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Cancer Cell–Extrinsic Roles for the Androgen Receptor in Prostate Cancer

Andrew W Hahn, Bilal A Siddiqui, Javier Leo, Eleonora Dondossola, Kaitlin J Basham, Cindy K Miranti, and Daniel E Frigo

Andrew W Hahn, Department of Genitourinary Medical Oncology and the David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; Contributor Information.

Corresponding author.

Correspondence: Daniel E. Frigo, PhD, Department of Cancer Systems Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA. Email: frigo@mdanderson.org.

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Abstract

Given the central role of the androgen receptor (AR) in prostate cancer cell biology, AR-targeted therapies have been the backbone of prostate cancer treatment for over 50 years. New data indicate that AR is expressed in additional cell types within the tumor microenvironment. Moreover, targeting AR for the treatment of prostate cancer has established side effects such as bone complications and an increased risk of developing cardiometabolic disease, indicating broader roles for AR. With the advent of novel technologies, such as single-cell approaches and advances in preclinical modeling, AR has been identified to have clinically significant functions in other cell types. In this mini-review, we describe new cancer cell–extrinsic roles for AR within the tumor microenvironment as well as systemic effects that collectively impact prostate cancer progression and patient outcomes.

Keywords: androgen receptor, prostate cancer, tumor microenvironment, bone, muscle, adipose, metabolic syndrome, cardiovascular

The androgen receptor (AR) has been the major therapeutic target in prostate cancer since even before the discovery of the receptor in the late 1960s (1-3). Two decades earlier, Charles Huggins performed his seminal work demonstrating that depletion of androgens via surgical castration or chemical castration with estrogen benefitted men with metastatic prostate cancer through a mechanism that was unknown at the time (4). Following the discovery of AR and antibodies that could recognize the protein, it was quickly deduced that AR expression and transcriptional activity promoted prostate cancer cell biology and was, thus, the central driver of the disease.
Correspondingly, prostate cancer cells became the predominant models to study AR pharmacology and biology. Within prostate cancer cells, AR regulates multiple processes including cell proliferation, survival, migration, invasion, metabolism, differentiation, and DNA repair (5-8). The broad array of genetic and enzymatic alterations that occur within prostate cancer cells to help maintain AR activity following hormone therapy, such as *AR* gene and enhancer amplifications, expression of constitutively active AR splice variants, increased intratumoral androgens, and somatic AR ligand-binding domain mutations, further underscores the sustained importance of AR even in the late stages of the disease (9, 10). Yet we know from multiple clinical trials testing AR-targeting therapies, and preclinical studies disrupting AR in specific cell types, that AR signaling modulators clearly have on-target side effects (ie, disruption of physiological AR functions in other tissues) (11). Defining how cancer cell–extrinsic AR activity impacts prostate cancer stands to improve our understanding of how AR-directed therapies work and why they fail. This knowledge will aid the development of new rational, biologically based combination therapies, and inform the intensity of AR-directed therapy necessary to treat the disease more effectively. In this mini-review, we discuss emerging roles for AR in prostate cancer. More specifically, recently described cancer cell–extrinsic functions for AR in prostate cancer are described to help provide a broader perspective of how targeting this receptor impacts both tumor growth and patient quality of life.

Immune System

Epidemiological data reveals sex differences with regards to both autoimmune disease and cancer incidence (12). On average, females have lower rates of cancer incidence and mortality, but increased risk of developing autoimmune diseases (13, 14). These sex differences have in part been attributed to sex hormones such as estrogen and testosterone (15, 16). These observations raised the possibility that AR signaling, which predominates in men compared with women, may have immunosuppressive functions and partly explain these sex differences. With regards to androgens, administration of the potent androgen dihydrotestosterone leads to involution of the thymus, the primary lymphoid organ in which T cells mature (17). AR is expressed across cell types of both the adaptive (T cells and B cells) and innate (eg, macrophages and monocytes) immune system (15). Consistent with this immunosuppressive role for AR signaling, androgen deprivation therapy (ADT, the backbone of treatment for advanced prostate cancer) increases thymic output of T cells (18), interferon-γ signaling (which is necessary for T cell–mediated antitumor immune responses) (19), antigen-specific T cell immunity (20), density of T cells within the prostate tumor microenvi-

ronment (21), and expansion of bone marrow B cells (22) (Fig. 1). It has recently been shown that AR bound directly to *Ifng* gene enhancers in $CD8^+$ T cells, and that suppression of T cell–intrinsic AR function promoted interferon-γ signaling (23).

The AR-mediated immunological effects led to the hypothesis that combining AR inhibition with immune checkpoint therapies (ICTs), which block T cell inhibitory molecules, would promote antitumor responses. Unlike tumor types such as melanoma and lung cancer that are characterized by high tumor mutational burden and neoantigen load associated with a high density of intratumoral T cells and have demonstrated improved long-term survival in many patients with ICTs, prostate cancer has relatively few intratumoral T cells and low response rates to ICTs (24-26). Although, preclinical data in murine models supported the combination of AR inhibition plus ICTs (27), clinical trials of ADT plus anticytotoxic T lymphocyte associated protein-4 (28-30) and enzalutamide (a second-generation AR inhibitor) plus anti-programmed death-ligand 1 (31) showed no benefit.

The lack of demonstrated benefit with combined anti-AR and ICT is likely due to the complex and dynamic interactions of AR signaling within the tumor immune microenvironment that remain incompletely understood. For example, maximal T cell infiltration occurs within weeks after AR inhibition, followed by a subsequent decline, suggesting that the timing of ICT relative to AR inhibition may influence the response (21) (Fig. 2). Additionally, the initial T cell infiltrate following AR inhibition is biased toward Th1 cells, which promote antitumor immunity, but is subsequently replaced by Th17 and regulatory T cells, which suppress antitumor immunity (32, 33). Furthermore, in addition to lymphoid cells such as T cells, subsets of myeloid cells, specifically myeloid-derived suppressor cells, have been demonstrated to drive castration resistance and promote tumor survival via secretion of interleukin-23 (34) and interleukin-8 (35). Interestingly, myeloid-specific genetic ablation of *Ar* in syngeneic mouse models increases prostate cancer growth, suggesting that AR may play an antitumor role in certain innate myeloid cell populations (36, 37). Given the breadth of myeloid cell types, additional studies are needed to delineate the specific myeloid subtypes directly regulated by AR, their individual contributions to tumorigenesis, and how their roles evolve over the course of the disease. Critically, given the known differences between human and murine immunity, detailed characterization (eg, utilizing single-cell and spatial technologies) of biopsies from patients both prior to and while receiving treatment will be essential. This will allow prioritization of relevant biological mechanisms that can subsequently be tested in coclinical animal models and to increase the probability of successful translation to patients.

Fibroblasts and Smooth Muscle Cells

AR is prominently expressed (~25-75% by immunohistochemistry (IHC)) in the stromal compartment (38-42), in both fibroblasts and smooth muscle cells (SMCs) of the prostate gland (43). AR's functional roles in these different compartments were determined using genetically engineered mouse models in which the *Ar* gene was specifically deleted in either the epithelium, fibroblasts, or SMCs using Probasin-Cre, FSP-Cre, or (transgelin) Tgln-CRE, respectively (43-47). Strikingly, loss of AR in the epithelium did not significantly disrupt glandular structure, but it did inhibit the expression of AR target genes involved in glandular secretion and led to hyperproliferation of epithelium, suggesting a normal growth suppressive role for epithelial AR (46, 47). Loss of AR in fibroblasts severely inhibited luminal cell differentiation, a phenotype also seen upon chemical castra-

tion (44). Loss of AR in SMCs led to altered ductal invaginations (45). Combined loss of AR in both fibroblasts and SMCs generated a more profound phenotype, including epithelial cell apoptosis, suggesting both are contributing unique signals to epithelial homeostasis (48). These findings corroborated prior tissue recombination and implantation models using urogenital mesenchyme from mice deficient in AR (49). This stromal AR dependency was observed in a human microfluidic-based bioengineered epithelia/stroma coculture model, where stimulation of stromal cells with androgens was sufficient to induce luminal cell differentiation of the neighboring basal epithelial population, and stromal cells with inactive AR did not (50). In the same model system, intrinsic AR function in the stroma is also not required for luminal cell survival or proliferation (51). In fact, in normal epithelium, AR overexpression suppresses growth (38). This is in stark contrast to prostate cancer, where AR drives both survival and proliferation. The basis for this difference remains unresolved. However, these developmental studies suggest that AR in the stromal compartment is critical for prostate gland organogenesis and normal glandular homeostasis.

One of the major outstanding questions is how stromal AR exerts its effects on the epithelia. It was originally postulated that AR must induce the expression of secreted factors that act on the epithelium (52). Attempts to unambiguously identify the nature of these factors have been complicated by the lack of accurate models. Ex vivo studies have identified 2 morphogens, FGF10 and FGF7 (aka KGF), which are sufficient to induce luminal cell differentiation of basal cells and, in some models, are induced by androgen (44, 52-56). However, other reports provide evidence that neither is robustly controlled by androgens in the stroma (57-59). While much work has focused on the canonical nuclear functions of AR in stroma cells, it is possible that non-nuclear AR actions are important as has been reported in prostate cancer cells (60). The recent identification of putative membrane-localized ARs including membrane-localized AR and unrelated androgen-interacting receptors may add to the complexity (61). Resolution of all these questions will require additional studies and improved models.

Human tissue studies demonstrate that stromal AR expression is lost with increasing Gleason grade and is associated with poor outcomes (40, 62, 63). In 1 study, AR in patient-derived fibroblasts was found to suppress the migration of cocultured human prostate cancer cells by blocking chemokine production (64). Since stromal AR maintains tissue homeostasis, loss of stromal AR is further expected to disrupt normal glandular structure through decreased secretion of androgen-dependent morphogens. The mechanism by which AR is lost in the stroma is not known. One possibility is that simple cancer-associated fibroblast (CAF) conversion could alter the mesenchymal lineage such that AR is no longer expressed (65). Alternatively, there may be more direct mechanisms mediated by other tumor-secreted factors. In fact, the mechanisms that control *AR* gene expression in fibroblasts have not been identified. Studies in different prostate cancer lines and other cell types suggest fundamental differences in how *AR* gene transcription is controlled depending on the context and species (66-68). Understanding these mechanisms will be critical for efforts attempting to restore stromal AR function in prostate cancer to help renormalize the tissue and impair disease progression. Therefore, AR's stromal functions are fundamentally important in patients receiving ADT, where AR function is not only suppressed in the tumor but also in the stroma. One study suggests that in some cells, NF-kB signaling suppresses AR expression (67),

whereas in tumor cells, it enhances AR expression (66, 69). Hence, 1 possibility is to therapeutically suppress NF-kB, which would lead to the correct repression of AR in tumor cells and enhance its activity in stroma.

While human tissue studies have repeatedly linked AR loss in the stroma as a mechanism of progression, preclinical studies have suggested that AR expression in the stroma is critical for tumor initiation in prostate cancer genetically engineered mouse models (48, 70, 71). However, in another study in which *Ar* was genetically ablated in SMCs, loss of AR promoted oncogenesis through a mechanism that leads to disruption of luminal cells. This result is consistent with a loss in glandular homeostasis (72). It is not clear what the source of discrepancy is in these studies. Of note in the mouse, oncogenic disruption often occurs in the context of gland development, whereas, in humans, oncogenic disruption occurs postdevelopment and during aging. Another possibility is that there are fundamental differences in AR actions in fibroblasts vs SMCs. Signaling in the stroma may also be needed early in tumor initiation to drive the proliferation or maintenance of the "cell-of-origin" until the tumor is established and then is no longer dependent on stromal AR. It is established that normal stroma is repressive to tumor initiation, while the subsequent disruption of the stromal compartment is required to switch from noninvasive prostatic intraepithelial neoplasia (PIN) to high-grade invasive carcinoma. Invasive carcinoma is accompanied by a CAF phenotype and loss of stromal AR. The relative contribution of AR loss vs CAF conversion and how they each contribute to tumor progression needs to be further established.

Systemic Metabolism, Adipocytes, and the Cardiovascular System

Contemporary ADT is primarily via gonadotropin hormone-releasing hormone (GnRH) agonists, such as leuprolide or goserelin, or antagonists, such as degarelix or relugolix, that decrease production of luteinizing hormone and follicle-stimulating hormone. Greater androgen signaling inhibition (ASI) has also improved survival for men with advanced prostate cancer. ASI may be AR antagonists to target paracrine and autocrine signaling or CYP17A1 inhibition to target production of androgen precursors from the adrenal gland and adipose tissue. While ADT and ASI are effective at stopping prostate cancer cell growth, these therapies also have profound effects on the host given the central role of androgen signaling in male physiology, including impacts on the musculoskeletal system (described in the next section), adipocytes, insulin and lipid metabolism, and ultimately cardiovascular health.

Clinically, body composition significantly changes in men receiving ADT and ASI. ADT increases total fat mass, with subcutaneous adipose tissue increasing more than visceral adipose tissue (73). ADT also causes a loss of skeletal muscle mass and quality, which puts men treated with ADT at risk for sarcopenia and sarcopenic obesity (74). Adverse body composition changes occur in ~70% of men treated with ADT and the risk increases with age, but the individual vulnerabilities to body composition toxicity are not well understood (75). Human preadipocytes and adipocytes express AR, and murine studies demonstrated that androgens shift mesenchymal pluripotent cells towards a myogenic lineage and an AR-mediated pathway inhibits differentiation into adipocytes, which is mitigated with ASI treatment (76, 77). In human subcutaneous adipose tissue, androgens, via AR, inhibit adipogenesis where adipose stem cells normally would differentiate into preadipocytes and then into adipocytes, ultimately limiting adipocyte number and storage (78).

Androgens may also modulate lipolysis in a depot-specific manner (79). Adipose tissue regulates exposure to androgens in an autocrine manner by modulating levels of androgens via AKR1C, 17-βHSD, and SRD5A activity (79).

ADT and ASI impact endocrine and paracrine levels of insulin and adipokines, which worsens hemoglobin A1C control and exacerbates body composition changes (80). In murine models, germline *Ar* knockout reduces insulin sensitivity, increases leptin levels (a satiety hormone with other functions), and produces leptin resistance (81). In these same models, AR in the hypothalamus regulates leptin-mediated STAT3 signaling, and loss of AR impairs STAT3 nuclear localization in the arcuate nucleus potentially explaining leptin resistance (82). To date, the mechanism(s) underlying insulin resistance with ADT is unclear.

Ultimately, ADT increases total cholesterol, low-density lipoprotein, high-density lipoprotein, and the risk for cardiovascular disease (83). Clinical studies suggest that treatment with GnRH agonists is associated with an increased risk of cardiovascular disease compared with GnRH antagonists or orchiectomy (84). It is worth noting that the degree of cardiovascular risk with ADT varies between population-based studies and clinical trial cohorts where risk is actively managed by cardiologists (85-87). The aforementioned changes with ADT indirectly increase the risk for cardiovascular events, and preclinical studies also suggest a direct role of the androgen–AR axis in atherosclerotic disease. In murine models, a high-fat diet increases the size of atherosclerotic lesions in castrated mice compared with sham-operated mice, and subsequent testosterone supplementation in mice reduces the atherosclerotic lesions in castrated mice, if aromatase is active, suggesting in this case a protective role for the estrogen receptor (88). These findings were supported by other murine models of cardiovascular disease such as ApoE-deficient mice (89).

Bone and Muscle

AR also plays essential functions in the musculoskeletal system (90). Androgens stimulate longitudinal and radial bone growth, with an accelerated bone apposition in men during puberty, and are essential to maintain bone mass in adults (90). Conditional ablation of *Ar* in prepubertal and postpubertal mice results in reduced total body bone mineral density, bone volume fraction, and increased bone turnover, confirming that AR is required to support bone health in both young and adult mice (91). Bone homeostasis depends on the well-controlled balance between bone-forming (osteoblasts) and resorbing (osteoclasts) cells. Osteoblasts express AR at higher levels in cortical bone than trabecular bone, with no sex-related differences (92). Male mice with targeted deletion of *Ar* in mature osteoblasts or osteocytes have lower cancellous bone mass, but no cortical bone phenotype (91). AR activation stimulates osteoblast differentiation and proliferation, improves the production and organization of bone matrix, the biosynthesis of extracellular matrix proteins, and suppresses apoptosis (93, 94). AR is also expressed by osteoclasts; however, experimental evidence suggests that it plays an indirect role in modulating the biology of these cells, most likely by regulating their interactions with osteoblasts (95). As an example, low testosterone levels lead to increased secretion of receptor activator of nuclear factor kappa-B ligand by osteoblasts, which stimulates osteoclast resorptive activity (96). Interestingly, targeted deletion of *Ar* in the mesenchymal cell lineage, besides decreasing bone volume and trabecular number, shows an increased osteoclast number in the cancellous compartment, while targeted deletion of *Ar* in

myeloid cells does not show any bone phenotype (97). These results suggest that the effects of androgens on cancellous bone result from AR signaling in osteoblasts—not osteoclasts. Accordingly, osteoclast-specific knockout of *Ar* driven by cathepsin K-Cre does not alter the bone microarchitecture or osteoclast surface (98).

AR also critically regulates muscle mass and function. AR is expressed in several muscle cell types, including muscle fibers, fibroblasts, smooth muscle cells, and endothelial cells, with predominant expression in satellite cells (99). Conditional knockout of *Ar* in satellite cells affects fiber-type distribution, decreases force production of the limb muscles, and perineal muscle mass (100). Genomic *Ar* knockout in male mice shows decreased muscle mass, reduced force production, and increased fatigue resistance due to altered expression of molecular regulators that maintain myoblasts in a proliferative state and delay their terminal differentiation (101). Recent studies in myofiber-specific *Ar* knockout mice identified a fast-type, muscle-specific novel splicing variant of myosin light-chain kinase 4 as a target of AR in skeletal muscles (102). In addition, AR increases the reutilization of intracellular amino acids that favors protein synthesis and muscle fibers generation, including both type I and type II (103).

ADT side effects translate to bone fragility in patients (93, 104). A prospective study on ~50 000 prostate cancer patients identified a significantly higher fracture rate in men who underwent ADT compared with non-ADT (105), with a 21% to 37% increase in fracture risk in the absence of antiresorptive therapy (105). Other analyses on additional patient cohorts treated with ADT confirmed a higher risk of bone fractures (106, 107) and showed a significant decline of bone mineral density, with a mean decline of 1.6% to 3.7%, depending on the bone type, which is faster than the normal yearly bone loss rate for what is already an aging population (108). As noted above, a further contribution to androgen deprivation–dependent bone fragility is related to sarcopenia, the loss of muscle mass that is replaced by fat deposition (109). Sarcopenia has been shown to be a predictor of fracture risk (110). Taken together, these data indicate that targeting AR has detrimental side effects on body composition and bone quality. Whether targeting AR in bone cells directly impacts the ability of metastatic prostate cancer cells to form skeletal lesions is less clear.

Conclusions and Future Perspectives

AR is the central driver of prostate cancer and, thus, remains the primary therapeutic target for this disease. Research over the past decade has highlighted important roles for AR not only in prostate cancer cells, but also in other cell types. AR cancer cell–extrinsic functions within the tumor microenvironment as well as peripheral to the tumor impact the efficacy of anti-AR treatments and mediate on-target side effects (prostate cancer cell nonautonomous activity) of this class of drugs. As new technologies are deployed to help map AR functions across different tissue and cell types throughout disease progression, it is anticipated that we will be able to develop improved treatment combinations that optimize the therapeutic index for individual patients. For instance, while great strides have been made toward delineating AR's roles in T cells, AR's function in myeloid cells has remained more enigmatic, suggesting a need to better define AR functions in explicit myeloid subtypes while accounting for potential species-specific differences (eg, rodent vs human). Given the immunosuppressive roles of AR in T cells, but the potential immune-activating roles of AR in some myeloid cells, the ratio of certain myeloid cells to T cells could ultimately de-

termine the effectiveness of AR signaling inhibitors in the tumor immune microenvironment and, thus, sensitivity to immunotherapies. A more in-depth understanding of the myeloid subsets that promote disease progression, when they appear, and how they respond to AR-targeted therapy could aid in the development of novel treatment regimens capable of overcoming the immunosuppressive prostate cancer milieu.

Our understanding of how systemic AR inhibition impacts patient quality of life, and, conversely, how the patient's composition influences antitumor drug efficacy continues to evolve. It is anticipated that an improved understanding of AR's regulation and role throughout the body will allow us to move beyond the current “1 size fits all” approach for treating men with prostate cancer. With the advent of new therapies with better antitumor effects, patients are living longer. As such, greater consideration for how these therapies also impact quality of life and linked comorbidities is required to improve patient care in this growing population.

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Abbreviations

ADT	androgen deprivation therapy
AR	androgen receptor
ASI	androgen signaling inhibition
CAF	cancer-associated fibroblast
GnRH	gonadotropin-releasing hormone
ICT	immune checkpoint therapy
SMC	smooth muscle cell

Contributor Information

Andrew W Hahn, Department of Genitourinary Medical Oncology and the David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.

Bilal A Siddiqui, Department of Genitourinary Medical Oncology and the David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.

Javier Leo, Department of Cancer Systems Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA. The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX 77030, USA.

Eleonora Dondossola, Department of Genitourinary Medical Oncology and the David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.

Kaitlin J Basham, Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA.

Cindy K Miranti, Department of Cellular and Molecular Medicine, University of Arizona Cancer Center, University of Arizona, Tucson, AZ 85721, USA.

Daniel E Frigo, Department of Genitourinary Medical Oncology and the David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. Department of Cancer Systems Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA. Center for Nuclear Receptors and Cell Signaling, University of Houston, Houston, TX 77204, USA. Department of Biology and Biochemistry, University of Houston, Houston, TX 77204, USA.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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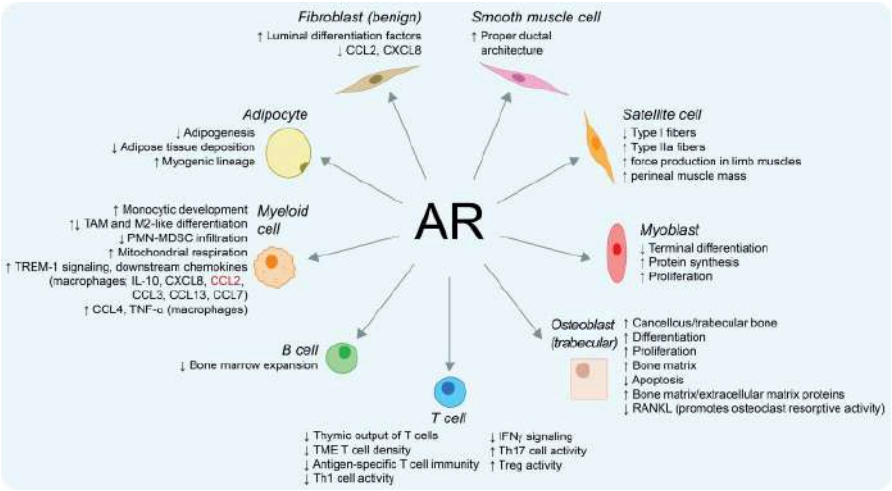
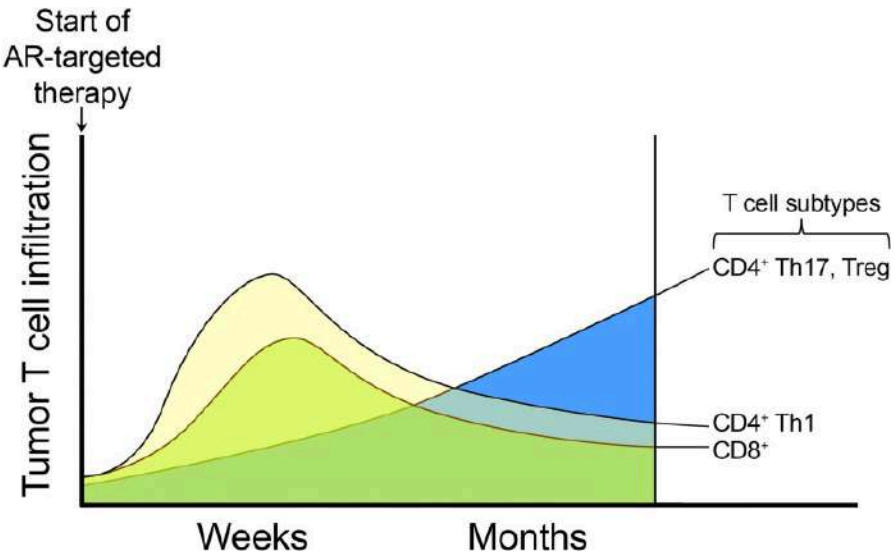
Figures and Tables

Figure 1.



Cancer-cell extrinsic roles for AR in prostate cancer. Shown are direct AR functions in indicated cell types that can impact prostate cancer patients. Text in red indicates that contradictory data exists (CCL2 has been reported to be both positively and negatively regulated by AR in macrophages). AR, androgen receptor; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; IL, interleukin; PMN-MDSC, polymorphonuclear-myeloid–derived suppressor cell; RANKL, receptor activator of nuclear factor kappa-B ligand; TAM, tumor-associated macrophage; Th, T helper; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; TREM-1, triggering receptor expressed on myeloid cells-1.

Figure 2.



Effects of AR inhibition over time on T cell infiltration into the prostate and prostate tumor. Inhibition of AR leads to an initial increase in the infiltration of anticancer T cells such as $CD8^+$ T cells and $CD4^+$ Th1 T cells. However, this initial influx of anticancer T cells is eventually followed by the emergence of procancer $CD4^+$ Th17 and regulatory T cells (Tregs).