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Role of Androgen Receptor in Prostate Cancer: A Brief Update

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Abstract

Androgen Receptor (AR) is a transcription factor for testosterone and dihydrotestosterone. Prostate cancer cells' survival, growth, and proliferative activity highly depend on a functional AR. The androgen receptor gene is located on chromosome X (Xq11-12) and encodes a 919 amino acid protein with four domains. Following androgen deprivation therapy, prostate cancer may temporarily undergo regression. However, in many cases, it adjusts and evolves to Castration-Resistant Prostate Cancer (CRPC), capable of surviving and progressing under low levels of androgen. These tumors, however, still have active androgen receptors that may be targeted by therapeutic intervention. Another way CRPC can resist therapeutic measures is by acquiring a neuroendocrine phenotype that is not dependent on androgen for survival and progression. Neuroendocrine carcinomas of the prostate may have several subtypes, including small cell, large cell, amphicrine, and carcinomas with Paneth cell-like cytoplasmic granules. These tumors may occur in pure form or may intermix with adenocarcinoma component. Although neuroendocrine carcinomas mainly develop following antiandrogen therapy, rarely, similar tumors may arise de novo in the absence of any therapy.

Androgen receptor plays a crucial role in the development, progression, and dissemination of prostate cancer. Suppression or complete elimination of AR has emerged as the prime target for current and future therapeutic strategies.

Keywords: Prostrate; Androgen receptor; Carcinoma; Neuroendocrine.

Introduction

Most prostate cancers depend on androgens for their survival, growth, and progression. The androgens activate Androgen Receptors (AR) within the tumor cells, causing cell proliferation and tumor progression. Androgen receptors are also present within the normal prostate's glandular epithelial cells and stromal cells and have a significant role in organ development and maintenance of normal prostatic function [1]. Charles Huggins and Clarence V. Hodges (1941) argued that prostate carcinomas are highly dependent on the presence of androgenic hormones for their growth and progression. Through their experiments, they showed that surgical removal of testes in patients with prostate cancer induces deprivation of androgen that may cause a marked regression of cancer [2]. Men with advanced prostate cancer are now routinely treated by androgen deprivation therapy. In addition to surgical castration, an androgen deprivation state may develop in a variety of other ways, including medical castration to inhibit androgen biosynthesis, as well as the use of antiandrogens that block the action of these hormones. This paper aims to review the structure, function, and pathophysiology of the androgen recep-

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tor and discuss the role that androgen deprivation therapy plays in the emergence of Castration-Resistant Prostate Cancer (CRPC) neuroendocrine carcinoma and other morphologic variants [3].

The androgens

Androgens include a multitude of hormones synthesized in the testes and adrenal glands. These hormones control and regulate the development and maintenance of male characteristics. Thus, the androgens control and modulate the embryological development of the primary male sex organs and play a crucial role in transforming male secondary sex characteristics during puberty. The principal androgen in males is testosterone, synthesized by the Leydig cells in the testis. The main subsets of adrenal androgens, including androstenedione and Dehydroepiandrosterone (DHEA), are produced in the innermost layer of the adrenal cortex, namely the zona reticularis. Only 1-2% of testosterone in the serum is present in a free state, while the rest is bound to sex hormone-binding globulin. After entering prostate cells, testosterone interacts with 5-alpha-reductase and converts to dihydroxy testosterone, a hormone with a high affinity for binding to AR. Within the prostatic cells, adrenal androgens are also changed to testosterone following interaction with 17-beta-hydroxysteroid dehydrogenase within the prostate cells [4].

Structure and function of androgen receptors

AR has a structure like other hormone receptors for estrogen, progesterone, and glucocorticoids. The gene for AR is located on chromosome X (Xq11-12) and consists of 8 exons that code a protein with approximately 919 amino acids [5,6]. AR includes four regions, namely, an NH2 terminal Transactivation Domain (NTD), a DNA-binding domain (DBD), a hinge, and a Ligand-Binding Domain (LBD) that are encoded by exons 1-6, as depicted in Figure 1.

The NTD contains a polymorphic repeat sequence of cytosine, adenine, and glutamine (CAG repeats). These repeats are of varying length ranging from 8-31, with most men having 19-25 repeats. Shorter repeats are associated with higher transcriptional activity of AR and an increased risk of prostate cancer [6,7]. The availability of androgens and the presence of a functioning AR are crucial for normal male sexual differentiation. In male fetuses a complete loss of a functioning AR is associated with complete androgen insensitivity syndrome [8].

Immunohistochemical analysis of prostatic tissue reveals strong cytoplasmic staining for AR in luminal cells, fibromuscular stromal cells, and endothelial cells while the basal cells are only weakly reactive. The function of androgens is exerted by binding to AR [9]. In normal prostate glandular epithelial cells, AR activation produces secretory proteins, such as prostate-specific antigens (PSAs). AR in inactive state is present in the cytoplasm along with heat shock proteins 70 and 90 that act as chaperone proteins [10]. The androgens, including testosterone and dihydrotestosterone (DHT), exert their function by binding to the ligand-binding domain of AR following which the AR undergoes a conformational change, enters the nucleus, forms a dimer. The AR dimer binds to the androgen-response element of targeted genes resulting in appropriate gene expression (Figure 2). Androgen receptor cofactors consisting of a group of p160 proteins, namely SRC-1, SRC-2, and SRC-3 modulate this action [6,11,12].

Virtually total dependence of prostate cancer on AR

Many cancers acquire key mutations crucial in maintaining proliferative activity in the tumor. Prostate cancers, on the other hand, have a low mutational burden compared to other cancer types. Several sequencing studies on early localized prostate cancers and advanced late-stage disease have demonstrated very few mutations. Thus, this cancer is unique because it has a relatively low mutational burden and entirely depends on the activation signal from the androgen receptor for proliferation, progression, and self-renewal [13,14].

Surgical and medical castration can eliminate or significantly reduce the amount of androgen produced by the testes. However, small amounts of androgens produced by the adrenal may sustain tumor growth and progression. In recent years, several potent non-steroidal antiandrogens such as Flutamide (Eulebicalutamide (Casodex) and nilutamide (Nilandron) have been available. These agents neutralize residual androgen activity as they bind to the AR but do not activate its transcriptional activity. Instead, they competitively block testosterone from binding to the AR [15,16].

Survival of prostate cancer patients has improved with the use of antiandrogens; however, resistance to androgen deprivation therapy develops in most prostate cancers as they become androgen-independent or Castration-Resistant Cancers (CRPC) [17].

Survival strategies of CRPC

Transcriptionally active ARs still drive most CRPCs which can grow under low androgen levels. Several mechanisms may be involved in the development and continued progression of CRPC under these conditions [5,18].

AR gene point mutations

Around 15-30 percent of CPRCs have point mutations in the LBD or NTD region of the AR gene. These mutations cause AR to lose its specificity for testosterone, so other hormones, such as progesterone and estrogen, can also activate the receptor. Even drugs such as flutamide, bicalutamide, and enzalutamide can interact similarly with AR.

Androgen receptor gene amplification

Approximately 30% to 50% of CRPCs may develop amplification of the AR gene. Marked overexpression of AR in these tumors may result in progression even with deficient levels of androgen under androgen deprivation therapy.

Changes in the production of androgen

Androgen deprivation therapy results in a lack of testosterone produced by the testes, although adrenal glands continue to produce small amounts of androgens. Normal prostatic cells and prostatic carcinoma cells may convert these into testosterone, a process that may be markedly enhanced in CRPC.

Altered activity of AR cofactors

Studies on patients with prostate cancer have revealed a significant role of several AR Cofactors in the development and progression of these cancers. Overexpression of AR cofactors may increase transcriptional activity and enhance cellular proliferation signal.

Androgen receptor variants

Many of the over 20 splicing variants of AR may be functionally active even without androgens because they lack the C-terminal domain.

Phenotypic plasticity and development of additional subtypes of prostatic cancer

Approximately a quarter of prostate cancers may become resistant to androgen deprivation therapy without any alterations in AR. The presumed mechanism underlying this change is phenotypic plasticity, which enables the cancer cells to undergo many non-genetic phenotypic cell state changes. These changes amplify the heterogeneity of cancer cells and allow them to acquire migratory, invasive, and chemo-resistant properties. Prostate cancer cells generally have epithelial phenotype and depend on androgen receptor signaling for growth and proliferation. Some tumors may progress to mesenchymal or neuroendocrine phenotypes that no longer require androgen receptor activation for proliferation and growth. Many transcription factors and signaling molecules the tumor cells produce are responsible for these phenotypic changes. These factors are typically involved in lineage programming during embryologic development. However, when expressed in prostate cancer, they induce lineage plasticity and reprogramming that promote resistance to hormonal therapy and increase the tendency for metastasis. No effective treatments are currently available to inhibit or reverse the tumor progression of prostate cancers that use mechanisms of linear plasticity for growth and progression [19-21].

Neuroendocrine carcinomas of the prostate

Normal prostate and prostatic adenocarcinomas contain small neuroendocrine cells randomly distributed among luminal and basal cells. These cells secret various peptide hormones that affect adjacent epithelial cells by paracrine activity. These cells, however, are not the source of neuroendocrine carcinomas of the prostate. With the use of androgen deprivation therapy, new tumor types have emerged that employ multiple AR-independent mechanisms for survival. A subset of CRPC tumors partially or entirely lose androgen receptor activity and PSA expression. These tumors employ tumor plasticity and acquire neuroendocrine phenotype for further progression and dissemination. Thus, these tumors are nonreactive or only focally positive for AR and PSA but manifest positive staining for neuroendocrine markers, including chromogranin, CD-56, synaptophysin, and neuron-specific enolase. Post-therapy neuroendocrine carcinomas may develop in 10-17% of CRPC. These carcinomas have low or absent androgen receptors and are not responsive to therapies that target AR signaling [22].

Small cell carcinoma is the most common neuroendocrine carcinoma of the prostate [23] (Figure 3). The morphology of this tumor is identical to small cell carcinoma of the lung. The tumor cells have scanty cytoplasm, slightly elongated hyperchromatic, molded nuclei with inconspicuous nucleoli, and a high proliferation rate. These tumors frequently show necrosis and crushing artifacts. In rare cases, the neoplasm may resemble a carcinoid tumor. Another uncommon variant is large-cell neuroendocrine carcinoma, with cells containing abundant cytoplasm and large pleomorphic nuclei frequently containing prominent nucleoli [24] (Figure 4). Rarely, the carcinoma cells depict large cell morphology but reveal a dual pattern of immunohistochemical staining where the tumor cells express neuroendocrine markers but also stain for AR and PSA [25]. These tumors may represent an intermediate stage of transdifferentiation from prostatic adenocarcinoma to neuroendocrine carcinoma and have been variably described as amphicrine carcinoma and large cell carcinoma with diffuse neuroendocrine differentiation [24,25]. This entity, however, still needs to be defined. Tumors with Paneth cell-like cytoplasmic granules are another uncommon variant of neuroendocrine carcinoma of the prostate. The prognosis of these tumors is determined by accompanying conventional adenocarcinoma component [24,26-28]. Rare cases of prostate cancer lacking both AR and neuroendocrine expression may be seen. These tumors may have variable morphologic features, including squamous, spindle cell, and small cell components [29,30].

De novo neuroendocrine carcinomas of the prostate are much less common, representing less than 2% of the prostatic carcinomas. These tumors occur in patients lacking any history of cancer therapy and have similar morphology to that of post-therapy neuroendocrine carcinoma, including small-cell, large-cell, and carcinoid-like patterns. The patients with these tumors usually present with an advanced disease and have a higher mortality rate [31,32]. The neuroendocrine features may be present in the primary location, metastatic site, or both [33].

Therapies targeting androgen receptor in prostate cancer: Current status and future directions

Following androgen deprivation therapy, prostate cancers usually relapse as they evolve into CRPCs with a strong tendency to develop metastatic disease. In the last decade, crucial advances in the treatment of prostate cancer have been made, and novel treatment strategies have been developed. The androgen receptor has emerged as the most crucial factor regulating the activity and spread of cancer cells. Consequently, most current treatment regimens are designed to block or modify the AR pathway. These therapies help to reduce androgen production and suppress AR activity. Unfortunately, these treatment modalities provide only temporary tumor suppression in CRPC patients and fail to produce a complete cure. This lack of curative relief is due to various factors, including AR gene mutations or splicing variations, which result in AR reactivation. Complete elimination of the AR protein in prostate cancer cells is a promising solution that can provide curative relief. Multiple strategies have emerged, and several potent agents that reduce AR protein levels were reported. The potential mechanisms involved include inhibition of heat-shock proteins, suppression of AR splicing, prevention of nuclear localization of AR, and suppression of AR N-terminal, among others [34-40]. Using small molecules to block AR dimerization and thus prevent its activation is another promising strategy against prostate cancer [41]. Thus, the elimination of AR protein or its function appears to be a realistic solution for avoiding AR reactivation during androgen deprivation therapy in prostate cancers.

Conclusion

In conclusion, this paper briefly updates the structure and function of the androgen receptor and reviews its role in the development and progression of prostate cancer. The androgen receptor is currently an essential target for prostate cancer therapy.

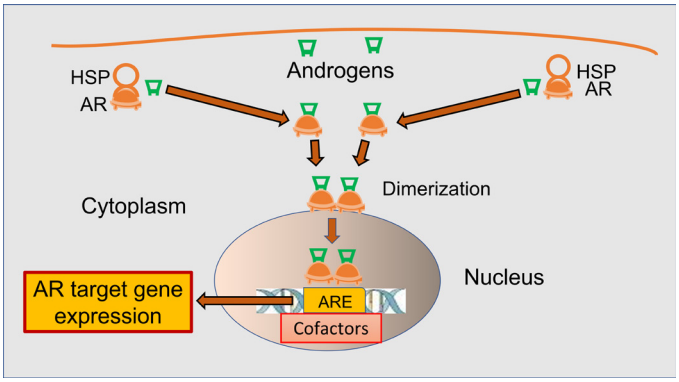

Figure 1: A cartoon showing the details of the androgen receptor gene that consists of 8 exons that give rise to a protein composed of four regions: from the N-terminal, an NH2 terminal transactivation domain (NTD) encoded by exon 1, a DNA-binding domain (DBD) encoded by exons 2-3, a hinge region encoded by exon 4, and a ligand binding domain (LBD) encoded by exons 5-6.

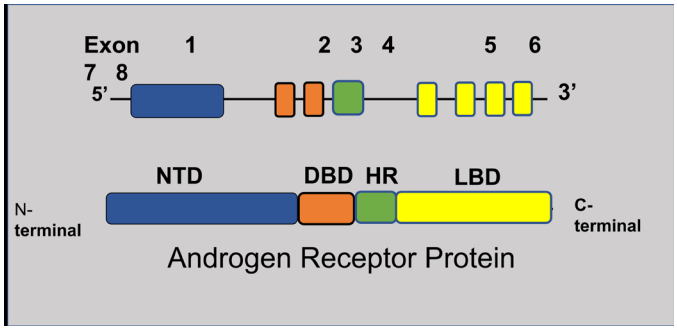

Figure 2: A cartoon depicting the sequence of events leading to the activation of the androgen receptor. The inactive receptor is typically bound to heat shock proteins (HSPs) 70 and 90, which act as chaperone proteins. After combination with androgen, the receptors disengage from HSPs, become activated, undergo dimerization, enter the nucleus, and bind to the androgen response element (ARE). These changes result in ARE protein expression that stimulates cellular proliferation and PSA production. Cofactors modulate the interaction of ARE and the DNA binding domain of AR.

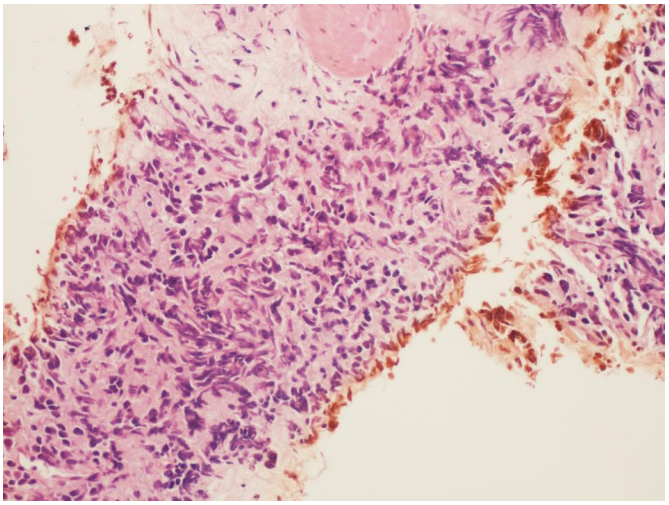

Figure 3: Needle core biopsy featuring small cell carcinoma composed of small, somewhat elongated cells with scanty cytoplasm and crushing artifact (Hematoxylin and eosin stain).

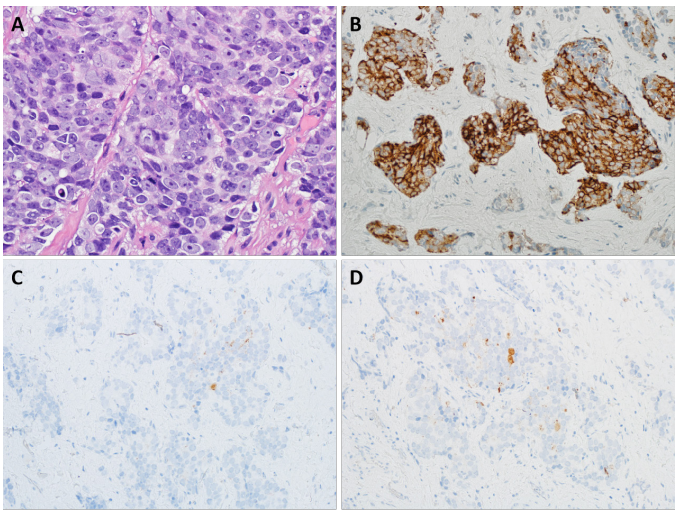

Figure 4: A. Large cell neuroendocrine carcinoma of the prostate comprises clusters of large cells with relatively abundant cytoplasm (Hematoxylin and eosin stain). **B**, Immunohistochemical staining of large cell neuroendocrine carcinoma with strong reactivity for synaptophysin and negative staining for PSA **C.** and androgen receptor **D.**

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