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.

β-arrestins 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, β-arrestins 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 β-arrestin2 mediates desensitization of the β₂-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-β-arrestin2 complex as it cycles through the endocytic vesicle compartments, by scaffolding E3 ligases that ubiquitylate both the β-arrestin2 itself and the β₂-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, β-arrestin2 was shown to serve as an AR co-repressor in the LNCaP prostate cancer cell line, raising the intriguing possibility that β-arrestin2 might be a prostate cancer suppressor molecule [24]. More specifically, β-arrestin2 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, β-arrestin2 siRNA-mediated knockdown in prostate cancer cells led to increases in the AR-dependent prostate-specific antigen (PSA) expression, whereas over-expression of β-arrestin2 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 β-arrestin2-mediated AR degradation in prostate cancer cells [24] suggests that β-arrestin2 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 β-arrestin2 acts as a co-repressor of AR-dependent PSA gene expression, via AR ubiquitination and subsequent degradation, in prostate cancer strongly implicates β-arrestin2 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 β-arrestin2 as a prostate cancer therapeutic target: β-arrestin2 was found to promote ERK (Extracellular Signal-Regulated Kinase)1/2-mediated mitogenic signaling and cell proliferation upon β₂-adrenergic receptor stimulation in LNCaP prostate cancer cells over-expressing this β-arrestin isoform [27]. More specifically, prostate cancer is usually accompanied by increased β₂-
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 potential of therapeutic targeting of βarrestin2 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.

**Disclosures**

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