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Performance Dynamics of Splice Ar Variants Re-define Constitutive Reactivation of the Androgen Receptor in Recurrent Prostatic Cancer Patients

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Abstract

Intra-genic rearrangements are a response to anti-androgen therapy and castration in patients suffering from advanced prostatic cancer. Constitutive re-activation of the AR (androgen receptor) in prostatic epithelial cells is re-defined in terms of molecular reconstitution of various organ systems in terms especially of performance dynamic indices. The various dimensions of trans-activation and trans-modulation of the AR receptor are hence incremental response that parallels and duplicates such systems as gene amplification and splicing events that in terms of their heterogeneous nature and structure encompass a wide range of reactivities. It is further to such performance indices that the identity of constitutive phenomena are inherent dynamics of the intra-genic rearrangements as further reflected in potential and real variations in sub-localization of the splicing variants in different sub-cellular compartments and nucleus.

Introduction

Intra-genic rearrangements in the synthesis and activation of AR receptors are a central referential system in the understanding of reactivation of the AR in patients with CRPC. Also implicated is the cross-reactivity of full-length AR molecule with splice variants of the AR receptor protein. Furthermore, the emergence of multiple splice variants appears to primarily determine sub-cellular localization of such splice variants, particularly in terms of cytoplasmic versus nuclear localization. B cell lymphoma gene number 2 (Bcl2) plays a pivotal role as a pro-survival molecule in association with androgen-related signaling implicating PTEN loss, PI3K/AKT phosphorylation and receptor tyrosine kinase activation in progression of androgen-independent prostate cancer [1]. Heat Shock Protein is stress-activated and acts as a multi-functional chaperone protein that is highly expressed in cancer and regulates cell signaling and survival in cancer progression [2]. A positive association exists between AR (androgen receptor) and pan-cytokeratin expression in circulating tumor cells in patients with metastatic castrate-resistant prostate cancer [3]. An association exists between HIF-1alpha and androgen receptor and unregulated HIF-1alpha might contribute to prostate cancer resistance in response to low androgen [4].

Splicing

The mechanisms of splicing of the AR appears to involve also proteolysis with contextual reference to molecular reactivities and constitutive self-assembly and activation by such processes as phosphorylation of serine, threonine, and tyrosine residues on the one hand, and such mechanistic processes as ubiquitination, sumoylation and adenylation of residues. Premature stop codons and the existing extensions of the COOH terminal domains allow for the progression of molecular splicing that may correlate with post-translational modifications of the AR molecule. It is significant to consider system pathways that relate gene mutation with the amplification of various gene sub-families in the realization of constitutively active AR molecules as referable particularly to reactivities of splice molecules with full-length AR molecule. Simultaneous blockade of androgen (Bicalutamide) and a selective oestrogen receptor modulator (Raloxifene) shows synergistic effect on PC3 xenografts [5]. MDV3100 is a potent androgen receptor antagonist with activity in castration

resistant prostate cancer (CRPC) but progression is frequent and implicates AR full-length or variants in cancer progression [6].

Intra-Genic Rearrangements

CRPC may develop through several mechanisms including up-regulation of AR, coactivators and steroidogenic enzymes [7]. Intra-genic exon skipping and splice variant synthesis constitute formulation of cryptic exon determination in the production of truncated AR molecules within systems of biologic response to castration and anti-androgenic therapy. It is well-known that the emergence of CRPC status after such therapy is inevitable with the reappearance of biochemical and morphologic evidence of tumor recurrence. Particularly recognized is the reappearance and progression of metastatic lesions within a context of blood-stream spread. As such, the significance of splice AR variants is an important consideration in further understanding the constitutive natural phenomenon of recurrent disease. In such terms, the further proliferation and migration of prostatic cancer cells is significant in terms of the observed high incidence of mutations in AR gene biology of blood-borne metastatic malignant cells. Inhibition of PIK/mTOR with BEZ235 increases overall levels of AR transcription that is more pronounced on AR splice variants and uncouples AR's transcriptional activity on canonical downstream targets in vivo [8].

Ar Receptor Dynamics

Transactivation and constitutive activation of the AR molecule are believed to constitute a working formula of progression in recurrent tumors in CRCP (castration-resistant prostate cancer) patients. It is within the inclusion of both donor and acceptor splice domains within rearranged AR genes that there evolves substantial receptor activation in these patients. A full variety of splice variants of the AR mRNA or pre-mRNAs has been reported particularly in xenografts of in vivo models of recurrent tumor growth in castrated mice. It is further to such considerations that the dimensions of splicing are themselves constitutive phenomena in the response to anti-androgen therapy and castration. Analysis of specific circulating tumor cells may optimize patient management by identifying those likely to respond to specific targeted agents [9].

System Profiles

System profiles of constitutive reactivations of the AR constitute a whole series of heterogeneous pathway mechanisms that involve the metastatic pathways in particular, and as referential indices of intra-genic rearrangements. It is also to implicitly recognize constitutive recurrence of tumor cells that there evolve systems of gene amplifications and also splicing variations as truncated AR molecules. Lysine-specific demethylase is a key regulator of the AR and oestrogen receptors and its levels correlate with tumor aggressiveness; it regulates vitamin D receptor activity [10]. Particularly crucial are the ligand-binding and DNA-binding sub domains of the AR molecule in terms of reactivation of this receptor after anti-androgen therapy or castration. Induction of transforming growth factor-beta-induced protein promotes prostate cancer growth and metastasis and this is related to dysregulated AR signaling [11]. In such terms, the emergence of metastatic lesions in these patients is constitutive response to initially suppressed androgen therapy. Sensing of such alterations in system pathways appears to constitute a series of splicing that is beyond the intra-genic rearrangement schemes of constitutive reactivation of the AR receptor.

Signaling by AR splice variants, including the clinically relevant AR-V7, is augmented by Vav3, a recognized AR coactivator in CRPC [12]. It is furthermore significant to consider the parameters of constitutive recurrence as essential constitutive splicing of the AR gene and its pre-RNA molecules of production. The performance of incremental splicing is further considered in terms of reactivity of such splicing and truncated protein variants with the full-length AR protein molecule itself. The splicing of AR variants AR-V7 as well as AR-V1 and AR-V9 is regulated coordinately by a single polyadenylation signal in AR intron 3 [13]. Performance increments as modulators of constitutive intra-genic rearrangements are hence tangible indices of the tumor recurrence and metastatic spread as well-delineated by the performance in turn of AR transactivation and trans-modulation of the receptor activities. The full-length receptor and one or more variants can be co-expressed in the same cell under various circumstances, allowing these variants to interact physically and functionally with the full-length receptor or one another during progression of prostate cancer [14]. Metformin and valproic acid synergistically induce a significant decrease in proliferation and an increase in apoptosis in tumor cells in the presence of p53 and androgen signaling [15].

Sub-Cellular Localization

The intra-nuclear localization domain of the variant AR splicing molecules is best characterized in terms of the concurrent presence of the full-length AR protein molecule and as further elucidated by dynamics of sub-cellular localizations of variant molecular forms. As such, such intra-nuclear localization of variant splicing molecules is a potential basis for the constitutive rearrangements within the AR gene. A clear understanding of the multiple transcription factors regulating the AR gene will probably help in advancing hormone therapies to enhance or inhibit receptor activity [16]. The central point of reference in understanding the tumor recurrence after anti-androgen therapies and castration is the core nature and identity dynamics of constitutive reactivation of the AR receptors and this may relate in fact to dynamics of intra-nuclear localization of various splice and truncated protein moieties. Such constitutive phenomena may arise as intrinsic and inherent attributes of the full-length AR protein molecule itself. Mechanisms such as AR over-expression, hypersensitivity, variants and reprogramming are responsible for developing hormone refractory prostate cancer/CRPC [17].

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Transformation of Ar Variant Molecules

Suppression of prostatic epithelial cells and of the transformed molecular variants of the AR protein is a significant constitutive response that arises within contexts of re-utilization also of extra-testicular androgen moieties such as those arising from the adrenals. Furthermore, the initial clinical suppression in tumor growth and spread are best viewed in terms of such therapy as systemic agonist actions on luteinizing hormone releasing hormone as achieved by pharmacologic actions of anti-androgen therapy.

Hence, pathway modulation in terms of potential control and suppression of recurrent prostatic cancer is best viewed as a systemic and widespread series of pathways that in turn modulate and further fine-tune the constitutive nature of intra-genic rearrangements and of the trans-activation/trans-modulation of the AR receptor. In particular, the constitutive reactivations of the AR molecule are essential elements in the virtual absence of ligand binding to the AR receptor. In such terms, performance dynamics are phenomena in the absence of ligand binding as revealed by current clinical forms of management of patients with metastatic tumor or with advanced local tumor growth and infiltration of tissues and organs. The development of anti-androgen action of the developed AR-DNA binding domain inhibitors bypass drug-resistance mechanisms of prostate cancer and target AR chromatin interactions [18].

Conclusion

Dynamics of constitutive reactivation of the AR receptor are viewed as inherent expressions of intra-genic rearrangements and as further projected by the system performances of pathways of positive feed-back response of splicing variants in cooperative synergism of the full-length AR molecules. Potential spread and re-growth of local and systemic deposits of prostate cancer cells are performance derivatives that help re-define the milieu of inter-activities within context of trans-activation versus trans-modulation of the AR receptor protein. System formulation hence hinges on the defined status of a constitutive micro-environment that is projected as systemic pathways of aberrant response and attempted re-constitution of the androgenic milieu within the body systems as a whole.

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