2/phospho-ATF2/phospho-ERK expression were significantly higher in tumors than in non-neoplastic urothelial tissues. Moreover, ATF2 expression was significantly elevated in high-grade and MI tumors, compared with lower grade and NMI tumors, respectively. Univariate analysis showed that patients with phospho-ATF2-positive or phospho-ERK-positive MI tumor had significantly higher risks of disease progression. Multivariate analysis further showed that phospho-ATF2 positivity (HR=5.317; P=0.012) and phospho-ERK positivity (HR=2.727; P=0.066) were associated with a lower cancer-specific survival rate. In addition, moderate/strong expression of ATF2 was an independent predictor for the recurrence of low-grade tumors following transurethral surgery (HR=2.956, P=0.045).

β-catenin is an integral component of the Wnt signaling pathway which is known to activate target genes, including a proto-oncogene *c-myc*, a cell cycle regulator *cyclin D1*, and a receptor tyrosine kinase receptor *epidermal growth factor receptor* (*EGFR*). AR signals have been shown to activate the Wnt/β-catenin signaling in bladder cancer cells (84,85). Co-expression of AR and β-catenin in the nuclei of bladder cancer cells was also documented (84). However, conflicting data exist in regard to an association between the status of β-catenin expression in bladder cancer and tumor behavior. Nonetheless, various studies demonstrated loss or reduced membranous staining of β-catenin in bladder cancer, compared with normal urothelium, and in higher grade/stage tumors, as well as nuclear β-catenin accumulation, as a hallmark of Wnt/β-catenin activation, in tumors, some of which were further associated with worse patient outcomes (17,84,94-97). In particular, aberrant expression of β-catenin in bladder cancer was found to be an independent factor of disease recurrence or progression (17). More specifically, nuclear β-catenin expression was an independent predictor of the recurrence (HR=5.851; P=0.002) or progression (HR=3.104; P=0.034) of NMI tumors (97).

CD24, a cell surface protein which functions as a cell adhesion molecule, has been shown to promote the development of urothelial tumor and its metastasis (87,98). Additionally, in bladder cancer cells, androgens activate CD24 via the AR pathway (87,98). Immunohistochemical studies have shown CD24 expression exclusively in bladder cancer cells, but not in adjacent stromal cells (98-100). Significantly elevated CD24 expression was also observed in higher grade/stage tumors, compared with lower grade/stage tumors (99,100), as well as in metastatic tumors, compared with primary tumors (98). Moreover, univariate analysis revealed associations between CD24 overexpression and the recurrence of NMI tumors (100) or cancer-specific mortality in patients with MI tumor (99). However, CD24 was found to be not an independent prognosticator (99).

The ErbB family, consisting of ERBB1/EGFR, ERBB2/HER2, ERBB3, and ERBB4, is a class of receptor tyrosine kinases that are well known to regulate survival signaling in urothelial cancer cells. Indeed, the efficacy of EGFR-targeted therapy has been assessed in bladder cancer (101). We have demonstrated that androgens induce the expression of EGFR and ERBB2, as well as phosphorylation of their downstream proteins Akt and ERK, in AR-positive bladder cancer cells (83), while EGF promotes their growth via modulating AR activity (102). Alterations of the ErbB family, including protein overexpression and gene amplification/mutation, have also been investigated in bladder cancer tissues, providing mixed results as to their prognostic significance (101,103-107). For example, some studies indicated ERBB2 overexpression as a poor prognosticator, while others failed to do. Meanwhile, EGFR or ERBB2 expression was shown to be up-regulated in MI bladder tumors in most of the studies. In a most recent meta-analysis of 9 studies involving 2,242 patients (104), ERBB2 expression was associated with poorer cancer-specific survival (HR=2.00; P=0.006).

ELK1, a member of the ETS-domain family of transcription factors, has been implicated in cell proliferation or cell cycle control, as well as apoptosis, via regulating the expression of various genes, including a proto-oncogene *c-fos*. Interestingly, the induction of urothelial tumorigenesis and tumor progression by ELK1 signals has been shown to be primarily AR-dependent (90,91,108). Androgens have also been found to activate ELK1 in both

non-neoplastic (91) and urothelial cancer (90) cells. Our immunohistochemical analyses revealed considerable induction in the expression levels of ELK1, as well as its activated form, phospho-ELK1, in bladder tumors, compared with non-neoplastic urothelial tissues (90). As expected, the expression of ELK1 or phospho-ELK1 versus AR in bladder tumors was significantly correlated. Although no strong associations between the levels of ELK1/phospho-ELK1 expression and tumor grades or stages were observed, positivity of phospho-ELK1 expression in NMI or MI tumors precisely predicted their recurrence or progression, respectively. Multivariate analysis further showed an association between phospho-ELK1 expression and cancer-specific mortality (HR =2.693; P=0.021). Additionally, in accordance with preclinical data in bladder cancer cells showing enhancement of cisplatin-mediated cytotoxicity by ELK1 inactivation (108), phospho-ELK1 positivity in MI tumors from patients undergoing cisplatin-based neoadjuvant chemotherapy was strongly associated with chemoresistance in subsequent immunohistochemical analysis (91). More recently, we stained for phospho-ELK1 in UUT cancer specimens (109). As with bladder cancers, the expression of phospho-ELK1 in tumors was significantly up-regulated, compared with corresponding non-neoplastic urothelial tissues, and was associated with that of AR. Elevated phospho-ELK1 expression was also marginally (P=0.085) and significantly (P=0.014) associated with muscle-invasion (i.e., pT2) and lymphovascular invasion, respectively. Moreover, patients with phospho-ELK1(2+) tumor had a significantly higher risk of cancer-specific mortality (HR=3.179 and P=0.013 in univariate analysis; HR=1.131 and P=0.802 in multivariate analysis), compared to those with phospho-ELK1 (0/1+) tumor.

GATA3 is a member of the GATA family of zinc-finger transcription factors, and its immunohistochemistry, as a marker of urothelial differentiation, has been widely used in diagnostic surgical pathology (110). Loss of GATA3 has been associated with the induction of the development (89) and progression (111) of urothelial cancer. While we demonstrated that androgens could down-regulate GATA3 expression in non-neoplastic urothelial cells, we failed to show comparable effects of estrogens in non-neoplastic urothelial cells or those of androgens in bladder cancer cells (89,111). In our immunohistochemistry in a set of tissue microarray, GATA3 expression was considerably down-regulated in the entire group of bladder tumors examined or a subgroup of low-grade/NMI tumors, compared with non-neoplastic urothelial tissues or high-grade/MI tumors, respectively (112). Nonetheless, GATA3 positivity in MI bladder tumors was associated with a significantly higher risk for disease progression even in a multivariate setting (progression: HR=2.435 and P=0.052; cancer-specific survival: HR=3.673 and P=0.040). By contrast, a recent study showed a strong association between GATA3 negativity in MI bladder cancers, as an independent predictor, and worse overall survival (HR=4.54; P=0.02) (113). We also assessed GATA3 expression in UUT urothelial carcinomas and found that GATA3 positivity, as an independent predictor, was associated with higher rates of progression-free survival in all 99 cases (HR=0.479; P=0.051) or 62 cases of MI tumors (HR=0.387; P=0.028) and those of cancer-specific survival in all cases (HR=0.354; P=0.034) or MI tumor cases (HR=0.402; P=0.072) (114). In bladder (112) and UUT (114) tumors included in our sets of tissue microarray, there were significant and marginal correlations, respectively, between GATA3 versus AR expression.

NF-κB, a protein complex of transcription factors consisting of RelA/p65 and others, is known to involve a wide variety of physiological and pathological processes. NF-κB inactivation is also referred to as GR transrepression. We have demonstrated functional interplay between AR and NF-κB signals in non-neoplastic urothelial and bladder cancer cells (34,37). Specifically, androgens could activate NF-κB, while NF-κB activators/inhibitors modulate AR expression. Preclinical data also indicated that NF-κB signals induced urothelial tumorigenesis and tumor progression in an AR-dependent manner. Immunohistochemical studies have shown elevated nuclear expression of p65 in higher grade or stage bladder cancers (25,115,116). We confirmed these observations and further demonstrated significantly increased expression levels of p65 and its active form phospho-p65 in bladder tumors, compared with corresponding non-neoplastic urothelial tissues (34). Survival analyses in patients with MI bladder cancer in multivariate settings further revealed associations between p65 overexpression and worse overall survival (HR=1.107; P=0.0003) (115) as well as between phospho-p65 positivity and disease progression (HR=6.424; P=0.003) or cancer-specific mortality (HR=4.718; P=0.012) (34). In 90 cases of UUT tumors, p65 expression was also found to be an independent predictor of overall survival (HR=2.237; P=0.037) or cancer-specific survival (HR=2.870; P=0.025) (117). In addition, immunohistochemistry in MI bladder cancer specimens from those who underwent neoadjuvant chemotherapy prior to radical cystectomy showed a strong association of phospho-p65 expression with

chemoresistance (37).

UGT1A is a key drug-metabolism enzyme especially involving detoxification of bladder carcinogens, including some industrial chemicals and cigarette smoke. It has been shown that androgen-mediated AR signaling and estrogen-mediated ERβ signaling are associated with reduction and induction, respectively, of the expression levels of UGT1A and its subtypes in SVHUC normal urothelial cells or normal mouse bladders (47,93). An initial immunohistochemical study demonstrated loss of UGT1A in 6 of 19 bladder tumors (118). Subsequent immunohistochemistry demonstrated reduced UGT1A expression in 145 bladder tumors, compared with non-neoplastic urothelial tissues, and inverse associations of UGT1A levels with tumor grade/stage (47). Decreased expression of UGT1A was also associated with the progression of high-grade NMI tumors (only in a univariate setting) or worse cancer-specific survival in patients with MI tumor [even in a multivariate setting (HR=3.413; P=0.010)]. In addition, UGT1A expression was positively and negatively correlated with the levels of ERα and ERβ, respectively, but not those of AR. In a recent immunohistochemical study in UUT urothelial carcinoma tissues, the expression of UGT1A was down-regulated in tumors, compared with non-neoplastic urothelial tissues, and in MI tumors, compared with NMI tumors (119). Furthermore, UGT1A positivity in M0 tumors was found to be an independent predictor for better cancer-specific survival (HR=0.28; P=0.018).

Conclusions

A growing amount of evidence has suggested a critical role of steroid hormone receptor-mediated signals in urothelial tumorigenesis and tumor progression. A variety of molecules, especially downstream targets of AR signaling, have also been shown to involve urothelial cancer outgrowth. Meanwhile, immunohistochemical studies in surgical specimens have revealed significant changes in the expression levels of several steroid hormone receptors and their related proteins in non-neoplastic urothelium versus urothelial tumor as well as in low-grade/NMI versus high-grade/MI urothelial tumors. More importantly, available data support that immunohistochemical detection of some of steroid hormone receptors and related molecules can serve as biomarkers/prognosticators of urothelial tumors, although the underlying mechanisms of how their signals regulate urothelial tumor outgrowth remain poorly understood. Further assessment of steroid hormone receptor signals, as well as other molecules whose expression/activity is directly or indirectly regulated by steroid hormones, may provide not only better strategies for the management of urothelial cancer but also more reliable predictive factors.

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