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Editorial

# βArrestin2 & Prostate Cancer

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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]. The deregulation of expression and activity of the androgen receptor (AR) is thought to be involved in the progression of prostate cancer to advanced disease [2,3]. 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 [3–5].

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 [6]. 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) [7], 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) [8]. 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 [9]. 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) [9]. 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 [9].

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 $\beta_2$-adrenergic receptor stimulation in LNCaP prostate cancer cells over-expressing this βarrestin isoform [10]. 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 $\beta_2$-adrenergic receptor-induced mitogenic kinase signaling (such as ERK1/2- and Src-dependent signaling).

In conclusion, 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 cascade 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. [11,12]. 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.

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