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RT – wichtig – einprägen – Key Points

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## Androgen Receptor Signaling (AR)

The **AR gene is located on the X chromosome** and is not necessary for survival, so germline loss-of-function mutations in the AR, resulting in the androgen-insensitivity syndrome, are frequent.

Most **AIPCs** (Androgen Independent Prostate Cancer) express the AR protein. Whereas some of these tumours, at least initially, have adapted to the low androgen environment, others acquire mutations that allow them to circumvent the normal growth regulation by androgens. It seems that many cases of AIPC do not develop from a loss of androgen signaling, but rather from the acquisition of genetic changes that lead to aberrant activation of the androgen signaling axis. These changes are usually missense mutations in the AR gene that decrease the specificity of ligand binding and allow inappropriate activation by various non-androgen steroids and androgen antagonists.

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### Androgen Receptor

Type 2: the promiscuous pathway - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2993607/

Targeting AR signaling in metastatic PC commonly produces robust clinical responses. However, disease progression is nearly universal. Potent AR antagonists appear to be shifting the phenotypes of resistant PCs to tumors that are devoid of AR activity, but the drivers of these resistant carcinomas are not known. Here we report that autocrine and paracrine FGF signaling is capable of bypassing a requirement for AR and find that FGF and MAPK pathways are active in metastatic AR-null PCs. Suppressing FGF and MAPK inhibits the growth of AR-null PC indicating that targeting the FGF axis may represent a therapeutic approach for those cancers resistant to AR-directed therapies and may circumvent treatment resistance if combined with initial AR pathway blockade.

A subset of patients with advanced castration resistant prostate cancer (CRPC) may eventually evolve into an androgen receptor (AR) independent phenotype, with a clinical picture associated with the development of rapidly progressive disease involving visceral sites and hormone refractoriness, often in the setting of a low or modestly rising serum prostate specific antigen (PSA) level (1, 2). Biopsies performed in such patients may vary, ranging from poorly differentiated carcinomas to mixed adenocarcinoma-small cell carcinomas to pure small cell carcinomas. These aggressive tumors often demonstrate low or absent AR protein expression, and in some cases express markers of neuroendocrine differentiation. Since tumor morphology is not always predicted by clinical behavior, the terms “anaplastic prostate cancer” or “neuroendocrine prostate cancer” have been employed descriptively to describe these rapidly growing clinical features. Patients meeting clinical criteria of anaplastic prostate cancer have been shown to predict for poor prognosis, and these patients may be considered for platinum based chemotherapy treatment regimens (3). Therefore, understanding variants within the spectrum of advanced prostate cancer has important diagnostic and treatment implications.

Aggressive Variants of Castration Resistant Prostate Cancer

Clin Cancer Res. 2014 June 1; 20(11): 2846–2850. doi:10.1158/1078-0432.CCR-13-3309.

The androgen receptor (AR) is known to have central roles in development and progression of prostate cancer (PCa). Patients with advanced PCa are treated with androgen-deprivation therapy (ADT),1 but often develop resistance to ADT, resulting in castration-resistant PCa (CRPC). Multiple studies reported that ADT increases activation of mechanistic target of rapamycin (mTOR).

Androgen receptor (AR) signaling is a distinctive feature of prostate carcinoma (PC) and represents the major therapeutic target for treating metastatic prostate cancer (mPCa).

### Significance

Targeting AR signaling in metastatic PC commonly produces robust clinical responses. However, disease progression is nearly universal. Potent AR antagonists appear to be shifting the phenotypes of resistant PCs to tumors that are devoid of AR activity, but the drivers of these resistant carcinomas are not known. Here we report that autocrine and paracrine FGF signaling is capable of bypassing a requirement for AR, and find that FGF and MAPK pathways are active in metastatic AR-null PCs. Suppressing FGF and MAPK inhibits the growth of AR-null PC indicating that targeting the FGF axis may represent a therapeutic approach for those cancers resistant to AR-directed therapies and may circumvent treatment resistance if combined with initial AR pathway blockade.

**AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer**

**Background**—The androgen-receptor isoform encoded by splice variant 7 lacks the ligand-binding domain, which is the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor. We hypothesized that detection of androgen-receptor splice variant 7 messenger RNA (AR-V7) in circulating tumor cells from men with advanced prostate cancer would be associated with resistance to enzalutamide and abiraterone.

Although enzalutamide and abiraterone represent breakthroughs in the treatment of metastatic castration-resistant prostate cancer, approximately 20 to 40% of patients have no response to these agents with respect to prostate-specific antigen (PSA) levels (i.e., they have primary resistance). Among patients who initially have a response to enzalutamide or abiraterone, virtually all eventually acquire secondary resistance. One plausible explanation for the resistance to both agents may involve the presence of androgen-receptor splice variants.

We found that AR-V7 can be detected reliably from circulating tumor cells and that detection of A R-V7 in tumor cells appears to be associated with resistance to both enzalutamide and abiraterone. In our study, no AR-V7–positive patient had any appreciable clinical benefit from enzalutamide or abiraterone therapy.

If this finding is substantiated by others, it is possible that AR-V7 could be used as a biomarker to predict resistance to enzalutamide and abiraterone and to facilitate treatment selection. However, our study does not prove a causal role for AR-V7 in mediating resistance to enzalutamide or abiraterone, and it remains possible that AR-V7 is a marker of more advanced disease or a higher disease burden.

N Engl J Med. 2014 September 11; 371(11): 1028–1038. doi:10.1056/NEJMoa1315815

**Key Points**: Question Can the measurement of the nuclear androgen receptor splice variant 7 (AR-V7) protein in circulating tumor cells (CTCs) be a treatment-specific biomarker in metastatic castration-resistant prostate cancer (mCRPC) at therapeutic decision points in the first-line, second-line, or third or greater line setting?

See also: <http://www.cancernetwork.com/oncology-journal/evolving-biology-castration-resistant-prostate-cancer-review-recommendations-prostate-cancer/page/0/1>

**AR-V7 Taxane Chemotherapy**

IMPORTANCE We previously showed that detection of androgen receptor splice variant 7 (AR-V7) in circulating tumor cells (CTCs) from men with castration-resistant prostate cancer (CRPC) was associated with primary resistance to enzalutamide and abiraterone therapy, but the relevance of AR-V7 status in the context of chemotherapy is unknown. OBJECTIVE To investigate whether AR-V7–positive patients would retain sensitivity to taxanes chemotherapy and whether AR-V7 status would have a differential impact on taxane-treated men compared with enzalutamide- or abiraterone-treated men.

JAMA Oncol. 2015;1(5):582-591. doi:10.1001/jamaoncol.2015.134

EPIC Sciences\_HRD\_Liquid Biopsy.pdf

Reactivation of androgen receptor-regulated lipid biosynthesis drives the progression of castration-resistant prostate cancer

W Han1,4, S Gao1,4, D Barrett1, M Ahmed2, D Han1, JA Macoska1, HH He2,3 and C Cai1

Oncogene (2018) 37, 710–721

### AR mutations

## Metastasis Framework

We can envision metastasis as one possible outcome from the somatic evolution of cancerous cells that have lost control over the integrity of their genome. The resulting cellular heterogeneity enables the selection for advantageous traits that allow malignant cells to overcome diverse environmental defenses, which normally preserve tissue structure and function. Primary tumors that continue to thrive in spite of these obstacles and exhibit genetic or phenotypic features indicative of stromal-cell co-option are often enriched in cells that are primed for the metastatic cascade. As these tumors go on to spew cells and soluble factors into the circulation, the entire body becomes an evolutionary playing field.

Cell 127, November 17, 2006 ©2006 Elsevier Inc.

## Immunotherapies

T cells that recognize tumor antigens are present in the tumor microenvironment, and their activity is modulated through stimulatory and inhibitory receptors. Once cancer is well established, the balance between these inputs is tipped toward immunosuppression (1, 2). The inhibitory signals on T cells are delivered through molecules such as cytotoxic T lymphocyte–associated protein 4 (CTLA4) and programmed cell death protein 1 (PD1) by interaction with their respective ligands expressed on cancer cells and/or antigen-presenting cells (APCs). However, these same tumor-reactive T cells express stimulatory receptors including members of the tumor necrosis factor receptor (TNFR) superfamily. Therefore, many attempts are being made to relieve the negative checkpoints on the antitumor immune response and/or to stimulate the activation pathways of the tumor-infiltrating effector T cells (Teffs).

Eradication of spontaneous malignancy by local immunotherapy

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Immune checkpoint inhibitors have emerged as a potent new class of anticancer therapy. The critical role of the immune system in limiting cancer progression has been recognized for some time. The myriad of genetic alterations found in many human cancers likely produces an array of tumor-specific neoantigens with the potential to be recognized by the immune system. Inhibition of the anticancer immune response has emerged as an important mechanism of tumor resistance to treatment.

Through the development of monoclonal antibodies that block the immune checkpoint receptors cytotoxic T lymphocyte–associated antigen 4 (CTLA4) and programmed death-1 (PD-1) or its ligand PD-L1, it has become possible to stimulate and/or magnify a patient’s endogenous antitumor immune response. These pathways may have distinct roles in immunomodulation, withCTLA4 believed to primarily regulate T cell proliferation in lymph nodes, whereas PD-1 primarily suppresses T cells in the tumor microenvironment. Immune checkpoint blockade has recently demonstrated remarkable efficacy across a range of tumor types, the treatment landscape for a range of tumors, particularly those with a high mutational load. Checkpoint blockade appears to be most effective against hypermutated tumors, suggesting that clinical responses correlate with an increase propensity to produce neoantigens for immune activation.

Nolan et al., Sci. Transl. Med. 9, eaal4922 (2017) 7 June 2017

With increasing interest in the role of neoantigens created by somatic mutations shaping the immune response to cancer (McGranahan et al., 2016; Rajasagi et al., 2014; Rooney et al., 2015), we might expect that purifying selection would suppress clones with mutations that elicit a strong immune reaction.

Cell 171, 1029–1041, November 16, 2017 – Universal Pattern of Selection in Cancer and Somatic Tissues

## Drug Naming – Nomenclature - Suffixes

These names are not chosen at random, however, and the specific ending can tell you the origin of the drug. All of them end in "-mab", but its the letter(s) that precedes the "-mab" that can tell you the origin of the antibody.

* If the letter is an "o", such as in technetium pintumomab, the antibody is of murine, or mouse, origin. These aren't usually used anymore as newer technology to make chimeric/humanized antibodies have largely replaced purely mouse sources.
* If the letters are "xi", such as in abciximab, the antibody is of chimeric origin, meaning a hybrid of mouse and human origin that is roughly 65% human.
* If the letters are "zu", such as in omalizumab, the antibody is of humanized origin. This is another hybrid of animal and human origin, but this type is "more" human, usually about 95% human.
* If the letter is a "u", such as in adalimumab, the antibody is of human origin (100% human).

The rest of the names are not random, either. The naming conventions for these drugs are much more extensive, and you can read further if you like:

These drugs are protein drugs like the tyrosine kinase inhibitors, and their names all end in "-mab". This is significant, as that ending tells you what type of drug it is: ***M***onoclonal ***A***nti***b***ody.

**“-mab”:** a monoclonal antibody (MAB)

**“-omab:** a mouse MAB (not used in humans therapeutically)

**“-ximab:** a chimeric (mouse/human) MAB (human constant region + mouse variable immunoglobulin regions)

**“-zumab:** a humanized MAB (has mouse CDR regions)

**“-umab”:** a fully human antibody

**“-nib”:** a protein tyrosine kinase inhibitor

# Carcinogenesis

Carcinogenesis involves series of events, often initiated with cells losing their growth control due to accumulated mutations, leading to uncontrolled proliferation. This usually involves the alteration of gene such as oncogenes, tumour suppressor genes as well as those involved in DNA repair mechanisms.

# Neuroendocrine prostate cancers (NEPC)

Therapeutic approaches designed to impair AR activity remain first-line therapy for men with metastatic PC. While resistance to AR-directed therapeutics is usually accompanied by reactivation of AR signaling, newer drugs with potent AR pathway antagonism appear to be shifting the phenotypes of resistant PC to anaplastic and NE carcinomas that are devoid of AR activity (Figure 7J). The AR-null/NE-null tumors evaluated in the present study were acquired from men after initial responses to AR antagonists, indicating that these agents effectively eliminated tumor clones dependent on the AR, but failed to eradicate cell populations that no longer required AR signaling. Defining the drivers of these resistant carcinomas is critical for the development of effective treatment strategies.

The RB tumor suppressor: a gatekeeper to hormone independence in prostate cancer?

The retinoblastoma tumor suppressor gene (RB1; encoding RB) is often cited as a gatekeeper, whose inactivation — direct or indirect — is a rate-limiting step for tumor initiation. However, in this issue of the JCI, Sharma et al. show that RB1 loss is a late event in human prostate cancer that is coincident with the emergence of castrate-resistant metastatic disease.

This role for RB1 was linked to both E2F transcription factor 1–driven upregulation of the androgen receptor (AR) and increased recruitment of the AR to target gene promoters.

Understanding the role of RB in preventing progression to CRPC at the cellular level.

The progression of prostate cancer through different stages, from PIN to adenocarcinoma to metastatic CRPC, has been associated with activation of specific oncogenes, such as Myc, and loss of key tumor suppressors, such as PTEN, at early stages of tumorigenesis (6). Detectable loss of RB1 at late stages upon progression to CRPC raises the intriguing question as to whether androgen deprivation is selecting for androgen independence through genetic loss/epigenetic silencing of RB1 in previously androgen-dependent cells, or whether such RB-deficient androgen-independent cells were present in low abundance throughout tumorigenesis, but now have a growth advantage over RB-proficient androgen-dependent cells, allowing them to expand to become the dominant tumor cell type represented.