

Original Article

Implication of androgen receptor in urinary bladder cancer: a critical mini review

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Received August 13, 2013; Accepted August 28, 2013; Epub September 12, 2013; Published September 15, 2013

Abstract: Cancer is probably the most dreaded disease of mankind and the bladder cancer is the fifth most common type of cancer worldwide. It is a major cause of cancer morbidity and mortality. From amongst the bladder cancer, the Transitional Cell Carcinoma (TCC) is the most prevalent cancer of the bladder and accounts for 90% of all bladder cancer cases. Despite such a high prevalence, the molecular mechanism involved in the induction of bladder carcinoma and its progression are poorly understood. Tumorigenesis and tumor progression of bladder carcinomas are thought to result from the accumulation of multiple genetic alterations. The Androgen Receptor (AR) gene is located on the q arm of X chromosome (q11-12) and considered as a ligand-inducible transcription factor that regulates target gene expression. The Androgen plays a vital role in the development and maintenance of the normal urinary bladder. The AR is also involved in the development and progression of urinary bladder carcinoma, which is the most common type of carcinoma. Mutation in AR alters the ligand binding ability that may cause the progression and development of bladder cancer. Tumorigenesis and tumor progression are thought to result from changes in the function of hormonal receptor gene. The accumulation of the changes in AR expressions, determines the tumor's phenotype and ultimately the patient's clinical outcome. The early detection of which may help in management and prediction, how will it behave and respond to the therapeutic regimen. The present review aimed to study the mechanism and alteration of AR gene that play a vital role in the tumorigenesis of bladder carcinoma.

Keywords: Androgen receptors, TCC, DNA-binding domain, tumour progression, CAG repeat

Introduction

Cancer is a notorious killer disease of both men and women [1-4]. Bladder cancer worldwide is a major and also the fifth most common type of cancer [1]. There are three major subtypes of bladder cancers: Transitional Cell Carcinoma (TCC), Squamous Cell Carcinoma (SCC) and Adenocarcinoma. Of these the transitional cell carcinoma (TCC) is the most prevalent which singularly constitute 90% of all bladder cancer cases [5-7]. Carcinoma of the urinary bladder is also reported to be the most common cancer in men [8]. Earlier investigators have shown that androgen receptor (AR) signaling plays an important and critical role in the genesis and development of bladder cancer, which may explain some of the differences between male and female tumors.

Tumorigenesis and tumor progression of bladder cancer are thought to result from changes in the function of hormonal receptor genes [9-11], inactivation of tumour suppressor, vascular endothelial growth factor [12] or promoter hypermethylation as in the case of other cancer types [2-4, 13-16].

The alteration in androgen receptor gene and over expression, determines a tumor's phenotype and ultimately the patient's clinical outcome. The detection of it at an early stage may help predicting how it will behave and act in response to the cancer therapy.

In the present paper, we have reviewed the mechanism and alterations of AR gene that play vital role in the tumorigenesis and tumor progression of bladder carcinoma, which might

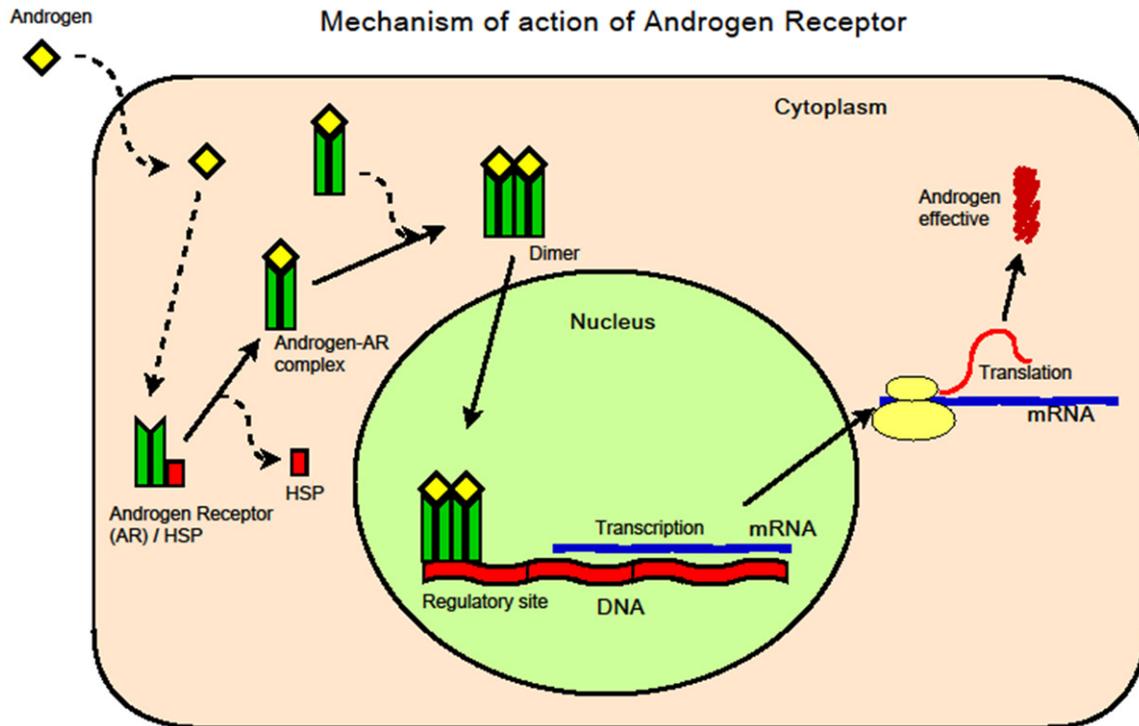


Figure 1. Mechanism of action of Androgen Receptor.

contribute to development of prognostic biomarkers. In addition, it will further strengthen the understanding towards the development of new anticancer drugs.

Structure and chromosomal location of androgen receptor

The Androgen Receptor is located on X chromosome (q11-12) and considered as a ligand-inducible transcription factor that regulates target gene expression [17]. The AR gene spans 90 kb on chromosomal DNA containing eight exons and encodes for a protein of about 917 amino acids [18, 19]. AR proteins consist of four domains: NH₂-terminal domain, a highly conserved DNA-binding domain (DBD), a hinge domain, and a ligand-binding domain (LBD) [20]. The DNA-binding domain (DBD) is critical in the recognition of specific DNA sequences (androgen response elements), and DNA-dependent dimerization of the receptor [21]. The another important ligand-binding domain (LBD) is situated in the AR C-terminal domain, is important in recognition and docking of androgens [22, 23]. The hinge region is important part of Androgen receptors that controls the trans activating properties of the androgen

receptor [24]. Both DNA and ligand binding domains play vital role in the targeting of the receptor to specific sequences. The domain that is structurally different is N-terminal domain (NTD) also plays a key role in the regulation of transcription process.

Mechanism of action of androgen receptor

Androgen plays a crucial role in the growth, differentiation and maintenance of urinary bladder and prostate tissue. Androgen demonstrates its activity in association with the AR that belongs to the nuclear receptor family. The actions of androgen are mediated by a specific receptor protein, the androgen receptor (AR) (Figure 1) [25, 26]. After binding to specific DNA-sequences, the receptor dimerizes with another molecule resulting into specific activation of transcription at discrete sites on the chromatin [27]. The androgen receptor therefore has a vital role in regulation of gene expression through the transcription factor activation via DNA binding.

Mutations in the androgen receptor gene

Molecular alteration or the mutation is the other import routes through which AR serves to

have an important role in the genesis of urinary bladder carcinoma. Earlier studies have revealed different type mutations in the AR [28]. The receptor protein contains: DNA-binding domain (DBD), C-terminal ligand binding domain (LBD) and a structurally distinct N-terminal domain (NTD) all these domains are very important for trans activation [29] and therefore all domains are important and essential for the normal functioning of AR. If any alteration occurs in any of these domains that can change the binding ability of androgen and thereby can alter the functions of AR. It is now well established that the germ line mutations occur in the AR gene that alters the receptor's function [30-32]. The somatic missense mutations in the LBD of the AR gene causes receptor variants with either reduced ligand-dependent activation or enhance the activity of receptors in response to ligands [33-37]. The nuclear receptors are reported to have high sequence homology in DBD, these, however, do show certain differences in the amino acids that directly associate with the DNA eliciting their specificity [38]. Alteration or mutation in DBD causes tyrosine conversion into cysteine and thereby causing androgen insensitivity syndrome [39].

Investigators have already found and reported that several types of mutations in AR gene including point mutations, Nucleotide insertions or deletions, and premature termination, complete or partial gene deletions, and intronic mutations [40, 41]. Point mutations causes amino acid substitutions and this type of mutation is predominantly localized to the AR Ligand Binding Domain.

The androgen receptor and bladder cancer progression

Urinary bladder cancer is considered to be heterogeneous and unpredictable lesions. There is a need for a better treatment of this lesion. Steroid hormone may have a role in the regulation of the development or function of the urinary bladder. Some of the investigators have also found the fact that steroid hormone receptors (eg: Estrogen and Progesterone receptors) have their roles in the normal urinary bladder and pseudo membranous trigonitis [42]. An experimental study showed that Progesterone Receptor is observed in the basal layer and Estrogen Receptor predominately in the superficial layer of the epithelium [42]. A study in ani-

mal model has also established that estrogen treatment increases the expression of Progesterone Receptor. Among various studies on molecular abnormalities associated with tumor progression and development, the AR gene seems to have beyond any doubt, very critical role in the genesis of urinary bladder carcinoma [43-45].

Androgens and the ARs have shown a vital role in the in carcinogenesis of the bladder cancer [46-48] therefore it may represent a potential therapeutic target [49]. Androgen receptor expression and the exact functional mechanism of androgen/androgen receptor via their signaling in bladder cancer development have remained so far elusive and unclear. The androgen receptors role in different types of cancer is well documented but still the urinary bladder cancer is not yet a considered/established as an endocrine-related neoplasm. A few investigations have now reported that AR, as a ligand-regulated transcription factor plays a vital role in the development and progression of bladder cancer [50, 51].

Some of the earlier investigators have also revealed the contrasting event and stated that there is no association between stage and loss of AR expression in bladder cancer [47]. While the other reported that higher level of AR expression in non-invasive tumors, and a progressive dwindling expression or the loss of expression with increasing pathologic stage [39]. An immunohistochemical study has however supported the latter view by showing that there is a negative expression of AR in the human urinary bladder [11]. The lower level of expression of AR in normal urinary bladder in contrast with the high expression of AR in the epithelial cells of malignant bladder tissue has found a place in some other studies as well [52, 53]. When the expression patterns of AR were examined in correlation with the stage and grade of tumor, it was found that the expression patterns were not found to be related with stage and grade of tumour.

Several mutational studies were performed on bladder cancer and revealed that the alteration in the sequence of (CAG)_n repeat in the AR gene play an important role in the genesis of bladder cancer. The point mutation in AR causes the loss of its binding ability to normal ligands. Through this, AR appears to be involved

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in the development and progression of carcinoma of bladder as well.

Although many earlier studies were made on AR to understand the exact role or mechanism of androgen and the AR in the genesis and progression of bladder carcinoma, but still the exact mechanism how the AR is exactly involved in the bladder cancer development and progression is not well defined. It underlines the necessity of further detailed analysis to unravel or know precisely the mechanism by which androgen affects the AR pathways therefore, paving of the way for the true characterization/identification of a novel prognostic marker and an important tool to tackle this heterogeneous disease with various biological characteristics i.e the human urinary bladder cancer.

Disclosure of conflict of interest

The authors have no conflicts of interest to disclose.

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