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-
Two diverse signaling pathways inside prostate cancer cells leading to disease progression that are regulated by β-arrestin2. See text for details. CA: Catecholamine; βAR: beta2-adrenergic receptor; βarr2: Barrestin2; DHT: dihydrotestosterone (androgen receptor agonist); Ub: ubiquitin; AR: androgen receptor.

Figure 1: Two diverse signaling pathways inside prostate cancer cells leading to disease progression that are regulated by β-arrestin2. See text for details. CA: Catecholamine; βAR: beta2-adrenergic receptor; βarr2: Barrestin2; DHT: dihydrotestosterone (androgen receptor agonist); Ub: ubiquitin; AR: androgen receptor.


