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Review Article

Novel Therapeutic Approaches for Metastatic Castrate Resistant Prostate Cancer

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Abstract

Metastatic prostate cancer remains an incurable disease since novel anti-androgens mildly increase the survival of patients leading to a stage with very limited therapeutic options. Rapidly proliferating prostate cancer cells maintain survival under hormonal therapy through activation of alternative oncogenic signaling regulating cellular activities mediating growth, proliferation and migration. Anabolic activities regulated by oncogenic pathways such as c-Myc and Akt have been found to promote prostate cancer growth and targeting aerobic glycolysis and lipid synthesis have been proposed as novel therapeutic approaches for patients with metastatic hormonal resistant prostate cancer. Rapid proliferation of progressive disease is associated with accumulation of DNA damage rendering inhibition of DNA damage repair pathways a particularly effective approach to target aggressive hormonal resistant disease. The supply of oxygen and nutrients is critical for the survival and growth of proliferative and aggressive disease rendering angiogenesis a highly important aspect of cancer cells' survival in this stage of disease. The aim of this review was to summarize the current knowledge about targeting these three pathways in the metastatic hormonal resistant prostate cancer.

Keywords: Prostate cancer; Anabolism; DNA damage; Angiogenesis

Introduction

Prostate Cancer (PCa) is the most frequently diagnosed cancer in men in the western societies [1] and despite the fact that the minority of patients is presented with metastatic disease it remains the second leading cause of cancer associated death in the same population [1]. It is known that primary PCa mainly managed with surgery, radiation or surveillance has excellent prognosis [2] while, metastatic disease usually in bones remains an incurable disease with variable course. In particular, patients who present with metastases are treated with systemic hormonal therapy resulting in a transient remission which is almost always followed by disease's progression [3]. This state is known as Castrate Resistant PCa (CRPC) and is related to poor prognosis and mean survival time of less than 20 months [4]. These data clearly suggest that the mortality of patients with PCa is mainly attributed to the high mortality rates of patients with metastatic disease rendering the management of this state of disease critical to change the course of PCa.

Particularly CRCP is defined as PCa progression despite serum testosterone levels of less than 20ng/dL. The mainstay of therapy for this stage of disease is chemotherapy with docetaxel or cabazitaxel [5,6]. Two novel agents, Enzalutamide, which inhibits Androgen Receptor (AR) signaling, and Abiraterone Acetate, which targets the androgen biosynthesis by adrenal glands, tumor microenvironment and cancer cells have been recently approved for treatment of chemotherapy naïve patients with metastatic CRPC [7,8]. The introduction of these novel agents increased the survival of these patients by 4-5 months but almost all of them progress in a state of disease with a very narrow range of treatment options [7,8] Of note, a novel inhibitor of AR, ARN-509 which was found to be more effective compared to Enzalutamide in pre-clinical studies [9] is currently evaluated in clinical trials [10]. Finally, Ra 233 (Xofigo) has been approved for the treatment of patients with mCRPC without extension of the metastatic disease in viscera [11]. Based on these advances, the survival of patients with mCRPC remains relatively poor and the therapeutic options for patients who develop resistance to novel anti-androgens are very restricted while there is no evidence from clinical trials that chemotherapy remains effective at this stage of disease.

Plethora of research groups focus on the discovery of novel therapies using single agents or combinational approaches for these patients evaluating multiple pathways up-regulated in CRPC cells [12]. The identification and development of strategies to target pathways that are specifically critical for the survival of aggressive PCa cells with hormonal resistance features could substantially improve the survival of these patients. However, one of the main considerations related to the discovery of novel targets is the presence of numerous cross-talks between oncogenic signaling providing survival benefits in cancer cells. The discovery of particular biological activities downstream of these pathways may give us the opportunity to develop novel agents acting by-passing the cross-talks developed in cancer cells.

The development of aggressive tumors has been linked with the acquisition of particular characteristics dependent on exceptional intracellular biologic activities. In particular, aggressive cancer cells are rapidly growing and proliferating with (i) increased needs for macromolecular synthesis (ii) accumulating numerous genetic alterations leading to genomic instability and (iii) promoting angiogenesis in the microenvironment not only for survival purposes

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but also for the development of distant metastasis. Most notably in the case of PCa, it has been reported that small percentage of these tumors present up-front resistance to hormonal therapy, develop visceral metastases and overall demonstrate very aggressive behavior, and have discrete molecular and histological features [13]. In order to develop therapeutic strategies against these tumors, the identification and understanding of those cellular activities that are critical for their survival is a necessity and can lead to the introduction of novel approaches for the improvement of survival in these patients.

The aim of this review was to summarize the current literature focusing on novel agents targeting biological processes critical for the survival of hormonal resistant PCa cells proposing new therapeutic approaches for patients with CRPC.

Aerobic Glycolysis and Lipid Synthesis

It is well known that highly proliferative cells need to generate and accumulate macromolecules such as proteins, nucleic acid and lipids to preserve growth and proliferation. The reprogramming of the metabolic pathways in cancer cells driving to increased glucose uptake favoring macromolecular synthesis instead of oxidative phosphorylation in the presence of adequate oxygen concentration is known as aerobic glycolysis [14]. It has been shown that critical mediators of aerobic glycolysis such as Hexokinase 2 (HK2), which promotes the cellular glucose uptake [15], and Fatty Acid Synthase (FASN) which catalyzes the final step of de novo lipid synthesis [16] are implicated in the progression of PCa. Indeed, Massie et al showed that the AR regulates the anabolic activities in PCa cells by stimulating the expression of an abundance of enzymes involved in the molecular pathways of aerobic glycolysis and lipid synthesis including HK2 and FASN [17]. Tahir et al found that Caveolin 1, a component of cellular membrane promoting PCa development and progression, induces the expression of Glut-3 and HK2 augmenting the uptake of glucose by PCa cells through the activation of IGF and Akt signaling [18]. These findings highlight the role of HK2 as a crucial molecule initiating the aerobic glycolysis in aggressive PCa cells.

The M2 isoform of pyruvate kinase (PKM2) induces aerobic glycolysis in cancer cells due to its low level of pyruvate kinase activity controlling the glycolytic flux to direct intermediate metabolites toward the anabolic pathways [19]. High levels of PKM2 have been detected in colon, lung and renal cell cancer [20-22] and its expression was suggested to be induced by PI3K/Akt signaling [23] and down regulated by PTEN [24]. Interestingly, PTEN is frequently deleted or mutated in PCa while PI3K/Akt signaling is strongly associated with PCa development and progression [12]. Wong et al recently concluded that aggressive PCa xenografts derived from PC stem-like cells have higher PKM2 protein levels compared to those produced from non-PC stem-like cells [25] of note, the authors demonstrated that these differences can be probably attributed to posttranslational modifications [25]. These data support the hypothesis that PKM2 may be another mediator of aerobic glycolysis with vital implications in PCa development and progression.

Moreover, it has been supported that FASN up regulation may be correlated with profound aggressiveness of PCa [26,27]. According to data from Migita et al, FASN expression in transgenic animals is associated with intense cell proliferation and confined apoptosis while the expression of this enzyme in human PCa samples is inversely consonant with apoptosis [28]. In addition, FASN up regulation was found to be associated with nuclear localization of Akt [29] and increased stabilization of β-catenin [30]. These data clearly suggest that FASN which regulates the lipid synthesis by cellular micromolecules such as glucose, is critical for the progression of PCa with various interactions with AR [31] and alternative oncogenic signaling. Finally, Priolo et al have recently proposed that different oncogenic pathways driven by Akt and c-Myc control the acquisition of different metabolic reprogramming in PCa cells [32]. In particular, it seems that Akt induces the accumulation of aerobic glycolysis precursors while c-Myc regulates the activation of lipid synthesis in PCa cells [32]. These interesting results suggest that aerobic glycolysis and even more lipid synthesis promote PCa growth and may be reasonable to target these pathways especially upon the development of resistance to hormonal therapy.

Wang et al in a recent report found that HK2, which is expressed in higher levels in PCa tissues compared to normal prostate epithelium, mediates PCa growth in the setting of PTEN and p53 deletions [33] which are substantially common genetic events in the aggressive, hormonal resistant PCa. Based on these findings targeting HK2 with novel agents such as 3BrPA [34] may show particular efficacy in highly aggressive metastatic disease and should be highly considered. What is more, numerous reports suggest that metformin, which induces glucose uptake but mainly boosts the catabolic intracellular activities increasing the sensitivity to insulin being an inhibitor of aerobic glycolysis, can inhibit the growth of PCa cells especially in combination with hormonal therapy [35,36]. Finally, inhibitors of two critical steps in lipid synthesis mediated by the enzymes Acetyl CoA Carboxylase 1 and FASN, namely TOFA and C-75, have been shown to increase apoptosis and decrease growth in multiple PCa cell lines [37,38]. Taking into account these data, it is reasonable to support that the introduction of novel aerobic glycolysis and lipid synthesis inhibitors may have significant potential in the development of promising therapeutic approaches for CRPC.

DNA Damage Repair

It is established that during the initiation and development of human malignancies the intracellular pathways implicated in the repair of DNA damage have different effect depending on the disease's stage. Notably, during primary stages of the disease, deficits of these pathways are expected to promote carcinogenesis through the accumulation of DNA damage [39]. Nevertheless, the latest stages of malignancies are characterized by increased genomic instability due to multiple alterations of DNA and increased replication stress that is why the presence of an intact DNA damage repair system is pivotal for the survival of these aggressive cancer cells [39]. Based on this concept, the accumulation of multiple DNA alterations, mutations and deletions create excellent therapeutic opportunities for the introduction of novel inhibitors targeting the DNA damage repair system.

Remarkably, it has been shown that AR promotes the p53/p21 mediated cell cycle arrest providing prostate cells the chance to repair the DNA damage caused by inflammatory cytokines and can induce prostatic carcinogenesis [40]. Moreover, Ide et al found recently that AR activates Chk2 signaling activating signaling implicated in the repair of H_2O_2 induced DNA damage [41]. It was

recently demonstrated that castration leads to reduction of Ku-70 protein, which is a critical molecule for the activation of non-homologous end join recombination implicated in the repair of DNA damage [42]. Lower Ku-70 levels were also associated with increased γH2AX foci in PCa samples [42] further supporting that AR is implicated in the activation of DNA damage repair suggesting that castration can significantly increase DNA damage. Consistent with these data, Goodwin et al showed that hormonal therapy and radiation synergistically inhibit the growth of hormonal sensitive and insensitive AR positive PCa cells inducing the accumulation of DNA damage as indicated by increased numbers of γH2AX and 53BP1 foci [43]. Moreover, it was demonstrated that genes implicated in the homogenous recombination which areupregulated in CRPC such as XRCC2 and XRCC3 are induced by androgens under radiation treatment [43]. further highlighting the critical role of AR in the activation of DNA damage repair signaling under genotoxic stress. This result is weighty since provides another presumable explanation for the synergistic effects of radiation and hormonal therapy, a regimen which has been used by clinicians for treatment of aggressive disease. Of note, Polkinghorn et al underlined in their study that androgens promote the expression of multiple DNA damage response genes orchestrating the response to DNA damage while combination of hormonal therapy and radiation therapy synergistically diminishes the growth of PCa cells [44].These findings highlight the role of AR in the regulation of DNA damage response which as mentioned above may initially inhibit the development of malignancies but eventually promote the survival of aggressive mostly cancer cells.

PARP is another molecule regulating the response to DNA damage through activation of base excision repair system and is now under extensive research in PCa. It has been found that PARP is critical for the activation of ERG-mediated transcription of numerous target genes which are up regulated in metastatic disease while PCa cells are susceptible to olaparib, a PARP inhibitor, when they express the ERG gene [45]. Moreover, Schiewer et al showed that PARP induces the transcriptional activity of AR inducing the expression of its targets such as PSA, TMPRSS2 and ERG [46]. Interestingly, the authors also demonstrated that PARP activity is up regulated in CRCP inducing the AR signaling under androgen deprivation [46]. These data support that PARP may be essential for the survival and growth of PCa cells not only through regulating DNA damage response but also forcing the activity of AR under hormonal therapy. Finally, MYB, a transcriptional factor implicated in the development and progression of several malignancies was lately found to be upregulated by hormonal therapy and AR inhibition [47]. More importantly, c-MYB and AR both regulate the expression of genes implicated in the activation of DNA damage response in PCa cells [47] suggesting that this pathway is fundamental for the survival of cancer cells and targeting it may be particularly effective for the inhibition of PCa growth.

Collectively, these data have revealed that the activation of DNA damage response is critical for the survival of PCa cells during the progression of the disease especially in the setting of resistance to hormonal therapy and acquisition of alterations leading to increased replication stress such as Akt and c-Myc activation and p53 deletion.

A significant number of reports have already focused on introducing DNA damage repair inhibition in the treatment of PCa mainly by combining it with traditional approaches such as radiation and hormonal therapy. Wang et al showed that knockdown of Chk1, a principal node mediating G2/M arrest and initiation of double strand break repair in PCa cells can ameliorate their sensitivity to radiation therapy [48]. Apart from Chk1, PARP inhibition sensitizes AR-positive PCa cells to genotoxic agents such as radiation and docetaxel, while veliparib (ABT-888), another PARP inhibitor, enhances the efficacy of castration in terms of tumor growth in VCaP and LNCaP C4-2 xenografts and inhibits the proliferation of PCa cells extracted from human primary prostate tumors. Furthermore, according to a recent phase I clinical trial, prostate tumors in BRCA1 mutation carriers present evidence of response to niraparib, another novel PARP inhibitor [49]. While PARP inhibition is also known to sensitize PTEN deficient and TMPRSS2-ERG fusion gene expressing PCa to radiation [50].

Finally, Li et al found that c-Myb and AR regulate DNA damage repair pathways confering resistance to PARP inhibition while combination of olaparib with AZD7762, a Chk1-Chk2 inhibitor synergistically increases the apoptosis of AR positive and negative PCa cells*in vitro* and *in vivo* [47]. It is obvious that the introduction of these novel agents targeting the DNA damage response pathways create the setting for the development of combinational approaches to improve the survival of patients with aggressive hormonal resistant PCa.

Angiogenesis

Angiogenesis is a well preserved biological activity portrayed by the formation of new vessels in the microenvironment which is considered indispensable during embryogenesis but is normally turned off in the adult human organisms. However, during the development of malignancies, the activation of intracellular pathways and production of growth factors with autocrine and paracrine activity in the tumor microenvironment induce the angiogenesis. The last is believed to be one of the hallmarks of tumor initiation and progression and therefore it is a candidate therapeutic target [51] while the formation of new vessels is required for tumor growth [52]. It is known that oxygen delivery and consumption are regulated by Hypoxia-Inducible Factors (HIFs) promoting the secretion of VEGF which is the chief regulator of angiogenesis in the tumor microenvironment [51]. Of note, hypoxia has been shown to induce the acquisition of invasive and metastatic properties which are associated with the development of resistance to chemotherapy [53]. Chronic inflammation of the peripheral zone of the prostate has been associated with the development of benign prostate neoplasia and PCa [54]. It is believed that inflammation of prostate microenvironment leads to secretion of growth factors and cytokines that may influence the activation of endothelial cells promoting the formation of new vessels [51].

It is widely observed that apart from HIF/VEGF signaling, multiple other intracellular signaling with implications in tumor microenvironment have been associated with angiogenesis encouraging cancer survival and metastasis. It has been demonstrated that activation of p38/MAPK signaling by Reactive Oxygen Species (ROS) produced as a result of the local inflammation in tumor microenvironment can activate endothelial cells to participate in

the synthesis of new vessels [51]. Interestingly, the development of resistance to hormonal therapy can lead to activation of p38/MAPK signaling associated with the development of a more aggressive and invasive phenotype characterized by induced angiogenesis and invasiveness [55]. This is another paradigm that hormonal therapy may promote the activation of multiple intracellular processes providing survival benefits to PCa cells and that combining traditional hormonal therapy with angiogenesis inhibition may be particularly effective for metastatic disease with aggressive features. Finally, the understanding of the molecular biology of the p38/MAPK induced angiogenesis can provide novel markers for the identification of cancers with metastatic potential.

CD105 (Endoglin) is recognized as a proliferation-associated endothelial marker, induced by hypoxia and is preferentially expressed in the actively dividing endothelial cells of microvessel in cancer tissues [56]. Numerous reports support that CD105 may better reflect the angiogenic potential in the tumors microenvironment compared to other markers such as CD31 or CD34 [57,58]. Interestingly, Miyata et al showed that tumors treated with neo-adjuvant hormonal therapy before castration have increased CD105-Microvessel Density (CD105-MDV) compared to tumors without neo-adjuvant hormonal therapy [59] suggesting that AR inhibition can lead to activation of oncogenic signaling promoting the synthesis of new vessels in the tumor microenvironment to enable the survival of PCa cells under the selective pressure of androgen depletion. These findings also accentuate the role of CD105 as a potentially major molecule for the promotion of angiogenesis especially under systemic hormonal therapy rendering its targeting another promising approach for mCRPC. Consistent with these data, El-Gohary et al showed that high expression of CD105 and VEGF in prostatectomy samples is associated with shorter survival [60] further supporting that this molecule is a more specific and sensitive marker for tumor angiogenesis than CD31 and can serve as a prognostic biomarker for primary PCa. Karzai et al. in a recently published phase I clinical trial evaluated the pharmacokinetics and pharmacodynamics of an antibody against CD105, called TRC105 in patients with mCRPC [61]. The authors demonstrated that the administration of TRC105 led to induction of plasma VEGF, reduction of CD105 and deceased PSA velocity suggesting a potential efficacy of this antibody in these patients [61]. The induction of VEGF probably suggests a compensatory mechanism for REC105 induced anti-angiogenic activity [61]. These data clearly suggest that CD105 is a critical novel target for PCa developing resistance to hormonal therapy and its combination with anti-androgens or AR inhibition may be of particular interest for patients with metastatic disease.

Apart from the formation of new vessels, reformatting of the tumor microenvironment is an important step of the angiogenesis. Up regulation and activation of multiple adhesion molecules are correlated with the progression of PCa. CD44 has been found to accumulate matrix metalloproteinase on the cell surface increasing the ability of cancer cells to invade the microenvironment resulting in induced angiogenesis [62]. Thus, this molecule, which induces the acquisition of pre-metastatic phenotype implicated in the epithelial-mesenchymal transformation and the development of resistance to docetaxel, has been brought out as a potential target in aggressive PCa [63].

Concusion

PCa is still the most common cancer among men in the western societies and metastatic PCa is considered yet an incurable disease with variable prognosis. Particularly, for patients with tumors which develop resistance to conventional hormonal therapy the therapeutic choices are limited to chemotherapy and novel anti-androgens such as Abiraterone acetate and Enzalutamide. Hormonal therapy and AR inhibition are proven to promote the induction of alternative survival oncogenic signaling inducing (i) growth using cellular macromolecules, (ii) DNA damage repair to relieve replication stress and (iii) angiogenesis to increase oxygen consumption and invasive activities. It should be noted that these three activities are highly connected since aerobic glycolysis conserve macromolecules production in the presence of oxygen from newly formed vessels including nucleotide synthesis which will be exploited for the repair of DNA damage resulted from increased replication stress. Based on this concept, it is reasonable to hypothesize that targeting directly these intracellular activities potentially in combination with AR inhibition or androgen depletion can proved to be particularly effective in treating patients with aggressive, metastatic disease. Further studies are required to confirm the efficacy of these combinations in preclinical *in vitro* and *in vivo* models and inaugurate their introduction in clinical trials.

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