REVIEW

Androgen receptor moonlighting in the prostate cancer microenvironment

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Abstract

Androgen receptor (AR) signaling is vital for the normal development of the prostate and is critically involved in prostate cancer (PCa). AR is not only found in epithelial prostate cells but is also expressed in various cells in the PCa-associated stroma, which constitute the tumor microenvironment (TME). In the TME, AR is expressed in fibroblasts, macrophages, lymphocytes and neutrophils. AR expression in the TME was shown to be decreased in higher-grade and metastatic PCa, suggesting that stromal AR plays a protective role against PCa progression. With that, the functionality of AR in stromal cells appears to deviate from the receptor's classical function as described in PCa cells. However, the biological action of AR in these cells and its effect on cancer progression remains to be fully understood. Here, we systematically review the pathological, genomic and biological literature on AR actions in various subsets of prostate stromal cells and aim to better understand the consequences of AR signaling in the TME in relation to PCa development and progression.

Key Words

- androgen receptor
- prostate cancer
- stromal cells
- endocrine treatment
- genomics

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Prostate cancer

Prostate cancer (PCa) is the second-most frequently diagnosed tumor type in men worldwide and the most-common male malignancy in developed countries (Torre *et al.* 2015). Annually, there are an estimated 1.1 million new prostate cancer cases worldwide and 300,000 cancer-related deaths (Ferlay *et al.* 2015). The main risk factors for PCa are ethnicity, family history and genetic predisposition. Moreover, prevalence increases with age, with the highest incidence between 70 and 75 years (Leitzmann & Rohrmann 2012).

The majority of patients present with localized disease, in which the tumor is confined to the prostate. PCa is often detected after the development of lower urine tract complaints, while an increasing percentage of patients are being diagnosed before developing any

symptoms as a result of prostate-specific antigen (PSA) testing (Leach *et al.* 2015). PSA is a serine protease, specifically secreted by epithelial prostate cells, which remains expressed in prostate cancer cells. Likelihood of recurrence after primary treatment is commonly estimated by the prognostic TNM classification of malignant tumors (tumor, lymph node involvement and distant metastasis) and the Gleason Score (GS); both prognostic scores based on histopathological features of the tumor.

Treatment options largely depend on stage and grade of the disease, as well as age, health condition and expected life span of the patient. For primary local treatment, a choice is made between radiotherapy and radical prostatectomy. Radical prostatectomy can be combined with extended pelvic nodal dissection (Briganti *et al.*

2012), while radiotherapy can be combined with adjuvant androgen deprivation therapy (ADT) (Mottet *et al.* 2017). Both treatment modalities are considered equally effective in curing the disease (Kupelian *et al.* 2005, Peeters *et al.* 2006, Mottet *et al.* 2017). However, approximately 35% of patients will develop a rise in PSA and a smaller proportion will develop metastatic disease (McLeod 2005). These patients cannot be cured, but the disease can be treated with ADT to which virtually all patients will respond.

The prostate cancer microenvironment

Stromal cells in an organ are all non-epithelial cells that jointly constitute the connective tissue. During normal tissue development, epithelial–stromal interactions are fundamental in order to maintain organ homeostasis. In prostate cancer, the tumor is surrounded by a large variety of stromal cells including resident fibroblasts, myofibroblasts, endothelial cells as well as innate and adoptive immune cells: the tumor microenvironment (TME). Apart from cells, tumors are influenced by soluble factors such as cytokines and other extracellular molecules that constitute the extracellular matrix (ECM). Components of the ECM are secreted by the tumor and the stromal cells, which can regulate tumor cell proliferation and migration (Joyce 2005). Moreover, cytokines released in the tumor microenvironment can control polarization of cells of the TME toward tumor-suppressive or tumor-promoting phenotypes (Corn 2012).

In multiple tumor types, including PCa, tumor-associated stromal cells are highly plastic compared to the normal epithelium-associated stromal cells (Paland *et al.* 2009, Dulos *et al.* 2012, Lanciotti *et al.* 2014). During PCa development and progression, stromal cells show an altered phenotype, which leads to an increased ECM remodeling, angiogenesis, protease activity and immune cells infiltration (Rowley 1998). Tumor-associated stromal cells have been shown to undergo genetic alterations in the presence of a tumor, which might sustain the malignant phenotype (Hill *et al.* 2005).

Many studies have addressed the microenvironment as a prognostic factor in prostate cancer (Galon *et al.* 2012, Halama *et al.* 2012, Kadota *et al.* 2015, Fridman *et al.* 2017). Moreover, the TME gained a lot of interest over the last decades as a therapeutic target. Targeting various components of the TME might represent an alternative approach as compared to the classical therapies targeting cancer cells. This is an attractive concept, since (in contrast to tumor cells) stromal cells are normally regulated and do not show genetic instability. Based on this concept, new potential drugs targeting the cross-talk between cancer

cells and stromal cells, such as Src kinase inhibitors, TGF- β inhibitors and angiogenesis such as the vascular endothelial growth factor receptor inhibitors are now being tested in clinical trials (Bousquet *et al.* 2011, Araujo *et al.* 2012, Herbertz *et al.* 2015).

AR expression in prostate cancer cells

Nuclear receptors such as AR, but also estrogen receptor, glucocorticoid receptor and progesterone receptor are all expressed in prostate tissue and play a role in prostate cancer development and progression (Arora *et al.* 2013, Christoforou *et al.* 2014, Chen *et al.* 2017). AR is expressed in the epithelial cells of primary and metastatic PCa and regulates a variety of cellular functions (Heinlein & Chang 2004). AR is a steroid hormone receptor located on chromosome Xq12 and a member of the nuclear receptor family (Rathkopf & Scher 2013). Its transcript comprises of 8 exons and 3 functional domains: the N-terminal transactivation domain (NTD) in exon 1, the DNA-binding domain (DBD) in exon 2 and 3 and the C-terminal ligand-binding domain (LBD) in exon 5–8. The AR transcript is translated into an 110kDa ligand-dependent transcription factor (van de Wetering *et al.* 2015) that plays a critical role in prostate cancer development and progression by regulating the transcription of genes involved in cell proliferation, migration, differentiation, cell cycling and apoptosis (Heinlein & Chang 2004).

After entering the target cell, testosterone is converted into dihydrotestosterone (DHT) by 5- α -reductase, which has a high affinity for AR (Fig. 1). Upon DHT binding, AR dissociates from the heat-shock protein 90 complex (Hsp90) and undergoes intra-molecular conformational changes at the N- and C-terminal of the receptor (N/C interactions) (Schaufele *et al.* 2005). Consequently, the AR-DHT complex translocates into the nucleus where the receptor dimerizes (van Royen *et al.* 2012, Hu *et al.* 2017) and binds the DNA at androgen-responsive elements (ARE) of promoter and enhancer regions of various target genes (Tan *et al.* 2015).

AR/DNA binding is mediated by pioneering transcription factors (TFs) including forkhead box protein A1 (FOXA1), GATA-binding protein 2 (GATA2) and homeobox protein 13 (HOXB13), that render ARE regions accessible for AR to bind (Stelloo *et al.* 2018). Subsequently, a variety of co-regulators are recruited to the complex that can either activate (coactivators, e.g. steroid receptor co-activator 1 (SRC-1), androgen receptor co-activator 70- α (ARA70- α)) (Foley & Mitsiades 2016, Zhao *et al.* 2016) or repress (co-repressors, e.g. flightless I (FLI1), nuclear receptor co-repressor 1 (NCoR1)) (Hu *et al.* 2017) the expression of downstream-responsive genes.

Figure 1

Schematic view of AR genomic function in prostate cancer (PCa) cells. In PCa cells, testosterone diffuses into the target cell, where it is converted in the cytosol into dihydrotestosterone (DHT) by 5 α -reductase. Subsequently, DHT binds AR and induces the dissociation of Heat-Shock protein 90 (HSP90). DHT binding to AR promotes translocation into the nucleus, where AR dimerizes and binds the chromatin at androgen-responsive elements (AREs). AR binding at AREs is facilitated by other transcription factors (TFs) that regulate chromatin accessibility, such as FOXA1, GATA2 and HOXB13. Finally, chromatin-bound AR recruits co-regulators that promote the interaction and activation of RNA polymerase II (RNA polII) to regulate transcription of AR-responsive genes. Therapeutic interventions with anti-hormonal drugs are aimed to block the various steps of the AR genomic cascade: LHRH agonists and antagonists lower the levels of testosterone synthesized in the testicles; CYP17 inhibitors interfere with the biosynthesis of androgens in the gonads and adrenal glands; 5 α -reductase inhibitors block the testosterone-DHT transformation by inhibiting the 5 α -reductase enzyme; and antiandrogens bind AR and prevent the ligand-mediated AR translocation into the nucleus and binding to the DNA.

AR as a therapeutic target

Since AR signaling modulates the expression of critical genes involved in prostate cancer proliferation and migration, inhibiting AR action is the mainstay of treatment of metastasized disease and as an adjuvant treatment (Uhlman *et al.* 2009). Understanding the molecular mechanisms of AR function is essential to develop new drugs targeting any of the steps of the AR signaling cascade. Currently, multiple drugs targeting these steps in the AR pathway are introduced in clinical practice or are in clinical development (Table 1).

ADT is achieved by physical castration or luteinizing hormone-releasing hormone (LHRH) agonists and antagonists. The latter two interventions lower the level of the testosterone produced by the testicles by inhibiting the production of luteinizing hormone (LH) from the pituitary gland (Gomella 2009). Furthermore, anti-androgen treatment is commonly prescribed to PCa patients. Anti-androgens such as bicalutamide, flutamide and enzalutamide act by directly blocking AR function, while others such as the CYP17A1

inhibitors ketoconazole and abiraterone acetate inhibit extragonadal and intratumoral synthesis of androgens (Gomella *et al.* 2010).

Despite the very high response rate to AR targeting interventions in metastatic PCa patients, progression into metastasized castration-resistant prostate cancer (mCRPC) is inevitable, which is hallmarked by high morbidity and mortality (Elrefaey *et al.* 2014). In contrast to the previous belief that PCa developed a hormone-refractory stage (Chang 2007), we now know that prostate cancer cells develop a hypersensitivity to testosterone (Fujimoto *et al.* 2007), resulting in activation of the AR cascade at castrate levels of circulating hormones. In this mCRPC stage of the disease, AR remains expressed and a driver of disease progression (Eisenberger *et al.* 1998). Enzalutamide and abiraterone have shown clinical activity in mCRPC in combination with ADT (Efsthathiou *et al.* 2012, Hussain *et al.* 2014), which confirms continued androgen dependence of PCa cells in this late stage of the disease.

Apart from further anti-hormonal interventions, taxane chemotherapy and radio nucleotides have also

Table 1 Hormone therapy for prostate cancer patients: established drugs and clinical trials.

Established therapies	In clinical trial
Androgen biosynthesis blockade Ketoconazole (Uhlman <i>et al.</i> 2009) Abiraterone (Valdman <i>et al.</i> 2010)	TAK-700 (Vacchio <i>et al.</i> 2005)
Androgen receptor blockade Bicalutamide (van de Wetering <i>et al.</i> 2015) Nilutamide (Vasu <i>et al.</i> 2003) Flutamide (Visakorpi <i>et al.</i> 1995) Enzalutamide (Vuk-Pavlovic <i>et al.</i> 2010)	Galeterone (van Royen <i>et al.</i> 2012) ARN509 (Vignozzi <i>et al.</i> 2012) ODM-201 (Viselli <i>et al.</i> 1995)
LHRH agonists Goserelin (Wang <i>et al.</i> 2001) Histrelin (Whitacre <i>et al.</i> 1999) Leuprolide (Wikstrom <i>et al.</i> 2009) Triptorelin (Wunderlich <i>et al.</i> 2002)	
LHRH antagonists Degarelix (Yu <i>et al.</i> 2010) Abarelix (Yu <i>et al.</i> 2013a)	
AR NTD blockade –	EPI-506 (NCT02606123)
AR-targeted mustard conjugates Estramustine phosphate (Yu <i>et al.</i> 2014)	
Androgen therapy –	Testosterone cypionate (Yu <i>et al.</i> 2013b)

shown activity in mCRPC in combination with ADT (Hotte & Saad 2010).

The underlying mechanism of this high sensitivity to testosterone in mCRPC has been unraveled in recent years. Altered AR functions commonly occur, which are thought to develop during continued selection pressure induced by treatment (Taplin *et al.* 1995). The molecular mechanisms by which impaired AR activity is associated with PCa development and progression is complex and includes AR amplification, constitutive active AR splice variants, extra testicular testosterone synthesis (Taplin *et al.* 1995, Visakorpi *et al.* 1995, Koivisto *et al.* 1997, Marcelli *et al.* 2000, Hu *et al.* 2017), overexpression of AR cofactors (Buchanan *et al.* 2001, Heemers & Tindall 2007), gain-of-function AR mutations in the LBD (Steinkamp *et al.* 2009) and intracrine androgen production (Locke *et al.* 2008).

Alternative spliced AR variants represent a key factor in resistance to hormonal intervention and are often found in mCRPC (Dehm & Tindall 2011). One of the best characterized AR variant is AR-V7 (AR3), which is composed only of exon 1–3, which encode the NTD and DBD and is therefore capable of DNA binding (Hu *et al.* 2009). However, it is ligand independent and constitutively active. AR-V7 was significantly upregulated during PCa progression, and expression was correlated with disease recurrence after radical prostatectomy (Guo *et al.* 2009). Importantly, overexpression of AR-V7 in circulating tumor cells was associated with resistance to androgen ablation treatments in PCa patients (Antonarakis *et al.*

2017b). Currently, occurrence of AR-V7 in circulating tumor cells is being validated as a predictive biomarker for anti-hormonal treatment insensitivity (Scher *et al.* 2016).

AR expression in prostate cancer microenvironment

There is a growing interest in the impact of stromal AR signaling on the development and progression of prostate cancer. While a large number of studies addressed the role of AR in epithelial cells, only a limited number of reports were focused on the role of AR in the stroma (Leach & Buchanan 2017). However, it is well established that AR is expressed in stromal cells (Table 2) and stromal AR is lost during PCa progression (Singh *et al.* 2013, Cano *et al.* 2007, Singh *et al.* 2014). In various studies, decreased stromal AR expression was shown to be associated with biochemical relapse and poor prognosis (Henshall *et al.* 2001, Li *et al.* 2008, Wikstrom *et al.* 2009). These results suggest a protective role of stromal AR against PCa progression, which would be in contrast to the well-established role of AR in PCa cells. However, the role of AR in stromal cells of the TME remains largely unclear. Given the growing evidence for a key role of the TME in PCa development and progression, exploring the expression and function of AR in the tumor microenvironment is highly relevant.

The underlying mechanisms by which stromal AR expression is lost during prostate cancer progression remain largely unknown. However, some hypotheses

Table 2 Functional and genomic features of AR signaling in the various cells of the prostate cancer microenvironment.

Cell type	AR role	Possible effect in PCa	DNA-binding location	Function	Pioneering factors	References
Prostate cells	Maintenance of prostate development and morphogenesis. Regulation of cell growth and migration	Increased proliferation and migration	Distal intergenic and introns	Enhancer	FOXA1, GATA2, HOXB13	Choudhry <i>et al.</i> (2006), Chimal-Ramirez <i>et al.</i> (2013), Christoforou <i>et al.</i> (2014), Chen <i>et al.</i> (2017)
Fibroblasts	Regulation of cytokines secretion and cross-talk between stromal and epithelial cells (cytokine–cytokine receptor interaction, cell adhesion, ECM-receptor interaction)	Up- or downregulation of tumor cell growth and migration	Distal intergenic and introns	Enhancer	c-Jun, c-Fos, ATF, ZFX	Lahita (1997), Gomez <i>et al.</i> (2000), Knutson & Disis (2005), Kupelian <i>et al.</i> (2005), Ko <i>et al.</i> (2008), Lai <i>et al.</i> (2012a), Kantoff <i>et al.</i> (2010a), Keil <i>et al.</i> (2014), Kissick <i>et al.</i> (2014), Kumar <i>et al.</i> (2016), Antonarakis <i>et al.</i> (2017b)
T lymphocytes	Suppression T cells proliferation. Promotion of differentiation of FoxP3+ T cells (Tregs) and Th2/Th1 T cells ratio (via downregulation of IL-2, IFN- γ , and IL-12)	Increased number of 'pro-tumor' T cells	–	–	–	Miller & Hunt (1996), Marcelli <i>et al.</i> (2000), Leav <i>et al.</i> (2001), Liva & Voskuhl (2001), Mantalaris <i>et al.</i> (2001), Mercader <i>et al.</i> (2001), Messingham <i>et al.</i> (2001), Ling <i>et al.</i> (2002), Liu <i>et al.</i> (2003, 2005), McLeod (2005), Miller <i>et al.</i> (2006), Li <i>et al.</i> (2008), Locke <i>et al.</i> (2008), Madan <i>et al.</i> (2008), Leitzmann & Rohrmann (2012), Lessard <i>et al.</i> (2012), Lin & Wang (2016), Liao <i>et al.</i> (2017)
B lymphocytes	Negative regulation of B cells development and differentiation and antibodies production	Reduced humoral immune response	–	–	–	Mohler <i>et al.</i> (1996), Nakajima <i>et al.</i> (1996), Mueller & Fusenig (2004), Li <i>et al.</i> (2008), Mottet <i>et al.</i> (2017), Nash <i>et al.</i> (2017)
Neutrophils	Positive regulation of neutrophils maturation, proliferation and inflammatory cytokines production (IL1- β , IL-6, TNF)	Increased innate immune reaction	–	–	–	Nimmerjahn & Ravetch (2008), Niu <i>et al.</i> (2008a)

(Continued)

Table 2 Continued.

Cell type	AR role	Possible effect in PCa	DNA-binding location	Function	Pioneering factors	References
Macrophages	Negative regulation of TLR4, CCL2 and FcγR expression. Increased CCL4 production. Up- and downregulation of TNF	Decreased immune response and phagocytosis. Promotion of tumorigenesis. Up- or downregulation of EMT genes	–	–	–	Olumi <i>et al.</i> (1999), Roden <i>et al.</i> (2004), Joyce (2005), Peeters <i>et al.</i> (2006), Rettew <i>et al.</i> (2008), Gomella (2009), Paland <i>et al.</i> (2009), Nonomura <i>et al.</i> (2011), Ricke <i>et al.</i> (2012), Rathkopf & Scher (2013), O'Hara & Smith (2016), Pu <i>et al.</i> (2016)
Dendritic cells	Negative regulation of inflammatory cytokines production (TNF, IL1-β, IL-6, etc.)	Decreased antigen presentation	–	–	FOXO3	Rowley (1998), Romagnani (1999), Royuela <i>et al.</i> (2001)
Endothelial cells	Induction of VEGF-mediated cell growth. Increased VCAM-1 expression. Increase TNF-α-induced apoptosis	Increased angiogenesis	–	–	–	Schuurs & Verheul (1990), Sempowski <i>et al.</i> (2000), Schaufele <i>et al.</i> (2005), Sfanos <i>et al.</i> (2008), Singh <i>et al.</i> (2013), Scher <i>et al.</i> (2016)

have been proposed, including increased epithelial AR expression during PCa development resulting in increased uptake of androgens by epithelial AR, which outcompetes stromal AR, possibly leading to reduced expression (Leach & Buchanan 2017). Another option is that distinct inactivating AR mutations might occur in stroma. However, this remains an unexplored hypothesis as the only data available on AR-inactivating point mutations were originated from prostate cancer cells (Eisermann *et al.* 2013). Finally, epigenetic modifications have also been proposed, such as changes in methylation status of the AR promoter (Keil *et al.* 2014).

Interactions between stromal cells and PCa cells are frequently mediated by soluble factors, such as cytokines (Zhang & Huang 2011). Testosterone and other sex hormones can modulate the adaptive and innate immune system; however, their effect might vary depending on the type of sex steroids. Indeed, estrogens are generally thought to promote pro-inflammatory cytokines production, whereas androgens are thought to suppress them (Ahmed 2010). The fact that males are in general more prone to infectious diseases and females are more prone to develop autoimmune diseases, supports this hypothesis (Schuurs & Verheul 1990, Lahita 1997, Whitacre *et al.* 1999, Choudhry *et al.* 2006). However, relatively little is known about the mechanisms by which androgens affect the immune system.

Suppression of the pro-inflammatory signals by androgens might be mediated through reciprocal repression between AR and the NF-κB signaling pathway, which is a well-known regulator of immune functions (De Bosscher *et al.* 2006, Kaarbo *et al.* 2007). Studies in rats showed that NF-κB was implicated in repression of the AR gene (Supakar *et al.* 1995). Moreover, NF-κB activation was shown to block the proliferation of androgen-dependent PCa cells, but not androgen-insensitive PCa cells (Nakajima *et al.* 1996). Also, in human benign prostatic hyperplasia cells, DHT-induced suppression of NF-κB-mediated inflammatory cytokine production was demonstrated (Vignozzi *et al.* 2012, Izumi *et al.* 2013). However, in LNCaP prostate cancer cells, no tethering of AR and NF-κB was observed at the level of chromatin binding upon stimulation with androgens and TNFα, suggesting that they would not compete for the same genomic locations (Ko *et al.* 2008). Instead, redistribution of the AR pioneer factor FOXA1 was observed together with increased NF-κB-binding sites in the chromatin. This phenomenon was suggested to possibly 'mask' AR-binding sites due to redistribution of FOXA1 binding in the presence of inflammatory cytokines stimulation. Therefore, a potential negative regulation of AR function would be possible by activation of the NF-κB via inflammatory cytokines such as TNFα.

In conclusion, AR expression in the PCa TME might profoundly affect the development of the disease.

Therefore, the exact actions of AR in stromal cells warrant further characterization. Importantly, AR is expressed in various cells in the PCa stroma, which might have different kinetics and might affect PCa development in different ways (Fig. 2). We will discuss the available data on AR actions in the various cells of the TME below.

The role of stromal AR signaling in PCa initiation

AR signaling is vital for normal prostate development and critically involved in PCa initiation. However, the exact role of stromal AR in PCa initiation still needs to be elucidated. Stromal AR activity in tumor formation was initially explored by grafting AR-negative or AR-positive

prostate tumor cells along with AR-negative or AR-positive urogenital sinus mesenchymal (UGM) cells in castrated mice, treated with or without androgen (Wang *et al.* 2001). Of mice grafted with AR-negative prostate cells and AR-positive UGM cells, 36% showed tumor formation when treated with androgen compared to 0.5% in untreated mice. These results suggest the direct impact of stromal AR signaling on PCa initiation.

Other studies explored the role of stromal AR in the early stages of tumor transformation by grafting prostate cells with wild-type or testicular feminized mice mesenchyme (Ricke *et al.* 2012). When androgens were injected in mice grafted with prostate cells and wild-type mice mesenchyme, tumor development was observed. In contrast, tumor growth was significantly

Figure 2

Potential role of androgen receptor (AR) signaling in the prostate cancer microenvironment. Schematic representation of AR signaling in prostate cancer cells and in the cells of the prostate tumor microenvironment (TME). In the TME non-immune cells, such as endothelial cells and cancer-associated fibroblasts (CAFs) and immune cells, such as neutrophils, dendritic cells (DCs), T cells, B cells and tumor-associated macrophages (TAMs) are found. As a result of AR actions, signals to the prostate cancer cells and to the microenvironment (boxed) can be activated. These signals might stimulate (arrow) or inhibit processes (truncated line). Solid lines indicate functions that have been established in prostate cancer, while segmented lines indicate putative actions based on known functions of cytokines. Signals that affect the TME cell itself, are indicated by a line looping back to the cell. In CAFs, opposite actions of AR signaling have been described (Lahita 1997, Koivisto *et al.* 1997, Kupelian *et al.* 2005, Koretzky 2010, Lai *et al.* 2012a, Kumar *et al.* 2016, Antonarakis *et al.* 2017a).

impaired when testosterone was injected in mice grafted with prostate cancer cells and AR-negative testicular feminized mice mesenchyme, suggesting that stromal AR plays a key role in PCa development. Notably, the presence of AR in the epithelial cells did not seem to affect the development of PCa. These data are supported by a study showing that AR-positive stroma induced PCa development in grafted, AR-negative, benign prostatic hyperplasia (BPH)-1 cells (Wang *et al.* 2001). However, PCa development was delayed in mice lacking stromal AR (Niu *et al.* 2008a).

Cumulatively, these studies imply a role of stromal AR in initiation and early stages of PCa development. However, the role of stromal AR in later stages of PCa progression, including development of metastasis and mCRPC might be different as stromal AR is reduced or even lost at those stages of the disease (Singh *et al.* 2013, 2014).

AR expression in prostate cancer-associated fibroblasts

Fibroblasts represent one of the most abundant cell populations in the TME and one of their primary functions is to produce the structural and regulatory components of the ECM and a large variety of cytokines (Barron & Rowley 2012). During prostate cancer development and progression, the stroma becomes reactive and undergoes structural and functional changes, which might affect the progression of the disease (Barron & Rowley 2012). Relatively little is known about the exact mechanisms by which fibroblasts become activated into cancer-associated fibroblasts (CAFs); however, their role in modulation of tumorigenesis and progression is well documented (Olumi *et al.* 1999, Mueller & Fusenig 2004). A recent study showed that CAFs in the TME of cutaneous squamous cell carcinoma are characterized by unique nuclear receptor (NR) expression profiles as compared to normal-associated fibroblasts, which might affect cancer cell invasiveness, proliferation and response to chemotherapy (Chan *et al.* 2017, Leach *et al.* 2017).

Recent studies described the genomic action of AR in immortalized stromal cells from BPH (PShTert-AR) and CAFs. Using chromatin immunoprecipitation, followed by massive parallel sequencing (ChIP-seq) in PShTert-AR cells, it was shown that AR binds the DNA upon testosterone stimulation via the activating protein-1 (AP-1) complex (Leach *et al.* 2017). However, this could not be confirmed in CAFs or primary embryonic prostate fibroblasts (EPFs) (Nash *et al.* 2017). In CAFs and EPFs, AR binding was

reported proximal to the known AR-responsive genes ATAD2 and ARL8B, which was shared with PCa cells (Nash *et al.* 2017). However, the vast majority of AR chromatin-binding sites in CAFs were specific for this cell type and not shared with prostate cancer cells. In the same study, the zinc-finger protein X-linked (ZFX) was identified as a potential AR co-factor in EPFs but not in CAFs. This suggests that ZFX may function as an AR co-factor during embryonic development of the prostate, which disappears during differentiation. However, also in prostate tumors, ZFX was shown to be elevated and to drive cell proliferation and survival (Tricoli & Bracken 1993, Jiang *et al.* 2012).

The consequences of AR signaling in CAFs for PCa development remains unestablished, since reports are not unequivocal. It was suggested that acceleration of human prostate cancer growth and migration was mediated by soluble factors secreted by CAFs (Gleave *et al.* 1991, 1992). Co-culture of CAFs in which AR was knocked down with PC3 prostate cancer cells resulted in decreased epithelial growth and diminished colony formation and invasion. This was mediated by reduced secretion of IGF1, FGF7, FGF10, SDF1, HGF and TGF β 2 (Yu *et al.* 2013a). In agreement with these results, conditioned medium of DHT-stimulated AR-positive WPMY-1 immortalized normal human prostate fibroblasts, significantly increased LnCap prostate cancer cell proliferation compared to non-stimulated fibroblasts (Tanner *et al.* 2011). Moreover, invasion of PCa cells co-cultured with WPMY-1 fibroblasts in which AR was knocked down, was significantly lower compared to co-culture with AR wild-type WPMY fibroblasts (Niu *et al.* 2008b). In contrast, it was reported that antisense oligonucleotide AR-silenced CAFs promoted PCa cells growth, colony formation and expression of stem cell markers by increased IFN- γ and M-CSF expression (Liao *et al.* 2017). Furthermore, castrated mice co-grafted with patient-derived PCa tissue and PShTert-AR-positive myofibroblasts showed a significant increase of apoptotic PCa cells compared to PCa tissue co-grafted with AR-negative myofibroblasts, suggesting that loss of AR in myofibroblasts protects PCa cells from castration-induced apoptosis (Leach *et al.* 2015). There is no clear explanation why AR signaling in fibroblasts is both associated with increased and decreased PCa cell proliferation, migration and apoptosis. A potential explanation of these contrasting findings might be related to differences in the fibroblasts' origins (normal fibroblasts or CAFs) or variation in the duration of AR stimulation of the fibroblasts in the various studies.

If AR actions in fibroblasts protects against prostate cancer development and metastatic potential, this would impact the way we look at anti-hormonal treatments. Although AR inhibition is the mainstay of metastasized disease treatment, this would also imply that this treatment has unwanted effects by disrupting the protective function of fibroblasts against disease progression.

AR expression in adaptive immune cells

The cell-mediated adaptive immune system largely consists of B and T lymphocytes. Various subsets of T cells have been described, most prominently CD8+ cells (commonly referred to as cytotoxic T cells) and CD4+ cells, also called T helper cells (Koretzky 2010). Moreover, various sub-populations of CD4+ T helper cells have been described in tumor inflammation, including the anti-tumor Th1 CD4+ cells, the pro-tumor Th2 CD4+ cells and regulatory T cells (Tregs) (Knutson & Disis 2005).

The CD8+ and CD4+ subsets of T lymphocytes are present in the PCa-affected prostate gland; however, an unequivocal correlation between CD8+ and CD4+ T lymphocyte infiltration and prognosis has not been established yet. The number of infiltrating CD8+ and CD4+ cells was shown to be increased in cancer compared to benign tissue; however, no correlation with malignancy grade (GS) was observed (Valdman *et al.* 2010). Moreover, the numbers of immunosuppressive Tregs were found increased in the prostate and peripheral blood of PCa patients compared to healthy men (Miller *et al.* 2006, Sfanos *et al.* 2008). However, a clear relation between T cell infiltration in the PCa TME and clinical outcome is yet to be established, as both increased and decreased numbers of infiltrating T cells into the PCa TME were found to correlate with shorter PSA recurrence-free survival after radical prostatectomy (Flammiger *et al.* 2012).

Expression of classical intracellular AR (iAR) has been documented in T and B cells, while in T cells also a surface AR (sAR) was described (Viselli *et al.* 1995, Benten *et al.* 1999, 2002, 2004, Wunderlich *et al.* 2002). The functionality and significance of this sAR remains to be elucidated. A few studies have suggested that AR signaling in immune cells alters cytokine production in T cells (Bebo *et al.* 1999, Liva & Voskuhl 2001), which may potentially affect prostate cancer development and progression (Izumi *et al.* 2014).

Thymic cells of AR knocked-out (ARKO) mice showed a lower expression of CD80/CD86 (also known as B7-2) activation marks compared to AR-proficient thymic

cells (Lai *et al.* 2012a), which are believed to be required for proper antigen-mediated activation of T cells (Vasu *et al.* 2003). AR-mediated activation of thymic cells was confirmed in another study where AR was shown to upregulate CD80 and CD86 by direct promoter binding (Lai *et al.* 2013). However, in thymic cells of ARKO mice, an increased expression of IL-7 and CCL21 was shown, while TGFβ1 and IL-6 expression was decreased. IL-7 and CCL21 were reported to promote thymopoiesis (Liu *et al.* 2005), while TGFβ1 and IL-6 were suggested to inhibit it (Sempowski *et al.* 2000). This would be in contrast to the suggested AR-mediated activation of thymic cells based on CD80/CD86 expression. However, reports on the role of CD80/CD86 in T cell activation are not unequivocal, since another study reported that double CD80/CD86-KO mice showed increased numbers of mature CD4 and CD8 splenic T cells (Vacchio *et al.* 2005), suggesting that increased CD80/CD86-mediated activation of T cells might negatively regulate the maturation and differentiation of T cells.

In mature T cells, AR signaling was shown to have a dual role. AR activation suppresses T cell proliferation in mice and *in vitro* (Roden *et al.* 2004), and it modulated the balance between CD4+ Th1 and Th2 (T helper cells) response, skewing the differentiation toward the Th2 phenotype in peripheral blood of ADT-treated PCa patients (Kissick *et al.* 2014). A possible explanation for AR-mediated Th2 polarization is the suppression of IL-2, IFN-γ and IL-12 expression in T cells (Messingham *et al.* 2001, Kissick *et al.* 2014), which are known to be key signals for the Th1 polarization (Romagnani 1999, Bettelli & Kuchroo 2005). In CD4+ T cells, AR was found to bind an intronic region of the protein tyrosine phosphatase non-receptor type 1 (Ptpn1) locus (Lessard *et al.* 2012). Moreover, ptpn1 expression was decreased in CD4+ cells isolated from patients undergoing ADT (Kissick *et al.* 2014). In the same study, upregulation of Ptpn1 in human and mouse androgen-treated CD4+ T cells was associated with IL-12 inhibition, which prevented STAT4 phosphorylation and ultimately blocked Th1 polarization, potentially contributing to a sustained tumor-specific immune response. The AR-mediated Th1 to Th2 T cell switch might support PCa development and progression as Th2 T cells have been widely described to favor a pro-tumor and immunosuppressive microenvironment, through cytokines that support the presence of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) (Grivnenkov *et al.* 2010, Chimal-Ramirez *et al.* 2013).

AR is also expressed in immature murine B cells (Mantalaris *et al.* 2001). *In vitro* and *in vivo* studies showed that blockade of AR signaling enhanced B cell lymphopoiesis, demonstrating that B cell development is negatively regulated by androgens and AR signaling (Smithson *et al.* 1998, Ellis *et al.* 2001, Altuwaijri *et al.* 2009). These data suggest that hormonal therapy increases the generation of young B cells; however, it is not clear how this might affect PCa.

AR signaling seems to affect maturation of T and B cells. However, there is limited data on the relevance of AR signaling in T and B cells for prostate cancer development. In T cells, AR signaling regulates the expression of various cytokines that might affect PCa development.

AR expression in innate immune cells

Cells of the innate immune system (e.g. macrophages, dendritic cells (DCs), MDSCs and neutrophils) promote phagocytosis and lysis of bacteria and virus-infected cells and are critically involved in the immunological response to cancer development and progression. Within the same subset of innate immune cells, various phenotypes may be present that affect PCa development and progression. The effects of androgens on innate immune cells functions are largely unexplored; however, several androgen-driven mechanisms of action have been proposed, as further discussed below.

Neutrophils and polymorphonuclear cells

Neutrophils or polymorphonuclear neutrophils (PMNs) kill tumor cells by either phagocytosis or releasing toxic oxygen-free radicals (Elrefaey *et al.* 2014). It is suggested that neutrophils can be present in the TME as N1-like neutrophils (anti-tumorigenic) or N2-like neutrophils (pro-tumorigenic), and therefore, contribute to both suppression and promotion of the tumor (de Oliveira *et al.* 2016). Although a clear distinction between these two neutrophils phenotypes in PCa and correlation with survival is lacking, an elevated neutrophils-to-lymphocytes ratio in the peripheral blood is associated with lower response rates to abiraterone and docetaxel treatment in mCRPC patients (Templeton *et al.* 2014, Cao *et al.* 2016, Gu *et al.* 2016).

AR expression is not established in human neutrophils; however, AR was strongly expressed in mouse neutrophils (Mantalaris *et al.* 2001). A study in ARKO mice reported significant reduction of neutrophil proliferation and maturation (Chuang *et al.* 2009),

possibly via reduced phosphorylation of STAT3 and ERK, which are essential for myeloid cells differentiation. As a consequence, production of chemokines and cytokines such as IL1- β , IL-6 and TNF- α was also reduced in granulocytes of ARKO mice. This would suggest that AR in neutrophils decreases the number of neutrophils and supports their phenotype. However, in the same study, ADT did not significantly affect peripheral blood neutrophil counts in patients. Although an impact of AR signaling in neutrophils on PCa development and progression has not been established, an AR mediated inhibition of neutrophil maturation may be associated with a better clinical outcome as high neutrophil-to-lymphocyte ratio in prostate cancer patients is associated with biochemical recurrence and shorter overall survival (OS) in several clinical studies (Templeton *et al.* 2014, Cao *et al.* 2016, Gu *et al.* 2016).

Macrophages

Macrophages are found in most organs of the human body and are derived from circulating monocytes, which differentiate into macrophages when entering the tissue (Italiani & Boraschi 2014). Unlike neutrophils, macrophages are capable of repeated phagocytosis and can secrete inflammatory cytokines (Elrefaey *et al.* 2014). However, similar to neutrophils, phenotypic subsets occur with contrasting actions on tumor cells. M1-like and M2-like macrophages are so-called pro-inflammatory macrophages and TAMs, respectively (Elrefaey *et al.* 2014). The number of infiltrating TAMs in the prostate cancer microenvironment was predictive for disease progression after hormonal therapy (Nonomura *et al.* 2011). Moreover, increased numbers of cancer-associated M2 macrophages was associated with extra-capsular tumor extension (Lanciotti *et al.* 2014).

In general, androgens are thought to inhibit macrophage function *in vivo* and *in vitro* (Miller & Hunt 1996). For instance, AR knockdown suppresses migration of the macrophage cell line THP-1 (Huang *et al.* 2014), suggesting that AR in macrophages might support the migration ability of these cells. However, AR knockdown in THP-1 cells also induces expression of CCL2, which promotes EMT and enhances invasiveness of malignant cells (Izumi & Chang 2013, Izumi *et al.* 2013).

Moreover, androgen stimulation of murine macrophages reduced the expression of Toll-like receptor 4 (TLR4) (Rettew *et al.* 2008). Downregulation of TLR4 expression alters the MyD88-dependent and-independent pathways, which leads to decreased expression of various

pro-inflammatory molecules such as IL1- β , COX2, CXCL1, TNF- α , CCL3, IL-6, IL-12, IRF1, CXCL10, TNF1 and CCL5 (Bjorkbacka *et al.* 2004). Furthermore, expression of receptors for the Fc region of IgG (Fc γ R) on macrophages was reduced in guinea pig models after testosterone stimulation (Gomez *et al.* 2000). As Fc γ R expression in innate cells is crucial for phagocytosis and the release of inflammatory mediators (Nimmerjahn & Ravetch 2008), these data suggest that AR activation in macrophages decreases antibody-mediated phagocytosis via reduction of Fc γ R expression.

Interestingly, co-culture of normal prostate epithelial RWPE-1 cells with the THP-1 macrophage cell line induced prostate tumorigenesis in 3D cultures (Fang *et al.* 2013). In the presence of THP-1 macrophages, RWPE-1 cells differentiated into a disorganized aggregate structure, suggesting that soluble factors secreted by THP-1 cells interfere with the normal development of well-organized spheroids of glandular prostate epithelial cells also called prostaspheres. These observations were confirmed *in vivo* as all mice injected with both RWPE and THP-1 cells developed tumors, while none of the mice injected with either RWPE or THP-1 alone developed tumors. In the same study, the expression of several EMT-associated genes in RWPE-1 cells was increased after co-culture with THP-1 macrophages, including CCL4. CCL4 was previously identified as an AR-responsive gene and proposed as a main driver of tumorigenesis and EMT (Lai *et al.* 2012b). In this study, antibody-based blocking of CCL4 in the co-culture experiments showed significant reduction of THP-1-mediated cell migration and EMT-related gene expression in RWPE-1 cells. AR expression in THP-1 macrophages was proposed to be responsible for the cross-talk between THP-1 cells and RWPE-1 cells as knocking down AR in THP-1 cells reduced CCL4 expression. This key role of AR-mediated CCL4 expression was confirmed *in vivo*, since macrophage-AR knockout (M-ARKO)/PTEN^{+/-} mice showed decreased CCL4 levels and reduced preneoplastic prostatic intraepithelial neoplasia formation when compared to tumors from PTEN^{+/-} mice. Although these findings demonstrate a role of AR in macrophage-associated inflammatory response, the underlying mechanisms remains unclear.

In conclusion, these results suggest that AR signaling affects multiple functions of macrophages, including migration, cytokine production and phagocytosis. All of these might affect prostate cancer development. Moreover, macrophages might increase prostate cancer cell EMT mediated through AR-regulated CCL4 expression.

Dendritic cells

Dendritic cells (DC) share many features with macrophages and play an important role in T cell activation and assist their regulation into Th1 and Th2 differentiation.

Very little is known about the role of AR in DCs. DCs do express AR and androgens decrease production of the inflammatory cytokines IL1- β , IL-6 and TNF- α (Corrales *et al.* 2006). In agreement, DHT-stimulated bone marrow-derived dendritic cells showed decreased IL-6, which is fundamental for the maturation of DCs, while production of anti-inflammatory cytokines IL-4 and IL-10 was increased upon DHT treatment (Zhao *et al.* 2014). However, the genomic mechanisms of AR signaling in DCs as well as the possible effect thereof on PCa development and progression are yet to be explored. As a result of AR-mediated impairment of DCs maturation, activation of CD8⁺ T cells may be suppressed, preventing effective tumor killing. Therefore, we speculate that AR function in DCs might promote the progression of PCa via preventing CD8⁺ T cell tumor-specific activation.

AR expression in endothelial cells

Endothelial cells are key components of blood vessels. Abnormalities in growth, function and organization of endothelial cells often occur in concert with the development and progression of atherosclerosis and cancer. Very little is known about the effects of androgens on endothelial cells. Human umbilical vein EA.hy926 endothelial cells have a functional AR, and AR stimulation increases TNF- α -induced apoptosis of these cells (Ling *et al.* 2002, Liu *et al.* 2003). In contrast, another study reported that AR promotes endothelial cell proliferation through AR/VEGF-A/cyclin-A-mediated mechanisms (Cai *et al.* 2011). Given the opposing conclusions of studies exploring the effects of AR signaling in endothelial cells on proliferation and survival, a clear role of AR in angiogenesis and consequently PCa development remains elusive. AR stimulation induced vascular cell adhesion molecule 1 (VCAM-1) expression in endothelial cells, which led to increased monocyte binding to the endothelium, promoting monocyte migration into the TME (Death *et al.* 2004). Testosterone was shown to rapidly induce nitric oxide (NO) production in human aortic endothelial cells (HAECs) (Yu *et al.* 2010), which is known to support an immune suppressive microenvironment, promote cancer cell growth and prevent apoptosis (Grimm *et al.* 2013).

Altogether, these data would suggest a potential role of endothelial AR in PCa development and progression, mediated by increased angiogenesis and accelerated recruitment of immune cells into the PCa microenvironment.

Other steroid hormone receptors in the PCa microenvironment

Expression of other steroid hormone receptors (SHR) such as estrogen receptor (ER), glucocorticoid receptor (GR) and progesterone receptor (PR) has been described in the PCa stroma. However, their role in specific stromal cell types is largely unknown. Both ER α and ER β are expressed in the PCa-associated stroma (Gangkak *et al.* 2017). While ER α is predominantly found in the stromal compartment, ER β is mainly expressed in the basal-epithelial cells (Leav *et al.* 2001, Royuela *et al.* 2001, Gangkak *et al.* 2017). One study showed that increased expression of ER α but not ER β in the stroma was associated with advanced disease (Daniels *et al.* 2014). However, another study showed that PCa patients with ER α -positive stromal staining had a significantly lower risk of biochemical recurrence after local therapy (Slavin *et al.* 2014). In the same study, *in vitro* experiments revealed that stromal ER α reduced PCa cell invasion possibly by downregulating matrix metalloproteinase 3 (MMP3) expression and increased expression of thrombospondin 2 (Thbs2).

GR is expressed in the stroma of both human BPH and PCa (Mohler *et al.* 1996). Glucocorticoids play a key role in immune cells as they are potent anti-inflammatory agents that act via transrepression of GR through tethering to various TFs, including AP-1 and NF- κ B (Lin & Wang 2016). Therefore, targeting GR in PCa patients might potentiate the efficacy of current therapies.

PR is also expressed in the stromal compartment of PCa, and levels were lower compared to normal prostate stroma. Conditioned medium from PR-positive stromal cells inhibits prostate cancer cell migration and invasion, possibly via downregulation of CXCL12 and IL-6 production (Yu *et al.* 2014). Moreover, PR was shown to inhibit prostate stromal cell proliferation (Yu *et al.* 2013b).

These data suggest that activity of SHRs in the stromal compartment may affect PCa development and progression. However, there are limited data on their actions and no data on interactions between the various SHRs. More studies are needed to explore the exact role of SHRs in PCa cells and PCa-associated stroma.

New prospective for hormone therapy and immunotherapy in PCa

Immunotherapy was chosen by Science's editors as the 'breakthrough of the year 2013' and represents a new potential weapon for fighting cancer by exploiting the immune system. Although effective in melanoma, non-small-cell lung cancer and bladder cancer, thus far immunotherapy has shown limited efficacy in PCa patients (Higano *et al.* 2009, Kantoff *et al.* 2010b, Topalian *et al.* 2012, Beer *et al.* 2017).

One potential explanation for this lack of efficacy is the low mutational load of PCa cells, limiting the repertoire of neo-antigens that are required for recognition of cancer cells by activated T cells (Alexandrov *et al.* 2013). Another potential explanation for the low success rate of immunotherapy in PCa is the presence of an immunosuppressive TME. CD25+ and FoxP3+ Tregs as well as PD1+ exhausted T cells were found to surround prostate cancer islets in untreated PCa patients (Ebelt *et al.* 2009). Moreover, levels of circulating immune-suppressive CD14+HLA-DR^{low/-} MDSCs were significantly increased in the blood of PCa patients, compared to healthy controls (Vuk-Pavlovic *et al.* 2010). Importantly, MDSCs become more immune suppressive in the tumor and can differentiate into TAMs, supporting tumor growth (Kumar *et al.* 2016).

Non-immune stromal cells might also contribute to immune suppression by releasing specific stromal factors. Myofibroblasts present in the PCa microenvironment were shown to release CCL2, IL-6 and TGF- β , promoting differentiation of DCs into tumor-associated DCs (TADCs) via increased expression of IL-10 and PD-L1. This reduced the cross-presentation of tumor antigens to CD8+ T cells and TADCs-mediated T cell proliferation (Spary *et al.* 2014).

The effect of ADT therapy on the immune system remains elusive. ADT treatment is reported to increase the level of T cells in peripheral blood of mice (Roden *et al.* 2004) and in human PCa tissue (Mercader *et al.* 2001, Gannon *et al.* 2009). However, recent studies demonstrated that ADT suppresses T cell differentiation and activation, which hampers the efficacy of immunotherapy (Lai *et al.* 2012a, Pu *et al.* 2016). Moreover, others demonstrated that ADT also promotes the expansion of immunosuppressive Tregs and TAMs (Bao *et al.* 2012, Escamilla *et al.* 2015), which counteract the accumulation of tumor-infiltrating lymphocytes observed upon ADT treatment.

Mouse prostate tumor (Myc-Cap)-bearing mice treated with CpG, a TLR9 agonist which activates

DCs, showed a suppressed tumor-specific CD8⁺ T cells immune response upon treatment with the AR antagonist flutamide. More specifically, AR antagonist treatment was shown to suppress T cells priming (Pu *et al.* 2016). These data suggest that AR inhibition impairs the efficacy of immune checkpoint inhibitors treatment of PCa patients. Furthermore, it was recently reported that ADT decreases the expression of the immune checkpoint marker, programmed death ligand 1 (PD-L1) possibly limiting the effect the anti-PD-L1 immune checkpoint therapy (Calagua *et al.* 2017).

Recent advances of vaccination therapy in PCa treatment led to the development of sipuleucel-T, a therapeutic vaccine shown to prolong OS of mCRPC patients treated with ADT (Kantoff *et al.* 2010a). Clinical outcome of sipuleucel-T treatment was not affected by ADT, as no difference in efficacy was found between patients treated with ADT compared to patients that were treated with ADT after completion of sipuleucel-T treatment (Antonarakis *et al.* 2017a). However, a small study in sipuleucel-T-treated patients suggested that vaccination followed by treatment with the anti-androgen nilutamide improved survival, as compared with patients who first received anti-androgen therapy and then vaccine (Madan *et al.* 2008).

All together, these data suggest that AR blockade impairs the tumor-specific immune response. Additional studies are required to optimize combination strategies for the treatment of PCa patients.

Conclusions

In this review, we explored the role of AR in various cells of the prostate cancer microenvironment and its potential effect on the development of prostate cancer. Understanding the functional mechanisms of AR expression in the stroma is relevant, since unwanted effects of hormone therapy can be expected as AR in the epithelial and stromal compartments controls different signaling pathways. However, these putative opposing effects have not been explored. Cell-specific AR targeting has been described in mouse studies using the Cre/Lox system (De Gendt & Verhoeven 2012, O'Hara & Smith 2016), but not in the context of cancer. Opposing effects on prostate cancer growth of stromal and epithelial AR signaling might be targeted by endocrine agents with cell type-selective actions. Drugs that would specifically target AR in the stroma or in the cancer cells might have an enhanced anti-cancer activity with less side effects, either alone or in combination with ADT. Another approach

would be to target cell-specific genes downstream of AR in prostate cancer cells. For instance, hormonal therapy could be combined with agents blocking the AR-mediated cytokine release or the receptors thereof, which support PCa development and progression.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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