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Tumour Review

The hallmarks of castration-resistant prostate cancers

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ABSTRACT

Prostate cancer has become a real public health issue in industrialized countries, mainly due to patients' relapse by castration-refractory disease after androgen ablation. Castration-resistant prostate cancer is an incurable and highly aggressive terminal stage of prostate cancer, seriously jeopardizing the patient's quality of life and lifespan. The management of castration-resistant prostate cancer is complex and has opened new fields of research during the last decade leading to an improved understanding of the biology of the disease and the development of new therapies. Most advanced tumors resistant to therapy still maintain the androgen receptor-pathway, which plays a central role for survival and growth of most castration-resistant prostate cancers. Many mechanisms induce the emergence of the castration resistant phenotype through this pathway. However some non-related AR pathways like neuroendocrine cells or overexpression of anti-apoptotic proteins like Hsp27 are described to be involved in CRPC progression. More recently, loss of expression of tumor suppressor gene, post-transcriptional modification using miRNA, epigenetic alterations, alternatif splicing and gene fusion became also hallmarks of castration-resistant prostate cancer. This review presents an up-to-date overview of the androgen receptor-related mechanisms as well as the latest evidence of the non-AR-related mechanisms underlying castration-resistant prostate cancer progression.

Introduction

Prostate cancer (PC) is the second leading cause of cancer-related death in men in the western world after lung cancer [1,2]. According to the American Cancer Society estimates in 2013, over 230,000 American men will be diagnosed with prostate cancer and nearly 29,720 will die of the disease [2]. PC progresses from diagnosis to death through a series of clinical states characterized by the extent of the disease, the hormonal status (castrate or non-castrate) and the presence or absence of metastases. Before choosing a PC treatment, some parameters are considered for each patient such as age, health, stage and grade of the disease, PSA level...etc. Treatments can be applied as mono- or combined therapies. Common options for PC treatments include: active surveillance, surgery (prostatectomy), radiation therapy, chemotherapy or hormone-therapy (androgen deprivation therapy ADT). Active surveillance is often used when an early stage, slow-growing PC is found in older men. It may also be suggested when the risks of surgery, radiation therapy, or hormonal-therapy outweigh the possible benefits. Most patients initially respond well to androgen deprivation (ADT) leading to disease regression. Unfortunately, PC will ultimately become unresponsive and recur within 1–3 years after ADT as a castration-resistant prostate cancer (CRPC) [3]. CRPC is an incurable and highly aggressive terminal stage of PC, seriously jeopardizing the patient's quality of life and lifespan. The management of CRPC is complex and has opened new fields of research during the last decade leading to an improved understanding of the biology of the disease and the development of new therapies [4–7]. This review presents an up-to-date overview of the androgen receptor (AR)-related mechanisms as well as the latest evidence of the non-AR-related mechanisms underlying CRPC progression.

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From castration-sensitivity to castration-resistance

Growth of the prostate gland is initially dependent on androgens. Under constant stimulation by androgens, the prostate gland gradually develops into PC, which is the rationale for androgen deprivation therapy (ADT). Tumors that relapse CT were first thought to be "an drogen-independent", but very low levels of androgens may still be detectable in the tissues and serum of advanced patients [8,9]. ADT provides selective pressure leading to outgrowths of CR cancers [10]. Most advanced tumors resistant to CT still maintain expression of a functional AR showing that the AR pathway plays a central role for survival and growth of most CRPC [11–15] and constitutes an attractive target for therapy. Hence, how AR promotes cell proliferation and tumor growth is an extensive area of research and several mechanisms induce the emergence of the castration resistant phenotype [16]. In addition to AR-related-pathways, more and more non-AR-related pathways like anti-apoptotic proteins overexpression, mRNA splicing events, gene fusions loss of expression of tumor suppressor gene, post-transcriptional modification using miRNA, epigenetic alterations, have also become the new hallmarks of CRPC. PC growth and progression are driven by the accumulation of genetic and epigenetic alterations, events that will be reviewed here. Discovery and understanding of these mechanisms has led to the development of new generation of therapies for the treatment of CRPC [17]. Thus, 6 novel therapies have been approved by the Food and Drug Administration (FDA) for the treatment of CRPC in just the last few years (sipuleucel-T, cabazitaxel, denosumab, abiraterone, enzalutamide and Ra-223) and a few others demonstrating promising results in late-phase clinical trials (for review [4,6,7]).

AR-related pathways

Hypersensitive pathway

AR could become sensitive to low amounts of residual androgens through increased protein production. This theory of a hypersensitive AR pathway (Fig. 1, pathway A) is supported by the fact that many CR tumors show overproduction of AR resulting of a selective outgrowth following death of cells during CT [13,18,19]. Excess of AR production could result from AR locus amplification, increased mRNA transcription rates and/or stabilization of the mRNA or protein [20,21]. Regardless of the mechanism, AR overproduction is expected to contribute to PC growth by compensating for low androgens levels after ADT. Among latest therapeutic strategies developed and FDA-approved, Enzalutamide is a novel antiandrogen selected for novel clinical development with promising results [22], presenting great affinity for the AR, lacks agonists effects and inhibits not only ligand binding to the receptor in a competitive manner but also AR nuclear translocation and DNA fixation. Clinical results showed a slowing down in cancer cell growth, induction of cancer cell apoptosis and tumor regression [23].

Intracrine androgen metabolism

PC cells may survive ADT by regulating intracrine androgen synthesis within the prostate (Fig. 1, pathway B). This local synthesis of androgens is due to increased testosterone conversion to DHT resulting from overproduction of the 5α-reductase enzyme [24,25]. Increased 5α-reductase enzyme level results itself from a germline variant substituting valine to leucine at codon 89 [26]. This variant is commonly observed in African men, indicating a genetic influence in PC [13,19,27]. Intraprostatic androgens can also be synthesized from cholesterol or other precursors such as DHEA (dehydroepiandrosterone). DHEA could be converted to androstenedione, a substrate for conversion to testosterone. The expression of all the genes necessary for synthesizing androgens are described to be increased in CRPC compared to early PC analyzed from untreated patients [9,25,28,29]. Among the recently developed drugs, abiraterone acetate is an inhibitor of CYP17A, an enzyme involved in the intratumoral androgen biosynthesis. Abiraterone has been shown to be effective and very potent and represents the first hormonal therapy to be approved in the post-chemotherapy setting for CRPC [4,6].

Promiscuous pathway

The promiscuous pathway results in the AR being receptive to ligands other than DHT (Fig. 1, pathway C/D). AR mutations enhance AR ligand binding specificity [30–32] and its activation by weak adrenal androgens and other steroid hormones including DHEA, progesterone, estrogens and cortisol [33–37]. AR substitutions are referenced in a database (http://androgendb.mcgill.ca/). These mutations have various consequences depending on their localization [33,38,39]. For instance, cells from the LNCaP (castration-sensitive) cell line display an AR missense mutation in the ligand-binding domain. At codon 877, the threonine is substituted to alanine, which opens the AR sensitivity to a wide range of steroid ligands [40,41]. This mutation may also convert AR antagonists (flutamide and bicalutamide) to AR agonists. AR antagonist treatments may in fact select tumors expressing AR mutants activated by the therapeutic agents [42]. Other mutations, which occur in the AR DNA-binding domain or in the N-terminal domain, modulate the binding specificity of its co-regulators and the transcriptional activation of its target genes [43–45]. Interestingly, two mutations (T877A and Q640X) constitutively activate AR [46]. Finally, AR splice variants (AR3, 4 and 5), which have lost their C-terminal protein domain (ligand-binding domain) including the canonical nuclear localization signal (NLS), can activate AR target genes [47–51]. Mutants truncated in the N-terminal domain (DNA-binding domain) are still able to translocate into the nucleus and have ligand-independent transcriptional activity. Importantly, the expression of certain AR variants such as AR-V7 is associated with a short time to disease recurrence following radical prostatectomy [48,50,52]. These AR variants are key mediators of persistent AR signaling and androgen withdrawal therapies [53]. They represent a clinical challenge depending on their sensitivity to AR antagonists designed to target the AR ligand-binding domain. A small molecule (EPI-001) targeting the AR N-terminal domain has been recently designed and its efficiency against tumors expressing AR splice variants is under study [54]. Numerous pre-clinical studies show the efficiency of AR-siRNA strategy in inducing CR tumor growth inhibition and regression [55,56].

Outlaw pathway

The outlaw pathway (Fig. 1, pathway E) is functional when the AR pathway is activated by growth factors, cytokines and receptor tyrosine kinases. Growth factor pathways such as IGF1 (insulin-like growth factor) and EGF (epidermal growth factor) can bind and activate AR in the castrated state, when they are overexpressed [57]. IGF1 has been also described to be involved in CR evolution in an AR-independent fashion. IGF1 promotes cell growth, survival and differentiation of prostate cells and is increased in advanced cancers especially in metastases [58]. IGF1 can activate powerful oncogenic signaling pathways such as RAS, RAF, MAPK, or PKC leading to the transcription of target genes that promote cell growth and survival [59]. Cytokines like interleukin-6 (IL6) and interleukin-4 (IL4) are also activators of the AR pathway in CRPC [60,61]. Notably, IL6 could activate AR through the activation of MAPK (mitogen-activated protein kinase) and STAT3 pathways [62]. Moreover, tyrosine kinase receptors such as ERBB2 are overexpressed in CRPC, resulting in the increase of AR expression and activity via the activation of