Chapter 7
Resistance to Castration – Resistance to Drugs

Stefania Staibano

Abstract Up to 70 % of newly diagnosed patients with advanced prostate cancer (PCa) will progress to castration-resistant prostate cancer (CRPC) and, in most cases (from 50 to 70 %), will develop hematogenous bone metastasis. Once PCa cells spread to the skeleton, cancer-related death becomes inevitable, with a death burden of more than 28,000 cases in 2012, in the United States (Semenas et al, Curr Drug Target, 13(10):1308–1323, 2012).

To date, therapeutic regimens are unable to revert this fatal progression (Semenas et al, Curr Drug Target, 13(10):1308–1323, 2012).

Thus, PCa bone metastatic prostate cancer still represents a major clinical challenge.

Prostate cancer biology is tightly linked to AR, which regulates epithelial proliferation and suppresses apoptosis both in normal and in cancer prostate tissue, and is involved in the progression of the disease toward a castration-resistant state (Hodgson et al, World J Urol, 30(3):279–285, 2012). Our knowledge of the molecular mechanisms, responsible for the acquired resistance to ADT in prostate cancer, has exponentially progressed during the last years. For instance, we have recently learnt that it may be associated with the occurrence of AR splicing variants (Hu et al. 2011).

Surgical castration has shown to induce regression of advanced disease 40-years before the cloning of androgen receptor (AR) (Huggins et al, Arch Surg, 43:209–223, 1941; Lubahn et al, Science, 240:327–330, 1988).

Since then, hormonal therapy was held over as the main available therapeutic option for aggressive prostate cancers. In the last decade, however, chemotherapy was introduced to targeting the epithelium of metastatic, hormone-resistant prostate

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cancer (Pinto et al, Tumour Biol, 33(2):421–426, 2012; Hodgson et al, World J Urol, 30(3):279–285, 2012). The cytotoxic conventional drug Docetaxel was approved by the Food and Drug Administration in 2004, and still represents the standard first-line treatment for patients with castration-resistant prostate cancer (CRPC) (Sartor et al, Oncologist, 16(11):1487–1497, 2011). It produces sensible palliative effects on bone-metastasis-related symptoms, but prolongs only modestly the survival of patients (Hodgson et al, World J Urol, 30(3):279–285, 2012; Tannock et al, N Engl J Med, 351:1502–1512, 2004; Petrylak et al, N Engl J Med, 351:1513–1520, 2004). Docetaxel acts mainly by inducing apoptosis of target epithelial cells. The common intrinsic defects of mCRPC in apoptosis pathways, such as BCL-2 overexpression and/or phosphatase and tensin homolog (PTEN) loss (Mathew, Dipaola, J Urol, 178:S36–S41, 2007; Galsky, Vogelzang, Ann Oncol, 21:2135–2144, 2010), may constitute the rationale of the unsatisfactory rate of cure attributable to this drug (Srigley et al, Histopathology, 60(1):153–165, 2012). In recent years, similar effects on survival have been demonstrated also for several other chemotherapeutic agents, such as mitoxantrone, etoposide, cisplatinum, vinblastine–estramustine and taclitaxel.

Following progression after treatment with docetaxel, new cabazitaxel (XRP6258)-prednisone treatment regimens have led to a significantly longer overall survival, and other novel agents are currently being evaluated, including the cell-based immunotherapy sipuleucel-T, the androgen biosynthesis inhibitors abiraterone acetate and MDV3100, the chemotherapic Cabazitaxel, as well as the radionuclide alpharadin/Radium 223 (bone microenvironment targeting agents) (Sartor et al, Oncologist, 16(11):1487–1497, 2011; Liu et al, Front Endocrinol (Lausanne), 3:72, 2012; Antonarakis, Armstrong, Prostate Cancer Prostatic Dis, 14(3):206–218, 2011). To date, they seem to offer a survival advantage to patients, and look promising to improve the prognosis of metastatic CRPC.

However, the real clinical benefit of these systemic therapies remains still transient, probably due also to the well-known clonal heterogeneity of advanced prostate cancers, and the overall survival of patients that holds frustratingly steady.

The high cost of these therapies and the increasing complexity of clinical decision making, further underscore the need to multiply the efforts to develop more potent chemotherapy agents and/or novel AR/inhibitors agents that may better overcome resistance mechanisms to existing therapies (Liu et al, Front Endocrinol (Lausanne), 2012; Hodgson et al, World J Urol, 30(3):279–285, 2012; Armstrong, George, Urol Oncol, 26:430–437, 2008; Schrijvers et al, Adv Ther, 27:285–296, 2010).

Several recently developed drug candidates, directed against the metastatic cancer microenvironments or niches, show promising results in this direction (Hodgson et al, World J Urol, 30(3):279–285, 2012).

The efficacy of the standard-of-care therapeutic intervention directed to mCRPC will be greatly improved by our increasing understanding of molecular mechanisms of the acquired resistance to ADT and chemotherapy, which is expected to provide valuable insights also to new unfailing biomarkers of resistance, therapeutic response and disease progression of prostate cancer, allowing us to personalize the

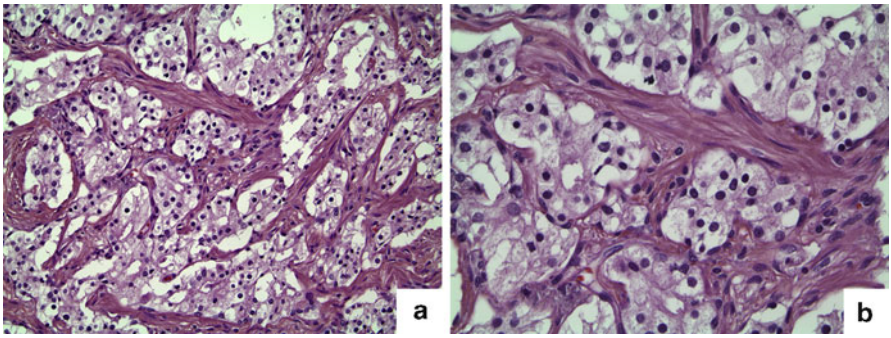


Fig. 7.1 Therapy modifications. (**a**) and (**b**) Two examples of therapy-modified neoplastic cells characterized by nuclear pyknosis, hyperchromasia, cytoplasmic clearing and vacuolation. Chronic inflammation usually flanks epithelial tumor changes

therapy for the single patients with mCRPC (Liu et al, Front Endocrinol (Lausanne), 3:72, 2012; Antonarakis and Armstrong, Prostate Cancer Prostatic Dis, 14(3):206–218, 2011).

The knowledge of the molecular mechanisms underpinning prostate cancer progression is changing dramatically our therapeutic approach to its advanced, metastasizing phase, opening up the chance to design and develop novel agents targeting the multiple pathways responsible for the lethal cancer phenotype, in a more efficient and safer manner (Corcoran and Gleave, Histopathology, 60(1): 216–231, 2012).

During the last decade, the landscape of treatment of prostate cancer has registered dramatic changes, due to the progressive advances in molecular biology. However, the acquired resistance to AR- and/or chemotherapy, so far, represents the unresolved cause of treatment failure in metastatic castration-resistant prostate cancers (Sun et al. 2012; El-Amm and Aragon-Ching 2013).

From the early seminal studies of Huggins and Hodges (1941) demonstrating the androgen-dependent nature of prostate cancer, maximal androgen blockade therapy still constitutes the cornerstone for the initial treatment for advanced disease (el-Rayes and Hussain 2002; Beekman and Hussain 2008) and, its fall-out on clinical response of patients, endlessly continues to be a matter of study (Srigley et al. 2012).

The effects androgen deprivation therapy (ADT) has on prostate tissue are strictly related to its duration, and become strikingly evident after 3 months of treatment. They are constituted by the overall decrease in number of the epithelial cancer cells, either clustered in small, atrophic glands, or present as thin cords/individual tumor cells. Therapy-modified neoplastic cells are, in fact, characterized by nuclear pyknosis, hyperchromasia, cytoplasmic clearing and vacuolation. Chronic inflammation usually flanks epithelial tumor changes (Humphrey 2003; Petraki and Sfikas 2007; Têtu 2008; Evans et al. 2011; Têtu et al. 1991; Bullock et al. 2002; Vallancourt et al. 1996; Civantos et al. 1995; Armas et al. 1994) (Fig. 7.1).

The rationale for ADT is that the competitive binding of the androgen receptors causes the block of testosterone-driven proliferation of prostate cancer cells, leading to apoptosis and clinical remission for about 18–36 months (Pienta and Bradley 2006; Beekman and Hussain 2008).

FDA-approved AR inhibitors for ADT lead to the achievement of castrate levels of circulating testosterone, corresponding to at least <50 ng/dL (Morote et al. 2007). Gonadal suppression can also be further supported by medical therapy targeting the hypothalamic-pituitary-testicular axis, such as the synthetic gonadotropin-releasing hormone (GnRH) agonists, which bind to GnRH pituitary receptors. This binding results in an initially increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) surge, causing a transient elevation of circulating testosterone, but leads, from one to two weeks after the onset of therapy, to GnRH receptors down-regulation, decreased LH and FSH production, followed by the final drop of testosterone to castrate level.

Several approaches to ADT have been proposed, since its introduction in the clinics. They range from surgical to pharmacological gonadal suppression, from monotherapy to combined ADT (Tannock et al. 2004), from early to delayed, from intermittent to continuous, and from primary gonadal suppression to peripheral blockade (Beekman and Hussain 2008) both at high and low doses (Chodak et al. 1995; Scher et al. 1997; Tyrrell et al. 2005).

Randomized phase III trials actually indicate that primary gonadal suppression, by continuous androgen deprivation therapy dosing, seems reliable as the standard for treating advanced prostate cancers (Langenhuijsen et al. 2013).

To date, besides the substantial absence of well-designed randomized trials analyzing the overall survival of patients, the most widely spread treatment, in this scenario, is the hormonal therapy with LH-RH analogues considering that the attractive alternative hormonal treatments (intermittent treatment, antiandrogen monotherapy, or antiandrogen plus 5 alpha reductase inhibitors) should be still evaluated with caution due to the short time experience (Antolin et al. 2012).

However, to date, patients receiving androgen deprivation therapy develop castration-resistant prostate cancer (CRPC) recurrences and, a surprisingly frequent finding shows that, even with stable castrate levels of serum testosterone, prostate cancer bone metastases continue to rely on androgen signaling for their growth (Scher and Sawyers 2005; Montgomery et al. 2008).

Starting from the hypothesis that progression to castration resistance is a function of permanent androgen withdrawal, it has been postulated then that intermittent regimens of androgen deprivation therapy, exposing prostate cancer cells periodically to androgens, may help maintain their androgen sensitive/dependent state. This approach is attractive, as it may minimize adverse side-effects of long-standing androgen deprivation.

Once again, clinical evidences frequently disregard the expected results. This could be due to the finding that AR-dependent signaling almost always occurs in CRPC, but it shows a substantial functional heterogeneity in tumor tissue (Antonarakis and Armstrong 2011).

Potential pathogenetic mechanisms could be represented by intratumoral AR amplification, further (second) mutations in the AR gene, that allow activation; low androgen levels or other endogenous steroids; truncated or alternatively spliced AR transcripts; constitutively activated AR; changes in levels of AR cofactors involved in ligand-independent activation of AR signaling; increased expression of enzymes involved in androgen synthesis; androgen synthesis by CYP17-independent pathways (and genetic changes in the *CYP17A* gene preventing its inhibition by the CYP17 inhibitors abiraterone and Orteronel (TAK-700)) (Antonarakis and Armstrong 2011); intracellular conversion of adrenal androgens to testosterone and dihydrotestosterone (Mostaghel et al. 2009); vicious loops mediated by cytokines and growth factors (Scher and Sawyers 2005; Debes and Tindall 2004; Feldman and Feldman 2001; Mohler 2008; Taplin 2008).

In other words, all these postulated processes allow prostate cancer cells metabolism to shift from endocrine "physiological" sources of androgens (testes and adrenal glands) to paracrine, autocrine, and intracrine aberrant, intratumoral sources.

Even considering these eveniences, tumors may still respond to the agents that block AR signaling within the tumor microenvironment. Second-generation AR-antagonists are available, including MDV3100.

MDV3100 is an oral non-steroidal AR antagonist with a binding affinity for the AR, which is five times greater than that of bicalutamide and shows a strong activity as AR-antagonist in castration-resistant tumors, even in the setting of overexpressed or constitutively activated AR. In addition, it does not exhibit any measurable agonistic activity, and reduces the AR translocation from the cytoplasm into the nucleus, with resultant tumoricidal activity as opposed to the cytostatic activity that first-generation anti-androgens (Antonarakis and Armstrong 2011).

Some additional androgen receptor (AR)-directed therapies with higher receptor affinity and specificity are currently under evaluation in clinical trials, and hold promises, in the near future, to improve the outcome of patients with advanced prostate cancer.

Prostate cancers with lower AR activity, or those exposed to prolonged periods of androgen suppression, may show up-regulation of other oncogenic pathways, including Src kinase (Park et al. 2008), clusterin, epithelial to mesenchymal transition pathways, PI3K, c-MET and others (Antonarakis and Armstrong 2011).

This has fueled the preclinical and clinical exploration of myriad molecular targets comprising alternative oncogenic pathways, targeting angiogenesis, tumor microenvironment, cell growth and proliferation, apoptosis, cell nutrition, DNA repair and epigenetic regulation (Hodgson et al. 2012).

So, we now hold a growing number of epithelial, stromal and epithelial-stromal targeting therapeutics. Specific biomarkers permit quantization and localization of therapy-induced effects within each compartment. For example, PSA levels reflect modulation of cancer epithelial cells, bone-specific alkaline phosphatase (BAP) levels reflect modulation of osteoblast activity, and urinary N-telopeptide (uNTx) levels reflect modulation of osteoclast activity (Cook et al. 2006).

The first therapy regimens with mitoxantrone and prednisone, was established in 1996 (NCCN 2011; Tannock et al. 2004). From 2004, the standard chemotherapy for the first-line treatment of patients with metastatic CRPC considers the use of docetaxel and prednisone (Petrylak et al. 2004; Tannock et al. 2004; Pinto et al. 2012).

At the time of writing we have great expectations concerningthe results of a randomized phase III trial comprising 1,500 patients with progressing mCRPC. The trial was performed comparing standard-schedule docetaxel and prednisone with and without the multi-targeted kinase inhibitor dasatinib, a molecule active against Src signaling. Src is a non-receptor tyrosine kinase that, in prostate cancer cells, is associated with testosterone-mediated cell proliferation; its overexpression is considered an important mediator of the transition to androgen-independent growth (Lee et al. 2001, 2004).

Src phosphorylation induces, in addition, the expression of pro-angiogenic factors, including VEGF, which, in turn, can activate Src also in endothelial cells, mediating the increases in vessels permeability and tumor-associated neo-angiogenesis (Park et al. 2007; Araujo and Logothetis 2010; Agarwal et al. 2012).

Among the therapeutic agents specifically targeting tumor microenvironment, several have shown target effects, but none has demonstrated yet any beneficial impact on disease progression or overall patients survival (Saad et al. 2002; Mathew et al. 2007; Carducci et al. 2007), when used as monotherapy in patients with mCRPC. This was the case of zoledronic acid (osteoclast inhibitor), imatinib (multitarget tyrosine kinase inhibitor), and atrasentan (selective endothelin, a receptor antagonist, which inhibits osteoblast proliferation).

The use of the osteoclast suppressor humanized monoclonal IgG2 antibody, Denosumab, significantly extended bone metastasis free survival by 4.3 months compared with placebo, delaying the onset of radiation to the bone. Denosumab is directed against RANKL (Schwarz and Ritchlin 2007), the receptor activator of NF-κB ligand, which is produced by bone marrow stromal cells and osteoblasts and stimulates osteoclasts differentiation, activation, and survival, RANKL is overexpressed by bone metastatic prostate cancer epithelial cells. The rationale of this therapeutic approach resides in the concept that, although prostate cancer bone metastases are osteoblastic, the development of these lesions involves an osteolytic response mediated by osteoclasts. However, the overall survival of patients was similar in both arms of the trial (Fizazi et al. 2011).

Endothelin antagonists represent another promising new class of stromal-targeting agents (Pinto et al. 2012). They are directed against the Endothelin-1 (ET-1) signalling peptide, which is involved in prostate cancer progression. ET-1 binds to and activates the ET_A receptor, which is overexpressed on prostate cancer cells and osteoblasts surface. ET-1 is overexpressed in prostate cancer cells as compared with benign tissue, and ET_A activation in tumors, has been shown to promote tumor cell proliferation and invasion, pro-angiogenic factors secretion, and apoptosis resistance (Nelson et al. 1996, 2003). In osteoblasts, ET_A activation promotes proliferation, survival, invasion, secretion of pro-angiogenic factors, resistance to apoptosis, and generation of osteoblastic metastatic disease (Guise

et al. 2003). In preclinical models, several newly-generated inhibitors of ET-1 signalling have shown to inhibit tumor cell proliferation and invasion, as well as the metastases development (Growcott 2009).

Nevertheless, the real improvement of patients survival, as well as the eventual correct protocol regimen, are still to be clarified (Pinto et al. 2012).

Thus, at present, stromal-targeting agents are commonly used in combination with epithelial-targeting chemotherapics.

Among the multiple self-protective molecular mechanisms acting in mCRPC, it has recently emerged the role of clusterin (Antonarakis and Armstrong 2011). Clusterin (CLU) is a stress-induced chaperone protein overexpressed in prostate tumors treated with androgen ablation or chemotherapy (Mita et al. 2009; de Bono et al. 2010; Zoubeidi et al. 2010). It is considered of importance in the cytoprotective defense from radio- and chemotherapy of the mCRPC (Tiligata et al. 2002).

Overexpression of CLU in prostate cancer is linked to the emergence of the treatment-resistant phenotype. In animal models, it is consistently up-regulated in castration-resistant regrowth (Miyake et al. 2000). In human tissue, the expression of CLU increases in hormone-naïve prostate cancer with increasing Gleason grade, and is up-regulated within weeks of androgen withdrawal (July et al. 2002). CLU binds to (and stabilizes) a wide variety of client proteins, and promotes cell survival and transformation through multiple mechanisms, including activation of the extracellular signal-related kinase (ERK) and Akt pathways, inhibition of ER stress, suppression of Bax activity, and release of nuclear factor kappaB (NF-κB) inhibition (Zoubeidi et al. 2010).

Expression of CLU is up-regulated by a number of different mechanisms, including stress-activated transcription factors (e.g. heat-shock factor-1), in response to endoplasmic reticulum (ER) stress, and as a downstream response to cytokines and insulin-like growth factor-1 receptor (Zellweger et al. 2001).

In prostate cancer cell lines, inhibition of clusterin resulted associated with a greater susceptibility to cytotoxic agents and radiation (Gleave et al. 2001; Zellweger et al. 2002). Therapeutic approaches with second-generation antisense anti-clusterin oligonucleotides (custirsen, OGX-011) (Chi et al. 2008), have produced the increase of sensitivity to androgen deprivation as well as chemotherapy in prostate cancer cell lines and xenograft models (Beer et al. 2004; Berthold et al. 2005).

Evaluation of OGX-011 in prostate cancer continues in a large phase III trial (SYNERGY) that is currently accruing. An anticipated 800 men with mCRPC will be randomized to treatment with standard-schedule docetaxel and prednisone, with or without OGX-011 640 mg by weekly intravenous infusion, until disease progression, unacceptable toxicity, or the completion of ten cycles. The primary endpoint is overall survival, and study completion is expected in early 2014 (Fig. 7.2).

Very interestingly, chemotherapy with genotoxic chemotherapy (mitoxantrone and docetaxel) has been shown to generate a response in micro-environmental stromal cells, promoting prostate cancer cell growth and resistance to subsequent cycles of treatment. This stromal response is due to DNA damage in fibroblasts

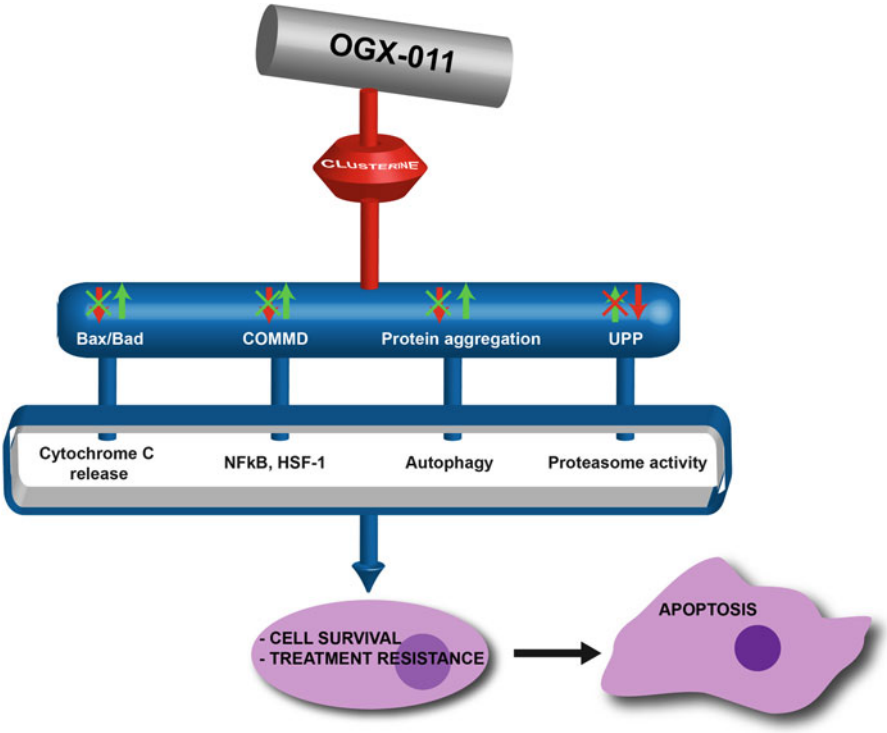


Fig. 7.2 Novel therapies designed to target non-ARmediated pathways: chaperone proteins. Clusterin, a chaperone protein, in prostate cancer cell lines, if overexpressed, results in androgen-independent growth, while clusterin gene silencing induces apoptosis and reduction in growth. Its expression is upregulated in patients with prostate cancer who have received androgen-deprivation therapy. Custirsen (OGX-011) is an antisense inhibitor of clusterin that acts suppressing clusterin expression in tumor tissue, when administered to patients with localized prostate cancer

and smooth muscle cells leading to a "30-fold" overproduction of WNT16B, which is secreted (and interacts) with adjacent prostate cancer cells, facilitating their proliferation, invasion, and therapy resistance (Sun et al. 2012) (Fig. 7.3).

7.1 What Considerations Can Be Drawn Basing on This Information?

Without any doubt, recent advances in the knowledge of prostate tumor biology, have lead us to no longer consider prostate cancer as a disease arising only from abnormally proliferating epithelial cells, but rather as the result of intricate interactions between prostate cancer epithelial and stromal cells. This has produced remarkable achievements in the development of therapy, particularly for metastatic castrate-resistant prostate cancer.

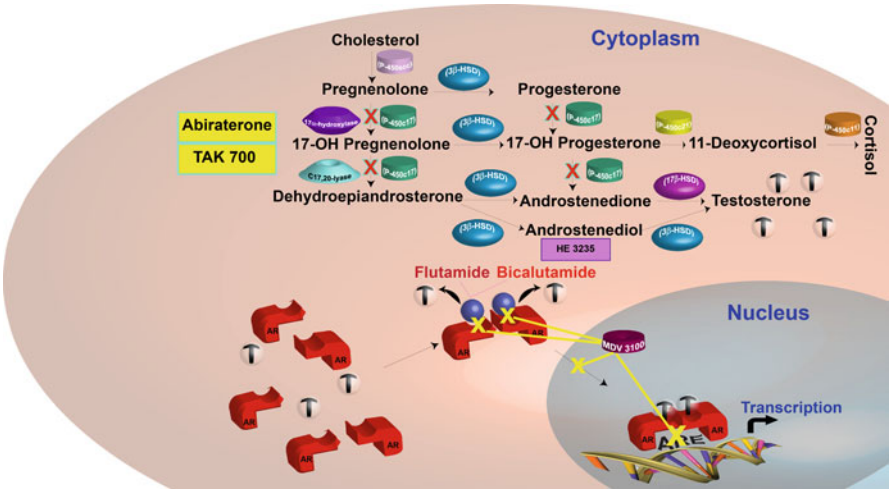
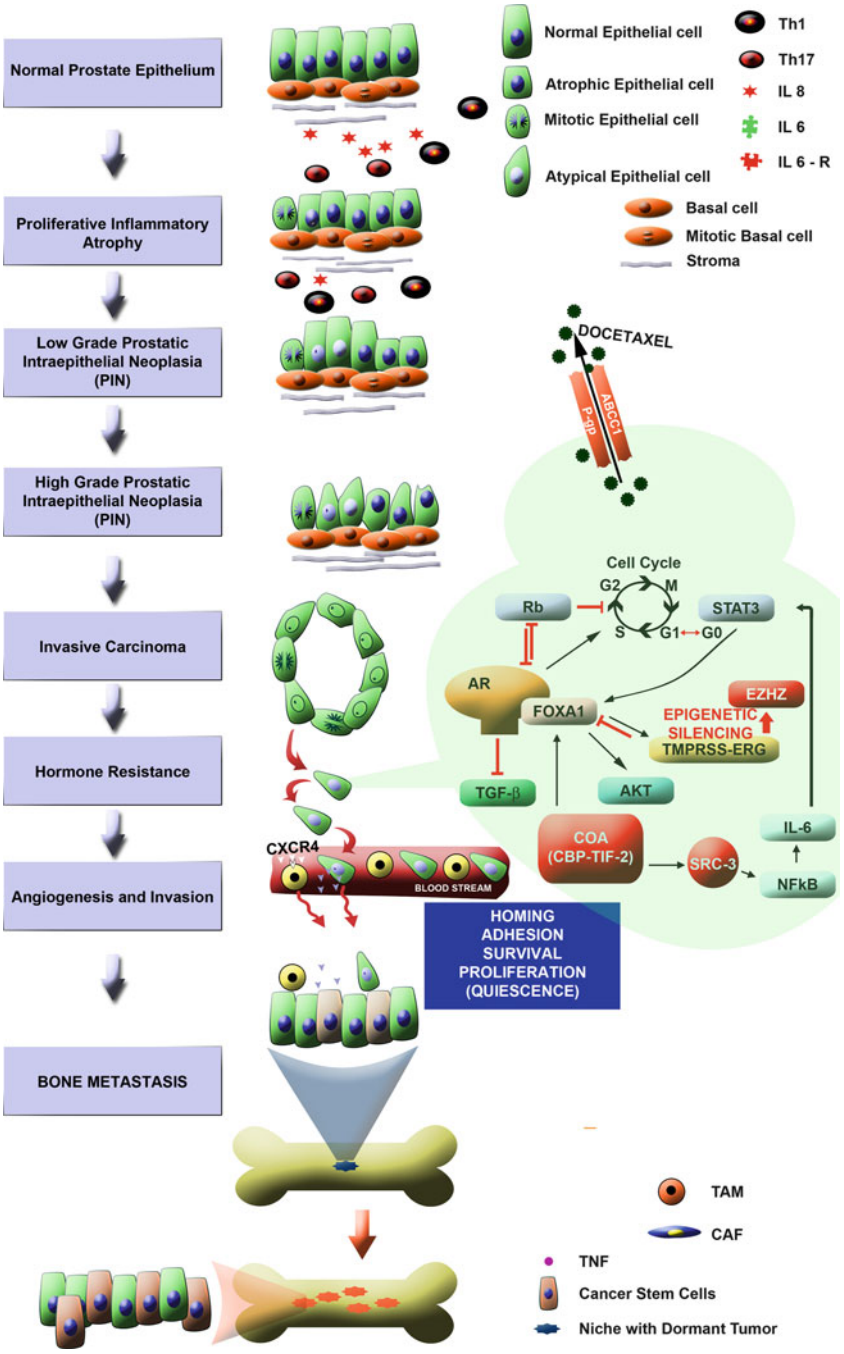


Fig. 7.3 Therapies designed to target AR-mediated pathways. Persistent AR activation is an important mediator of disease progression in CRPC and mechanisms involved include AR gene amplification or overexpression; AR gene mutation; enhanced AR signal transduction mediated via coactivators; and endocrine or autocrine activation of the AR, for example, by adrenal androgens or intratumoral production of dihydrotestosterone (DHT). AR-directed approaches include drugs that antagonize the AR or that reduce of androgen precursors. Among AR antagonists are included bicalutamide and flutamide, that inhibit the binding between AR and testosterone, and MDV3100, which exert its function by inhibiting interaction between testosterone and AR and between AR-testosterone complex and the ARE-sequences on DNA. Therapies that decrease androgen production are also being developed. Abiraterone acetate is a selective and irreversible inhibitor of cytochrome P450 (CYP450)c17, involved in androgen synthesis. TAK-700 is a novel CYP450c17 inhibitor similar to abiraterone

The goal of the next-coming therapy, then, will be to disrupt the crosstalk between epithelial and cancer cells and their microenvironment, through the use of new drugs targeting multiple signaling pathways, from androgen receptor signaling, to kinase receptor signaling, and immune surveillance. At last, we now hold a paramount variety of targets that can be manipulated to overcome AR- and chemo-resistance, and different strategies emerge for inhibiting their function.

The increasing knowledge of the crystal structures of the ligand-sites, or specific domains, of each protein active in the induction and maintenance of prostate cancer aggressiveness and therapy resistance, allows the progression of design and synthesis of novel inhibitors. By converse, in other instances the inhibition of metastasizing ability of cancer cells may be reached through the targeted disruption of protein transcription with antisense oligonucleotides.

In addition, new therapies may also consider the charming chance of a different delivery of the "old" drugs (Batist 2007; Gabizon et al. 2003; Ewer et al. 2004; Koukourakis et al. 2000). For instance, therapeutic nanoparticles targeted against the prostate-specific membrane antigen (PSMA) protein, which is expressed on the surface of prostate tumor cells that accumulate in tumors while bypassing healthy cells, have shown promising results in ongoing clinical trials.


Normal Prostate Epithelium
Proliferative Inflammatory Atrophy
Low Grade Prostatic Intraepithelial Neoplasia (PIN)
High Grade Prostatic Intraepithelial Neoplasia (PIN)
Invasive Carcinoma
Hormone Resistance
Angiogenesis and Invasion
BONE METASTASIS
Normal Epithelial cell
Atrophic Epithelial cell
Mitotic Epithelial cell
Atypical Epithelial cell
Th1
Th17
IL 8
IL 6
IL 6 - R
Basal cell
Mitotic Basal cell
Stroma
DOCETAXEL
ABCC1
P-gp
Cell Cycle
G2
M
S
G1↔G0
Rb
STAT3
AR
FOXA1
EZHZ
EPIGENETIC SILENCING
TMPRSS-ERG
TGF-β
AKT
COA (CBP-TIF-2)
SRC-3
IL-6
NFkB
CXCR4
BLOOD STREAM
HOMING
ADHESION
SURVIVAL
PROLIFERATION
(QUIESCENCE)
TAM
CAF
TNF
Cancer Stem Cells
Niche with Dormant Tumor

Nanoparticles homing docetaxel have been designed at Massachusetts Institute of Technology (MIT) and Brigham and Women's Hospital in Boston, and the early results have shown their selective accumulation at tumor sites, without side-effects, producing tumors shrunk even at lower drug doses than those usually administered (Corcoran and Gleave 2012).

There is great expectation on the successful therapeutic effect of an impressive number of new drugs in the near future, which could be safer and more manageable than old cytotoxic agents, and then could be used also at the earliest phases of prostate cancer, before it becomes lethal.

However, despite impressive preclinical activity, to date, most targeted therapies have failed in early clinical development (Corcoran and Gleave 2012). Pathway redundancy, target mutation, difficulty with drug delivery, toxicity, or overestimation of a target's importance in preclinical models, could all be responsible for this. Since international guidelines are obviously lacking, the gamble is, therefore, either to identify the more reliable targets to be translated into clinically useful drugs, and to design a rational approach to optimal treatment sequencing or even a combination therapy with these drugs (El-Amm and Aragon-Ching 2013).

Notwithstanding the several new therapies that have been shown to extend survival of mCRPC patients, but none of these approaches are curative, and annual mortality rates, from prostate cancer in the Western Countries, remain unacceptably high (Antonarakis and Armstrong 2011).

Fig. 7.4 Alterations in AR function in PCa and the development of CRPC. Following androgen ablation, increased AR levels and a dramatic shift in AR function is observed ultimately leading to the development of CRPC. AR binding sites (AR cistrome) are frequently marked by specific chromatin modifications introduced by pioneer factors as FOXA1, prior to hormone treatment. FOXA1 ablation causes massive reprogramming of the AR cistrome and consequentially its function with a survival and growth advantage. Androgens promote proliferation through signals that modulate critical regulators of the cell cycle. For the most part, the AR regulates the cell cycle through induction of signals that regulate G1-S phase transition through the promotion of G1 cyclin-dependant kinases (CDKs) and inhibition of the retinoblastoma (Rb) tumor suppressor gene. AR coregulators, such as SRC3, stimulate or decrease AR activity in a promoter specific manner. Elevated levels of SRC-3 are expressed in primary tumors. To activate AR transcriptional activity, SRC-3 coactivates AP1 that positively regulates Akt levels, leading to increase in proliferation and reduced apoptosis. Moreover, SRC-3 stimulates cellular motility by activating focal adhesion kinase signaling and invasion by activating AR-dependent expression of matrix metalloproteinases 2 and 13. IL-6 potentiate AR function and increased levels are associated with androgen independent growth, resistance to chemotherapeutic drugs and neuroendocrine differentiation. Continuous activation of the NF-kB pathway inhibits prostate regression following castration, maintains nuclear AR and sustains epithelial proliferation. TGF-b and AR signaling cooperate to maintain the differentiated state of the stroma in the benign prostate. In malignant epithelial cells, AR suppresses TGF-b receptor II (TbR-II) transcription and reduces TGF-b1 driven apoptosis, suggesting that AR action in malignant epithelial cells provides a growth advantage by suppressing TGF mediated pathways. CTC have the same TMPSS2-ERG fusion status as primary tumor and its expression is significantly increased by AR signaling. Overexpression of the oncogenic transcription factor ERG causes expression of epigenetic factors such as the methyltransferase EZH2 that epigenetically silences differentiating factors and tumor suppressors

The imperative goal for advanced prostate cancer therapy will be to successfully hit the specific driver mutations responsible for AR- and/or drug-resistance of advanced, metastasizing prostate cancer (Gerlinger et al. 2012). Many questions of interest have still to be properly addressed. The first refers to the optimal treatment of heterogeneous tumors harbouring different levels of the target mutation, which deserves to set up new personalized treatment algorithms based on the results of the genetic profiling of patients (Dora Dias-Santagata et al. 2010). In addition, we have to be aware that AR inhibition/chemotherapeutic drugs, as well as radiation therapy, may induce new advantageous mutations in prostate cancer cells, which after an initial positive clinical response, may increase again their survival and resistance (Semenas et al. 2012).

The future direction of prostate cancer care, then, will rely not only on our ability to detect and hit the molecular patterns responsible for the AR/chemotherapy-resistant phenotype of advanced, metastasizing cancers, but also on the chance to really personalize and potentially change therapy when resistance eventually recurs (Fig. 7.4).

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