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Gauging the Therapeutic Potential of β arrestin2 Targeting in Prostate Cancer

Anastasios Lymperopoulos*

Laboratory for the Study of Neurohormonal Control of the Circulation, Department of Pharmaceutical Sciences, Nova Southeastern University College of Pharmacy, Fort Lauderdale, FL 33328, USA

Prostate cancer represents a devastating, male sex-specific form of cancer, accounting for approximately one-third of all male cancer cases in the United States alone [1]. This cancer often presents as androgen-dependent, hormone receptor-positive disease that can be successfully managed with targeted therapies aiming at disrupting the function of the Androgen Receptor (AR). Although these therapies are initially effective, a significant portion of the cancer patients develop advanced androgen-independent, hormone-refractory disease [2]. Thus, it comes as no surprise that effective management of prostate cancer is still highly needed to combat the high mortality rate that accompanies this disease [1]. The deregulation of expression and activity of AR and of its interacting protein partners are thought to be involved in the progression of prostate cancer to advanced disease [3,4]. The AR is a member of the nuclear hormone receptor superfamily (ligand-regulated transcription factors), modulating expression of multiple genes involved in the normal development and/or malignant transformation of the prostate gland [4-6].

The AR may also participate in the transition of the prostate cancer to hormone-independent disease [7]. Indeed, approximately one-third of androgen-independent prostate carcinomas show amplification and over-expression of the wild-type AR, suggesting it adjusts to capture the low levels of circulating androgen [8,9]. In another one-third of androgen-independent cases, the AR is mutated allowing it to become activated by other steroids or even, remarkably, anti-androgens [2,10]. In the remaining one-third of androgen-independent cancers, no AR mutations or other alterations are observed, suggesting existence of additional AR-regulatory mechanisms. The AR protein undergoes several types of post-translational modifications, including phosphorylation [11], acetylation [12], SUMOylation [13], and ubiquitination [14]. However, the functional consequences and/or mechanistic involvement of these AR protein alterations with respect to prostate cancer pathogenesis and/or progression remain elusive.

βarrestins are cytosolic adapter proteins that were originally discovered as integral effectors of agonist-dependent G Protein-Coupled Receptor (GPCR) desensitization, based on their ability to terminate G protein signaling from the agonist-bound, active receptor [15]. Nowadays, βarrestins are known to possess two additional very important cellular functions: they also mediate agonist-bound receptor internalization (i.e. sequestration from the membrane into the interior of the cell) following receptor-G protein uncoupling (desensitization) [16], and they can also scaffold other proteins on themselves (form multi-protein complexes), thereby serving, in essence, as signal transducers in their own right (i.e. independently of G proteins) [17]. For example, the ubiquitous βarrestin2 mediates desensitization of the β_2-adrenergic receptor (a prototypic GPCR), its internalization via binding to endocytic machinery components such as clathrin and AP-2 [18,19], and signal transduction from the receptor-βarrestin2 complex as it cycles through the endocytic vesicle compartments, by scaffolding E3 ligases that ubiquitylate both the βarrestin2 itself and the β_2-adrenergic receptor [20,21] or by scaffolding the protein tyrosine kinase Src, which phosphorylates and transactivates growth factor receptors, such as the Epidermal Growth Factor Receptor (EGFR) [22,23].

Recently, βarrestin2 was shown to serve as an AR co-repressor in the LNCaP prostate cancer cell line, raising the intriguing possibility that βarrestin2 might be a prostate cancer suppressor molecule [24]. More specifically, βarrestin2 was found to form a complex with AR and the E3 ubiquitin ligase Mdm2, which, in turn, marks the AR for degradation in the proteasome (ubiquitination) [24]. As a result, βarrestin2 siRNA-mediated knockdown in prostate cancer cells led to increases in the AR-dependent prostate-specific antigen (PSA) expression, whereas over-expression of βarrestin2 causes suppression of PSA gene expression [24]. Of note, increased AR expression or activity (via activating mutations) is sufficient to convert the cancer growth from a hormone-sensitive to a hormone-refractory disease in some prostate cancer cases [25]. On the other hand, there are studies suggesting that AR plays both suppressive and proliferative roles in prostate cancer, and, indeed, in some patients diagnosed with hormone-refractory prostate cancer, the AR expression is lost, implying that diminished AR expression is associated with prostate cancer progression [26]. In light of these clinical findings, the finding of Daaka et al. about the βarrestin2-mediated AR degradation in prostate cancer cells [24] suggests that βarrestin2 might be responsible for the loss of AR expression in this subset of prostate cancer cases, which could render these prostate cancers dependent on other mitogenic or anti-apoptotic signals and pathways (and no longer AR-dependent). Nevertheless, the fact that βarrestin2 acts as a co-repressor of AR-dependent PSA gene expression, via AR ubiquitination and subsequent degradation, in prostate cancer strongly implicates βarrestin2 in prostate cancer pathology and identifies it as a potential new target for prostate cancer pharmacotherapy.

Another, more recent, study provides additional evidence to consolidate the validity of βarrestin2 as a prostate cancer therapeutic target: βarrestin2 was found to promote ERK (Extracellular Signal-Regulated Kinase)1/2-mediated mitogenic signaling and cell proliferation upon β_2-adrenergic receptor stimulation in LNCaP prostate cancer cells over-expressing this βarrestin isoform [27]. More specifically, prostate cancer is usually accompanied by increased β_2-

***Corresponding author:** Anastasios Lymperopoulos, Department of Pharmaceutical Sciences, Nova Southeastern University College of Pharmacy, 3200 S. University Dr., HPD (Terry) Bldg/Room 1338, Fort Lauderdale, FL 33328-2018, USA, Tel: 954-262-1338; Fax: 954-262-2278; E-mail: al806@nova.edu

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adrenergic receptor activation in patients [28]. Using LNCaP prostate cancer cells stably transfected to overexpress it, βarrestin2 was found to be involved in the β_2-adrenergic receptor-dependent activation of ERK1/2 and prostate cancer cell survival & proliferation [27]. In addition, βarrestin2 was found to form a complex with the c-Src kinase upon β_2-adrenergic receptor activation in these cells, and this complex formation was blocked by a c-Src inhibitor, resulting in suppressed prostate cancer cell proliferation [27]. Thus, in addition to its effects on the AR and on AR-dependent gene transcription in prostate cancer cells, βarrestin2 appears to promote prostate cancer growth also through stimulatory effects on β_2-adrenergic receptor-induced mitogenic kinase signaling (such as ERK1/2- and Src-dependent signaling) (Figure 1).

To sum up, βarrestin2 poses as a very attractive, novel molecular target for prostate cancer therapy, as it positively affects prostate cancer progression and cell proliferation through a variety of different signaling mechanisms, at least two of which have already been uncovered: a) enhanced AR degradation which converts the cancer from androgen-dependent to androgen-independent (castration-resistant, more advanced type of disease), and b) enhanced mitogenic signaling via, at least, c-Src and ERKs, which readily stimulates prostate cancer cell proliferation. As more and more prostate cancer-promoting signaling pathways in which βarrestin2 is involved get delineated, the value of targeting this ubiquitous protein adapter molecule for prostate cancer therapy will constantly increase, as well. Furthermore, given that its role in pro-carcinogenic signaling appears to be central, since it participates in more than one signaling cascades in prostate cancer cells, the potential of therapeutic targeting of βarrestin2 for prostate cancer could be enormous. Adding to this notion is the fact that βarrestin2 is seemingly involved in various other types of malignancies, as well, e.g. breast cancer, ovarian cancer, bladder carcinomas, etc. [29,30]. On the downside, its ubiquitous tissue/organ expression hints at its pharmacological targeting being most likely burdened with a multitude of side-effects, thus necessitating prostate tissue-specific drug delivery methods, in case a βarrestin2-specific inhibitor drug ever gets to be successfully developed and reach the clinical trial stage for prostate cancer therapy. Nevertheless, the urgent need to find new and innovative treatments for prostate cancer, given the paucity of currently available efficacious agents to combat this devastating disease, coupled with the apparently nodal role of βarrestin2 in the signaling pathways leading to proliferation inside the prostate cancer cells, make the benefit-to-risk ratio of developing a βarrestin2 inhibitor for prostate cancer therapy very favorable and, consequently, a goal a great deal worth pursuing.

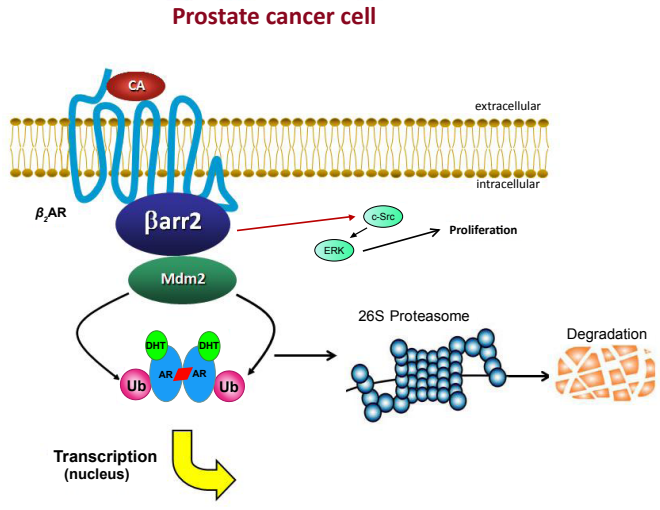

Figure 1: Two diverse signaling pathways inside prostate cancer cells leading to disease progression that are regulated by βarrestin2. See text for details. CA: Catecholamine; β_2AR: beta2-adrenergic receptor; βarr2: βarrestin2; DHT: dihydrotestosterone (androgen receptor agonist); Ub: ubiquitin; AR: androgen receptor.

Disclosures

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