

The role and mechanism of β -arrestins in cancer invasion and metastasis (Review)

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Abstract. β -arrestins are a family of adaptor proteins that regulate the signaling and trafficking of various G protein-coupled receptors (GPCRs). They consist of β -arrestin1 and β -arrestin2 and are considered to be scaffolding proteins. β -arrestins regulate cell proliferation, promote cell invasion and migration, transmit anti-apoptotic survival signals and affect other characteristics of tumors, including tumor growth rate, angiogenesis, drug resistance, invasion and metastatic potential. It has been demonstrated that β -arrestins serve roles in various physiological and pathological processes and exhibit a similar function to GPCRs. β -arrestins serve primary roles in cancer invasion and metastasis via various signaling pathways. The present review assessed the function and mechanism of β -arrestins in cancer invasion and metastasis via multiple signaling pathways, including mitogen-activated protein kinase/extracellular signal regulated kinase, Wnt/ β -catenin, nuclear factor- κ B and phosphoinositide-3 kinase/Akt.

ubiquitous scaffolding proteins initially identified during the purification of the β -adrenergic receptor kinase (2). β -arrestins are involved in various physiological and pathological processes, including G protein-coupled receptor (GPCR) desensitization, sequestration and vesicle trafficking (3). Four members of the arrestin family have been identified so far, including arrestins 1, 2, 3 and 4 (4). Arrestin1 and arrestin4 are visual arrestins, while arrestin2 (β -arrestin1) and arrestin 3 (β -arrestin2) are non-visual (5). Arrestin1 is localized in rods and cones, whereas arrestin4 is localized exclusively to the latter. β -arrestin1 and β -arrestin2 mediate GPCR desensitization and internalization, and are widely distributed throughout various tissues and cells (6). β -arrestin1 and β -arrestin2 accumulate in the cytoplasm of cells, however β -arrestin1 also accumulates in the nucleus (7).

β -arrestins serve a role as signal transducers by acting as multifunctional scaffolds, as downstream targets of various types of receptor or by participating in receptor-independent mechanisms (8). In addition, β -arrestin1 is recruited into the nucleus to mediate the transactivation of the epidermal growth factor receptor (EGFR) (9) and the vascular endothelial growth factor receptors-2 and -3 (10,11). The present review assessed the role of β -arrestins in the invasion and metastasis of cancer by interacting with certain signaling pathways, including the mitogen-activated protein kinase (MAPK), extracellular signal regulated kinase (ERK), Akt, Wnt and nuclear factor (NF)- κ B pathways (12-16).

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1. Introduction

Arrestins are a small family of proteins that regulate signal transduction at G protein-coupled receptors (1). β -arrestins are

2. Structure of β -arrestins

There are two types of β -arrestins: β -arrestin1 (53 kDa) and β -arrestin2 (46 kDa), located on chromosomes 7 and 11, respectively (17,18). The amino acid sequences of β -arrestin1 and β -arrestin2 are 70% identical (5) and sequence similarity between β -arrestins is highly conserved across vertebrate and invertebrate species, including humans, mice, rats and frog (19,20). At rest, β -arrestins exist as long chained molecules that contain two concave lobes (an N-terminal domain and a C-terminal domain), which are folded by two layers of antiparallel β -sheets (Fig. 1). The convex N-terminal domain contains a short α -helix and is linked to the C-terminal domain via a polarized core, which is formed through charged residues of salt bridge constitutes and functions to maintain

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its correct position (21,22). β -arrestin1 contains an additional cationic amphipathic helix that serves as a reversible membrane anchor (23). When inactive, the polarization core of β -arrestins relocates to the junction between the N- and C-terminal domains and the carboxyl tail of the C-terminus approaches the binding region. Following activation and subsequent polarization, the β -arrestin core is destroyed, the C-terminus carboxyl tail is released and the binding regions of clathrin and adaptin protein-2 (24,25), c-Jun N-terminal kinase (JNK)3 (26) and ERK1/2 (27) are exposed.

3. Function of β -arrestins in cancer invasion and metastasis

β -arrestins in the Src/MAPK signaling pathway. The MAPK pathway serves an important role in regulating the various physiopathological processes involved in tumorigenesis and the development of cancer (28). There are three main families of MAPKs: ERKs, JNKs and stress-activated protein kinases (p38/SAPKs) (Fig. 2) (29). The MAPK/ERK signaling pathway regulates the proliferation, migration and invasion of tumor cells, and is activated by various cell membrane receptors, including receptor tyrosine kinases, GPCRs and cytokine receptors (30,31). MAPK/ERK overexpression has been demonstrated to promote the epithelial-mesenchymal transition (EMT) (32-35) and the expression of matrix metalloproteases (MMPs) (36-38). Inhibiting the MAPK/ERK signaling pathway may therefore suppress tumor cell invasion and migration (39). β -arrestins, as scaffold proteins, are associated with certain components of the MAPK cascade and downstream targets of various GPCRs, which promote the progression of cancer (40).

Fong *et al* (41) demonstrated that the ability of lymphocytes taken from β -arrestin2-deficient and GPCR kinase 6-deficient mice to respond to chemokine receptor (CXCR)-mediated migration and invasion was markedly attenuated. Additional studies revealed that the CXCR7/CXCR4 complex recruits β -arrestin2, leading to the preferential activation of β -arrestin2-dependent signaling pathways, including ERK1/2, p38 MAPK and SAPK. However, the knockdown of β -arrestin2 expression using either small interfering RNA (siRNA) or a dominant negative mutant attenuated this increase in cell migration (42-44). In addition, it was demonstrated that isoproterenol, an agonist of β_2 adrenergic receptors, increases the formation of β -arrestin2-Src complex, resulting in the proliferation of prostate cancer cells (45). It has been determined that prostaglandin E2 (PGE2)-induced β -arrestin1 and Src activation is vital for the transactivation of EGFR, downstream activation of Akt, and the migration and metastasis of colorectal carcinoma cells (46). Lan *et al* (47) demonstrated that β -arrestin1 knockdown reduces tumor growth and survival in xenograft models, inhibits the activity of Src and suppresses Src signaling, thus inhibiting glioblastoma (GBM) cell proliferation and invasion. Ge *et al* (48) determined that the protease-activated receptor (PAR)-2 is upregulated by trypsin-like serine proteases and promotes cell migration by activating β -arrestin-dependent ERK1/2 signaling in MDA-MB-231 cells. The siRNA-mediated silencing of β -arrestin1 and β -arrestin2 reduces ERK1/2 activation and MDA-MB-231 cell metastasis. Additionally, Parisi *et al* (49) revealed that PAR-2 forms protein complexes

with β -arrestin and ERK signaling molecules that are enriched in pseudopodia. Insulin-like growth factor 1 receptor-induced ERK1/2 activation, initiated by β -arrestin1, associates with murine double minute 2 (50). Furthermore, nicotinic acetylcholine receptors (51), CXCR4 (52), CXCR7 (53) and KISS1 receptors (54) have been demonstrated to promote cancer invasion via β -arrestin-dependent MAPK signaling. In lung tumors, β -arrestin1-Src signaling is associated with the translocation of β -arrestin1 into the nucleus. Nuclear β -arrestin1 is then recruited to promote the transcription of E2 factor and histone acetylation (55).

β -arrestins in the Wnt signaling pathway. The Wnt family of secreted glycoproteins mediates the proliferation, invasion and migration of cells through β -arrestin-dependent (56) canonical and noncanonical signaling, which involves cell division cycle protein 42 (57), JNK (58) and the small G proteins RhoA and Rac (59). Wnt/ β -catenin signaling serves a fundamental role in various cellular processes. The stimulation of β -catenin activates certain downstream effector molecules (60-63) to initiate the transcription of specific target genes, including MMP9, cyclin D1 and c-Myc (64) in a variety of tumors (62,65-67). In addition, the Wnt/ β -catenin pathway may regulate the EMT, which is an important step in the induction of cell invasion and metastasis (68-70). The EMT involves various critical mesenchymal markers, including E-cadherin, vimentin, N-cadherin, zinc finger proteins (Snail/SNAI1 and Slug/SNAI2), twist-related protein 1 and zinc finger E-box-binding homeobox 1 and 2 (71,72). Previous studies have demonstrated that β -arrestins modulate the expression of these proteins via the Wnt signaling pathway (73-75), thereby regulating the EMT. During the EMT, epithelial cells lose their polarity and a transition occurs from an epithelial phenotype associated with the basement membrane, to a mesenchymal phenotype that promotes cell migration and invasion, the inhibition of apoptosis and degradation of the extracellular matrix (ECM). Previous studies have determined that the interaction between β -arrestins and disheveled segment polarity proteins (DVL) leads to the activation of Wnt signaling and lymphoid enhancing binding factor (LEF)-mediated transcription (Fig. 3) (76,77).

Rosanò *et al* (9) determined that endothelin-1 (ET-1) activates endothelin-A receptor (ETAR) and promotes ovarian cancer cell invasion and metastasis due to its interaction with β -arrestin scaffold proteins. β -arrestins may regulate ETARs by forming two trimeric complexes that stabilize β -catenin and induce the release and inactivation of glycogen synthase kinase (GSK)-3; one that interacts with Src and another that physically associates with axin. It has also been demonstrated that zibotentan (ZD4054), a specific ETAR antagonist, inhibits the engagement of β -arrestins in ETAR interactions and the β -catenin pathway (9). Rosanò *et al* (78) further demonstrated that the interaction between β -arrestin1 and β -catenin regulates the expression of certain β -catenin target genes by promoting the dissociation of histone deacetylase 1 and the subsequent recruitment of p300 acetyltransferase, leading to increased H3 and H4 histone acetylation and thereby inducing the transcription of genes required for cell migration, invasion and the EMT (78). The affected target genes included ET-1, Axin 2, MMP2 and Cyclin D1 (78).

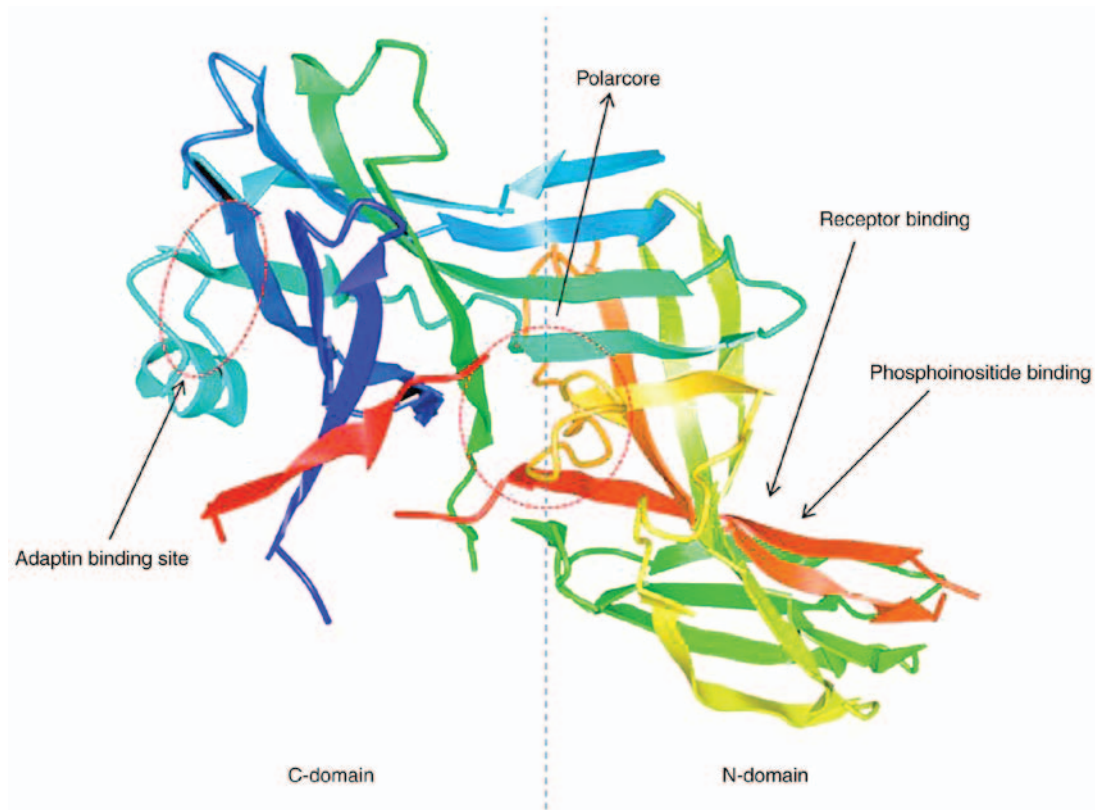


Figure 1. Schematic summary of β -arrestin domain structure that contains a polar core, a receptor binding site, a phosphoinositide binding site and an adaptin binding site.

Turm *et al* (79) revealed that protease-activated receptor 1 (PAR1) also induces the stabilization of β -catenin by promoting the binding of β -arrestin2 to DVL. Additionally, siRNA-DVL treatment led to a decrease in PAR1-induced cell invasion, the inhibition of LEF/T-cell factor transcriptional activity and a reduction of β -catenin accumulation (79). Bonnans *et al* (80) used intestinal tumors taken from $Apc^{\Delta14/+}$ and β -arrestin^{2-/-} mice to demonstrate that β -arrestin2 regulates cell proliferation, adhesion, migration and invasion, as well as ECM remodeling via the Wnt signaling pathway. Additionally, kinesin family member 3A (KIF3A), a member of the kinesin-2 family and a tumor suppressor, inhibits Wnt signaling by interacting with β -arrestin. KIF3A silencing enables β -arrestin to form a complex with DVL2 and axin, which stabilizes β -catenin, increases cell migration and invasion and upregulates stemness markers, thus promoting the malignant potential of cells (15). Duan *et al* (81) demonstrated that β -arrestin1 increases the migration and invasion of prostate cancer cells by initiating the EMT and modulating GSK-3 β / β -catenin signaling. Furthermore, it was determined that β -arrestin1 overexpression promotes the EMT in benign prostate RWPE-1 cells and that β -arrestin1 silencing induces the mesenchymal-epithelial transition in PC3 and DU145 cells, thereby inhibiting and upregulating the expression of E-cadherin and vimentin, respectively, in prostate cancer cells.

β -arrestins in the NF- κ B signaling pathway. NF- κ B is a dimeric transcription factor involved in immune regulation, cell migration, proliferation, survival, angiogenesis and apoptosis (82-84). The NF- κ B family consists of five members,

including NF- κ B1 (p50/105), NF- κ B2 (p52/100), RelA (p65), c-Rel and RelB, which are encoded by NFKB1, NFKB2, RELA, REL and RELB, respectively. NF- κ B is activated in different types of cancer and serves a vital role in the development and progression of tumors (85,86). The NF- κ B signaling pathway involves NF- κ B, the NF- κ B inhibitor (I κ B), the I κ B kinase (IKK) complex and IKK upstream kinases (Fig. 4). Following stimulation, the resulting signal increases the IKK-mediated phosphorylation of I κ B α , resulting in its ubiquitination and degradation (87). This leads to the release of NF- κ B, enabling it to enter the nucleus and regulate multiple downstream target genes (88). Previous studies have demonstrated that interfering with NF- κ B activation may regulate cell invasion, migration, proliferation and death (89,90).

Cianfrocca *et al* (91) demonstrated that interactions between ET-1, ETAR and β -arrestin1 activate NF- κ B signaling. In addition, β -arrestin1 and p65 form a nuclear complex that induces NF- κ B p65 transcriptional activity in epithelial ovarian cancer cells. However, these effects are inhibited by introducing an ETAR antagonist, such as BQ123, to cells or by silencing β -arrestin1 using short hairpin RNA (91). Seo *et al* (26) revealed that the β -arrestin2-associated type III transforming growth factor- β receptor negatively mediates the migration and invasion of MCF10A breast epithelial and MDA-MB-231 breast cancer cells via NF- κ B signaling. In addition, previous studies have demonstrated that β -arrestin2 directly combines with I κ B α , inhibiting its phosphorylation and degradation (82,92,93). It has been determined that β -arrestins are involved in NF- κ B signaling and induce the secretion of cytokines, thus serving an important role in the

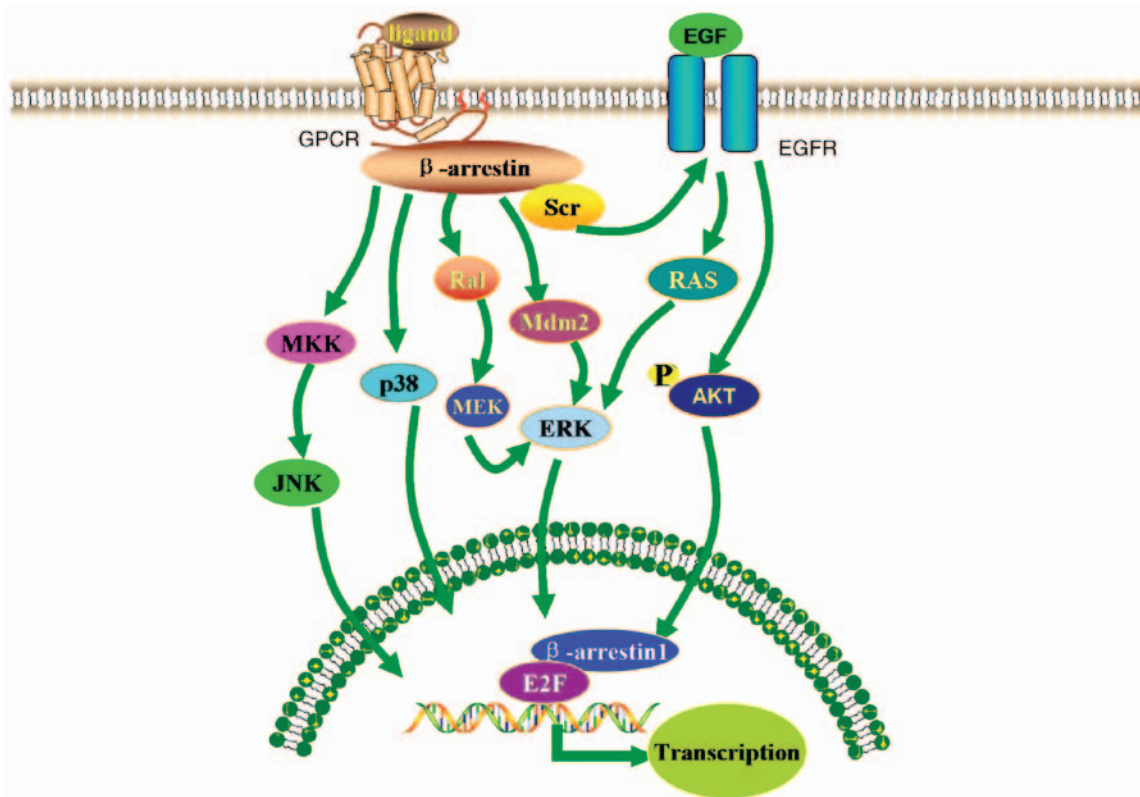


Figure 2. β -arrestin scaffold proteins, together with Src, are associated with multiple constituents of the mitogen-activated protein kinase cascade, downstream of various GPCRs, including JNK, p38 and ERK. Signaling may lead to the transactivation of EGFR to regulate cancer invasion and metastasis. GPCR, G protein-coupled receptors; JNK, Jun amino-terminal kinase; ERK, extracellular signal regulated kinase; EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; E2F, E2 factor; Mdm2, mouse double minute 2; MKK, mitogen activated protein kinase kinase.

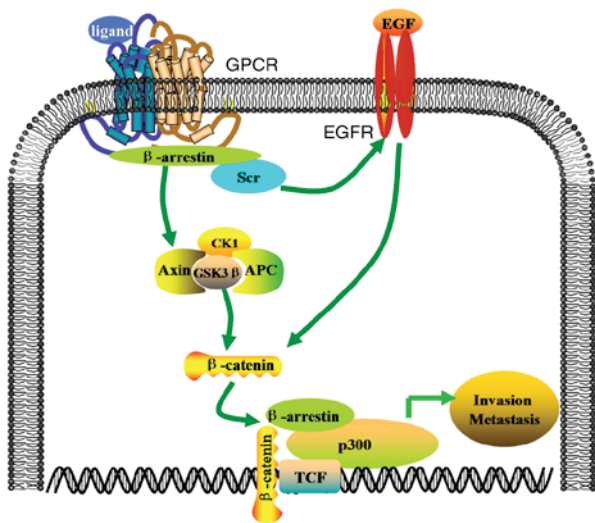


Figure 3. β -arrestin-Src complex induces the direct activation of Wnt/ β -catenin and EGFR transactivation, indirectly leading to β -catenin phosphorylation by promoting the formation of a nuclear β -catenin/TCF complex and recruiting p300 acetyltransferase on these promoter genes, consequently promoting cell migration. EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; GPCR, G protein-coupled receptor; Ck1, casein kinase 1; APC, adenomatous polyposis coli; GSK3 β , glycogen synthase kinase 3 β ; TCF, T-cell factor.

formation of an adaptive microenvironment that induces tumor progression (94,95). MMP9 expression is regulated by tumor necrosis factor- α via the induction of β -arrestin2-dependent

NF- κ B activity (16). Bedini *et al* (96) demonstrated that lipopolysaccharide (LPS)-induced cell migration and increased interleukin-1 β mRNA levels were consistently counteracted by nociceptin/orphanin FQ via β -arrestin2 and resulted in the decreased transcriptional activity of NF- κ B and AP-1.

β -arrestins in the phosphoinositide-3 kinase (PI3K)/Akt signaling pathway. The PI3K signaling pathway serves a primary role in regulating cell proliferation, differentiation, migration and trafficking, as well as maintaining glucose homeostasis (97). PI3K expression increases levels of phosphatidy-(3,4,5)-trisphosphate (PIP3), which recruits Akt to the cell membrane by binding to pleckstrin homology domains (98). Following activation of PI3K/Akt signaling, E-cadherin levels decrease and the expression of snail, slug, vimentin and N-cadherin increase (99-101), thereby inducing the EMT and promoting cell invasion and metastasis (102,103) (Fig. 5).

Zhang *et al* (104) demonstrated that CXCR7 expression is associated with invasion and metastasis in human osteosarcoma (OS) and that CXCR7 knockdown inhibits the proliferation and invasion of OS cells by decreasing the β -arrestin-dependent expression of PI3K, Akt, β -arrestin, proliferating cell nuclear antigen and MMP9. Zou *et al* (105) determined that the PI3K signaling pathway is involved in the β -arrestin1-mediated increase of MMP9 activity and angiogenesis. In addition, Alvarez *et al* (106) demonstrated that β -arrestin1 functions as an adaptor that recruits Src to the obestatin receptor (GPR39), leading to the formation of a GPR39/ β -arrestin1/Src complex, which activates the MMP

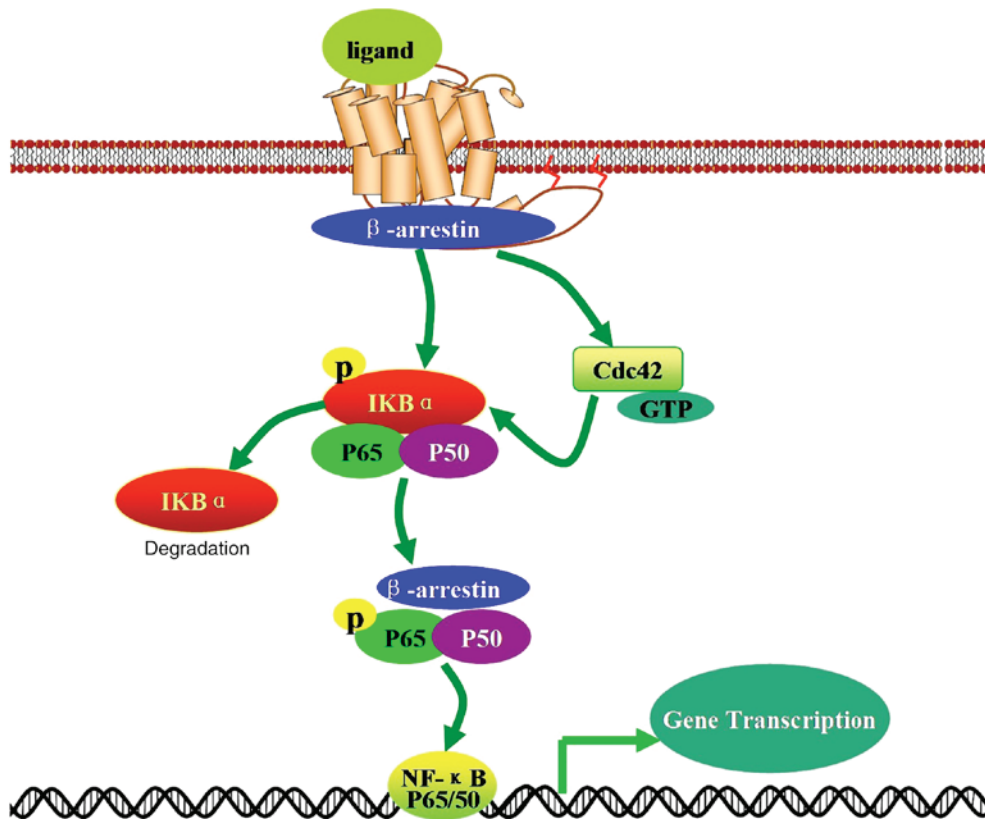


Figure 4. G protein-coupled receptor-mediated β -arrestin activation promotes p65 and I κ B- α phosphorylation and translocation and increases NF- κ B p65 signaling and transcription. Cdc42 regulates the interaction of β -arrestins with GTPases and promotes NF- κ B signaling. I κ B α , NF- κ B inhibitor; NF- κ B, nuclear factor- κ B; Cdc42, cell division cycle 42; GTP, guanosine-5'-triphosphate; p-, phosphorylated.

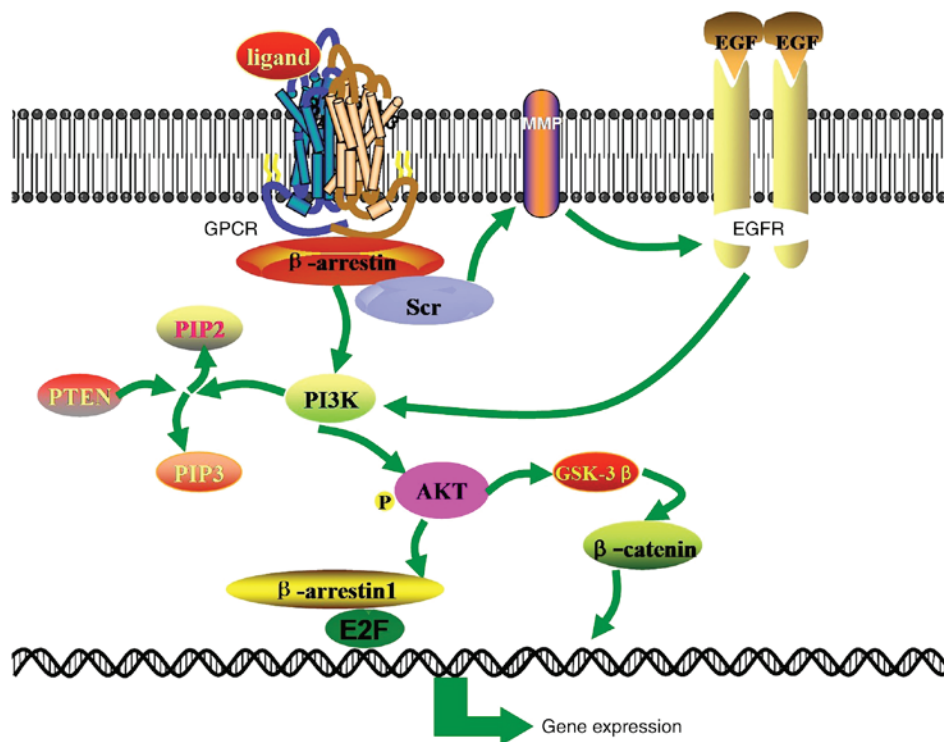


Figure 5. β -arrestin-induced PI3K activation increases membrane PI (3-5)P3 accumulation and activates Akt by inducing its phosphorylation. Activation of PTEN leads to the transformation of PIP3 to PIP2 and the suppression of PI3K/Akt signaling. The β -arrestin-Scr complex causes the transactivation of EGFR and the formation of nuclear β -arrestin1/E2F complex, and promotes the expression of downstream genes. PI3K, phosphoinositide-3 kinase; PIP3, phosphatidylinositol (3-5)-triphosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; EGFR, epidermal growth factor receptor; E2F, E2 factor; EGF, epidermal growth factor; GPCR, G protein-coupled receptor; PTEN, phosphatase and tensin homolog; GSK3 β , glycogen synthase kinase 3 β ; p-, phosphorylated; MMP, matrix metalloproteinase.

family and promotes EGFR transactivation. This activation is responsible for initiating various signaling pathways, including ErbB, PI3K, Akt, mechanistic target of rapamycin and p70S6K1. Nawaz *et al.* (107) demonstrated that the upregulation of microRNA-326 and β -arrestin1 results in the PI3K-dependent reduction of cellular proliferation, colony formation and migration capacity in glioma cells. Additionally, β -arrestins regulate tumor suppressor phosphatase and tensin homolog (PTEN) in PI3K signaling. It was demonstrated that β -arrestins increase the activity of PTEN and consequently suppress activation of the Akt pathway, thus inhibiting cellular proliferation (108). Therefore, β -arrestins serve various positive and negative regulatory effects in the PTEN, PI3K and Akt signaling pathways.

4. Conclusion

Cellular migration and invasion are two processes regarded as the main causes of cancer-associated mortality (109). Tumor metastasis is a complex cascade that involves the following stages: Exit from the primary tumor, cell migration, adherence and invasion via the basement membrane or ECM, entry into the physical circulatory system, further invasion into distant secondary organs or tissues, and the resumption of cellular proliferation (110).

The role of the β -arrestins as primary modulators of tumor invasion and metastasis is documented in the present review. β -arrestin1 is primarily localized in the cytoplasm and nucleus of cells, whereas β -arrestin2 is distributed in the cytoplasm alone (111). Consequently, β -arrestin1 and β -arrestin2 exhibit different functions in the regulation and progression of malignant tumors via various signaling pathways. β -arrestin1 and β -arrestin2 are involved in GPCR-mediated signaling pathways but β -arrestin1 may also participate in GPCR-mediated nuclear signaling. Kang *et al.* (112) demonstrated that δ -opioid receptor activation induces the translocation of β -arrestin1 into the nucleus and stimulates the transcription of β -arrestin-dependent p27 and c-fos, thereby facilitating histone acetyltransferase p300 recruitment, resulting in enhanced local histone H4 acetylation and gene transcription. Furthermore, β -arrestin1 and β -arrestin2 exert opposite effects in cancer progression by interacting with different signaling pathways. β -arrestins serve opposite roles in the development of lung cancer. EP4/ β -arrestin1/c-Src-mediated PGE2 activation induces the migration of lung cancer cells (113), whilst homology β -arrestin2 exerts the opposite effect (92). The anti- and pro-cancer effects exerted by β -arrestins in different types of cancer may depend on the tumor microenvironment (TME). The TME consists of various cells, including immune cells, fibroblasts, endothelial cells, perivascular cells, neurons, adipocytes and components of the ECM. Previous studies have demonstrated that the TME serves a vital role in tumorigenesis, tumor invasion and metastasis (114-116).

β -arrestins are scaffolding proteins and are involved in cancer-associated invasion and metastasis, due to their interaction with a range of receptor subtypes. A variety of β -arrestin-biased ligands, which readily associate with β -arrestin, have been identified, including nicotinic acetylcholine receptors, EP2- and EP4-receptors, endothelin type A ETARs and transforming

growth factor β (117). Biased ligands are able to specifically alter the conformation of a receptor, whereas a specific receptor conformation cannot activate all of its downstream signals in parallel and can only promoting a particular downstream signal (118). ZD4054 is an antagonist of β -arrestin-biased signaling in ETARs. ZD4054 selectively blocks β -arrestin signals, eliminates the effects of β -arrestins, decreases Src-EGFR-mediated transfer activation, inhibits the transcription of β -arrestin genes and prevents β -arrestin-mediated ovarian cancer cell invasion and metastasis (9). Therefore, the up- or downregulation of β -arrestins is vital to either promote or inhibit of tumor invasion and metastasis. Further studies that assess the function of β -arrestins in tumor invasion and metastasis via different signaling pathways may elucidate the anti-tumor mechanisms utilized by β -arrestins and provide a potential therapeutic target for the treatment of cancer.

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