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Treatment-induced changes in the androgen receptor axis: Liquid biopsies as diagnostic/prognostic tools for prostate cancer

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ABSTRACT

Prostate cancer progression and treatment relapse is associated with changes in the androgen receptor axis, and analysis of alternations of androgen receptor signaling is valuable for prognostics and treatment optimization. The profile of androgen receptor axis is currently obtained from biopsy specimens, which are not always easy to obtain. Moreover, the information acquired only provides a snapshot of the tumor biology, with strict spatial and temporal limitations. On the other hand, circulation is easily accessible source of both circulating tumor cells and circulating tumor DNA, which can be sampled at numerous time points. This Review will explore the potential use of androgen receptor axis alternations detectable in the blood in therapeutic decision-making and precision medicine for advancing metastatic castration-resistant prostate cancer.

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1. Introduction

Despite the high survival rates and recent progress in treatment modalities, prostate cancer (PCa) remains an important healthcare issue with a widespread socio-economic impact (Ferlay et al., 2015). In the majority of cases, PCa is organ-confined at the moment of diagnosis and a cure can be provided by prostatectomy or radiation therapy (>90% progression free survival). However, the more advanced forms of the disease can metastasize, mainly to the bone (90%) or lung (46%) (Chang et al., 2014) and are incurable.

The benchmark treatment for metastatic PCa is androgen deprivation therapy (ADT) combined or not with chemotherapy. Unfortunately, in most cases the disease will become resistant to ADT, hence the classification of “castration-resistant prostate cancer” (CRPC). At this stage, hormone therapy with AR-targeting drugs is considered. Unfortunately, although at first these approaches can be effective, the development of resistance is inevitable in most cases (Hotte and Saad, 2010). Development of resistance happens mostly via the reactivation of the AR axis, thus several novel compounds targeting the AR axis have been developed (Andersen et al., 2010; Helsen et al., 2014; Njar and Brodie, 2015).

During the progression of metastatic castration resistant prostate cancer (mCRPC), serum PSA measurements and bone scans may provide valuable prognostic information (Cornford et al., 2016), but because they do not report on the underlying mechanisms, their use in the development of personalized precision therapy is limited. To have an idea on the mechanisms that are involved in cancer progression for each individual patient, one would need markers that provide more precise information on the relevant metastases. Unfortunately, sampling multiple metastases or identification of the most relevant metastases is nearly impossible in current clinical practice.

One alternative source of information on disease progression could come from liquid biopsies. The term ‘liquid biopsies’ can indicate urine, blood, saliva or even spinal fluids. These can serve as minimally invasive diagnostic sources of information because

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biomolecules originating from tumor masses leak into the circulation. Like for most cancers, for prostate cancer, blood would be the preferred liquid biopsy because of the ease of collection and reproducible processing modalities. While blood has traditionally been used to follow PSA and other protein and metabolic markers, more recently, it is used as a source of tumor lipids (Butler et al., 2016), RNA (Sita-Lumsden et al., 2013), DNA (Wyatt et al., 2016), exosomes (Bobrie and Théry, 2013) and tumor cells (de Bono et al., 2008). In recent years, circulating tumor DNA (ctDNA) and the circulating tumor cells (CTCs) were added as blood-derived markers. Circulating tumor DNA provides robust information on irreversible changes of the genome in the tumor cells it originates from. CTCs on the other hand can be interrogated not only at the level of their DNA, but also at the level of other biomolecules or signaling pathways. Currently, CTC enumeration by the use of CELLSEARCH® is approved by Food and Drug Administration (FDA) as a means of predicting overall survival in metastatic PCa (de Bono et al., 2008). One caveat here is that it is still not clear which of the molecular changes in CTCs reflect the progression of the disease.

Recently, the FDA approved the first blood-based test for the detection of EGFR mutations in non-small cell lung cancer patients (http://www.fda.gov) (Voelker, 2016). This allows detection of specific, recurrent mutations, which can help the selection of the patients that could benefit from Erlotinib (Tarceva) therapy.

Because of the central role of the androgen axis in prostate cancer progression and treatment, we will focus our review on the use of ctDNA and CTCs to highlight their potential in therapeutic decision-making and precision medicine for advancing mCRPC.

2. Androgen receptor structure and function

The direct effects of the androgenic hormones like testosterone (T) and dihydrotestosterone (DHT) are mediated by the AR. The *AR* gene is located on chromosome X (q11-12) and contains 8 exons. With a length of 90 kb, it is the largest and most complex of all nuclear steroid receptor genes, encoding a protein of 920 amino acids (Lubahn et al., 1988; Tan et al., 2015). The AR is a multi-domain protein composed of the transactivation domain (NTD), a DNA-binding domain (DBD), a hinge region and a C-terminal ligand-binding domain (LBD).

The structure of the AR NTD is believed to be flexible and dependent on its interaction partners (Lavery and Mcewan, 2005; McEwan et al., 2007). The activation function 1 (AF1), which serves as docking station for co-regulators, is located in the NTD (Jenster et al., 1991). This AF1 is composed of two separate but functionally interacting transcription activation units (Tau-1 and Tau-5), each believed to recruit different co-activator complexes (Callewaert et al., 2006; Van Tilborgh et al., 2013). The FQNFL motif, located upstream of Tau-1, can interact with the LBD (see below), and is important for the functional interactions between the NTD and the LBD (A. Brinkmann et al., 1999).

The AR DBD recognizes very specific DNA motifs, which occur in promoter or enhancer regions of androgen regulated genes (Denayer et al., 2010). This domain consists of two zinc finger modules that are involved in dimerization as well as in positioning of the DNA-recognition α-helix into the major groove of DNA of the response elements (Shaffer et al., 2004).

The LBD of the AR consists of 11 α-helices (H) and 4 β-strands (A. O. Brinkmann et al., 1989; Matias et al., 2000). The ligand binding pocket is buried in the LBD and is surrounded by the N-termini of α-helices 3, 5 and 12. The folding of H12 over the ligand binding pocket forms the core of the activation function 2 (AF2), since this forms a binding groove on the surface of the LBD. This surface is recognized by LxxLL-motifs present on the surface of the co-activators (Estébanez-Perpiñá et al., 2007; Rastinejad et al., 2013; Wurtz et al., 1996) or the FQNLF motif in the NTD (see above). Recently, the dimerization interface of the LBD was reported (Nadal et al., 2017).

The unliganded AR is located in the cytoplasm, in a complex with heat shock proteins (Echeverria and Picard, 2010). When the hormone binds, conformational changes in the LBD occur and the interacting proteins dissociate, thus exposing the nuclear localization sequence (NLS) located in the hinge region between the DBD and LBD. Subsequently, intramolecular N/C interactions occur and the receptor is transported to the nucleus where it forms intermolecular N/C interactions (van Royen et al., 2012). Once in the nucleus, the AR homodimer regulates gene expression via binding to androgen response elements (ARE), located in the promoter and enhancer regions of the AR target genes. These AREs are organized as inverted repeats of the 5′-AGAACA-3′ hexameric consensus sequence (Claessens et al., 2001; Wang and Brown, 2009). Even though the AR directly binds AREs *in vitro*, the *in vivo* accessibility of these binding sites is determined by many factors that shape the chromatin architecture (extensively reviewed in (Arora et al., 2013)). Once bound to the enhancers, the AR N/C interactions are lost and the AR serves as a scaffold for co-regulator proteins and complexes with diverse activities. Some of these proteins/complexes reshape the surrounding chromatin structure by reading, writing, or modifying the histone code, while other complexes mediate the recruitment of general transcription factors to the promotor regions. In this way, the AR and its co-regulators eventually orchestrate the expression of AR target genes (Claessens et al., 2008). The list of AR co-regulators is large and is still expanding (DePriest et al., 2016). The impact of additional levels of control for instance by miRNAs and lncRNAs under normal and pathological conditions are just starting to be unravelled (see contributions by Spahn and Feng elsewhere in this issue).

3. Prostate cancer and resistance to AR targeting treatment

The AR plays a pivotal role in the development, differentiation, homeostasis and secretory function of the normal prostate (Wilson, 2011). The AR is also a key player in many phases of prostate carcinogenesis (Huggins et al., 1941; Scher and Sawyers, 2005). The androgen deprivation therapy (ADT), which is lowering the levels of circulating androgens, is effective for most patients. However, after the initial good response, the disease will progress into what is called mCRPC. Surprisingly, at this stage of the disease the AR signaling pathway is reactivated, and it can be treated with compounds that block AR signaling either directly as antagonists of the AR protein (e.g. Enzalutamide, ARN-509) or indirectly via blocking androgen biosynthesis (e.g. Abiraterone acetate) (Helsen et al., 2014). These treatments are at first quite effective and have been shown to prolong the overall survival of mCRPC patients (Attard et al., 2009a,b; Cabot et al., 2012; De Bono et al., 2011). However, again most patients ultimately progress as the cancer develops resistance towards these drugs.

Multiple molecular mechanisms behind castration or anti-androgen resistance have been proposed (reviewed in (Claessens et al., 2014; Lorente et al., 2015; Shtivelman et al., 2014)). Surprisingly, reactivation of the androgen signaling axis explains how PCa cells survive in the absence of androgens or even in the presence of anti-androgens. The most common mechanisms are depicted in Fig. 1.

The *AR* gene can be amplified resulting in AR overexpression and persistent signaling (Palmberg et al., 1996). The *AR* gene amplifications and accompanied higher expression levels have been correlated with aggressiveness and therapy response in CRPC (Koivisto et al., 1997; Visakorpi et al., 1995). The concomitant increase in AR protein levels may lead to a sustained signaling under

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