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

QING SONG[1,2*], QING JI[1*] and QI LI[1]

[1]Department of Medical Oncology and Cancer Institute of Integrative Medicine, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203; [2]Department of Medical Oncology, Suzhou Hospital of Traditional Chinese Medicine, Suzhou, Jiangsu 215009, P.R. China

Received September 8, 2017; Accepted November 22, 2017

DOI: 10.3892/ijmm.2017.3288

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-κB and phosphoinositide-3 kinase/Akt.

Contents

1. Introduction

Arrestins are a small family of proteins that regulate signal transduction at G protein-coupled receptors (1). β-arrestins are 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)-κB pathways (12-16).

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

Correspondence to: Professor Qi Li, Department of Medical Oncology and Cancer Institute of Integrative Medicine, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, 528 Zhangheng Road, Shanghai 201203, P.R. China
E-mail: lzwf@hotmail.com

*Contributed equally

Key words: β-arrestins, mechanism, cancer, invasion, metastasis

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 Scr/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 isoproterenal, an agonist of β2 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, Parisis *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-arrrestin1-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).

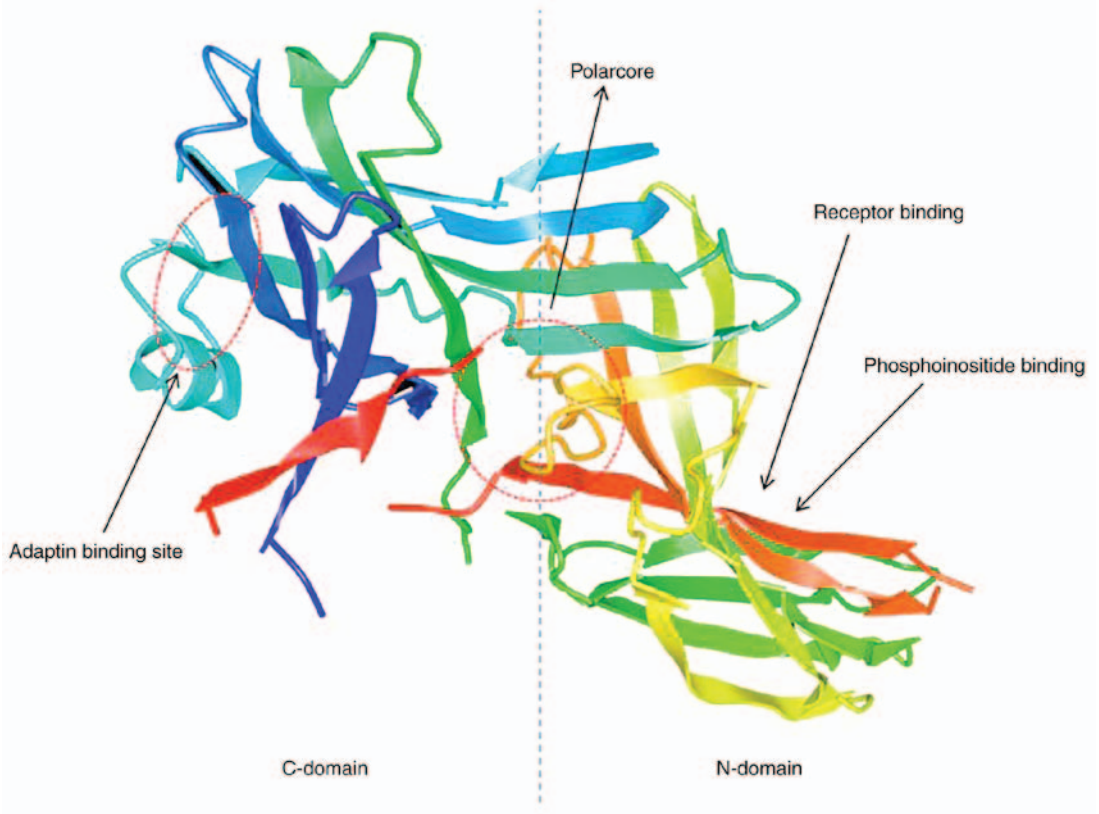

Figure 1. Schematic summary of β-arrestin domain structure that contains a polar core, a receptor binding site, a phosphoinositide binding site and an adaptin binding site.

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 $Apc^{\Delta 14/+}$ 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-3β/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-κB signaling pathway. NF-κB is a dimeric transcription factor involved in immune regulation, cell migration, proliferation, survival, angiogenesis and apoptosis (82-84). The NF-κB family consists of five members, including NF-κB1 (p50/105), NF-κB2 (p52/100), RelA (p65), c-Rel and RelB, which are encoded by NFKB1, NFKB2, RELA, REL and RELB, respectively. NF-κB is activated in different types of cancer and serves a vital role in the development and progression of tumors (85,86). The NF-κB signaling pathway involves NF-κB, the NF-κB inhibitor (IκB), the IκB kinase (IKK) complex and IKK upstream kinases (Fig. 4). Following stimulation, the resulting signal increases the IKK-mediated phosphorylation of IκBα, resulting in its ubiquitination and degradation (87). This leads to the release of NF-κB, enabling it to enter the nucleus and regulate multiple downstream target genes (88). Previous studies have demonstrated that interfering with NF-κB 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-κB signaling. In addition, β-arrestin1 and p65 form a nuclear complex that induces NF-κB 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-κB signaling. In addition, previous studies have demonstrated that β-arrestin2 directly combines with IκBα, inhibiting its phosphorylation and degradation (82,92,93). It has been determined that β-arrestins are involved in NF-κB signaling and induce thesecretion of cytokines, thus serving an important role in the

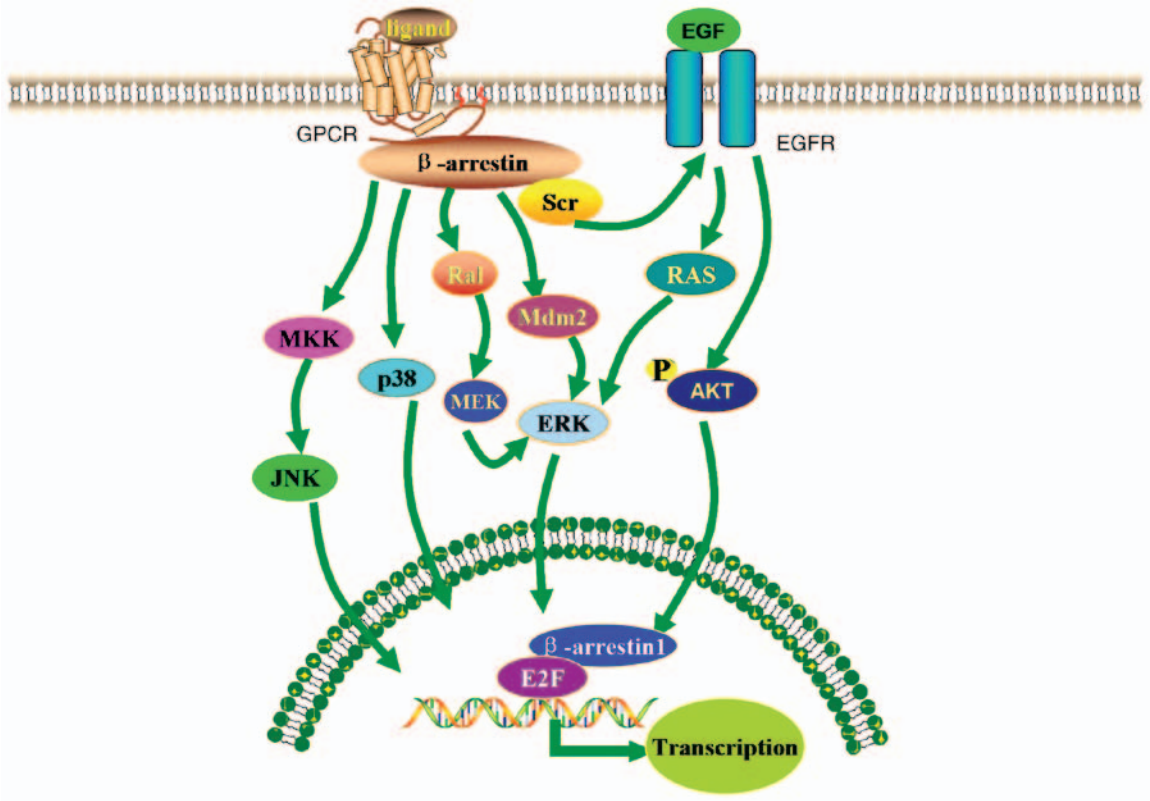

Figure 2. β-arrestin scaffold proteins, together with Scr, are associated with multiple constituents of the mitogen-activated protein kinase cascade, downstream of various GPCRs, including JNK, p38 and ERK. Signaling may lead to the transactivation of EGFR to regulate cancer invasion and metastasis. 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.

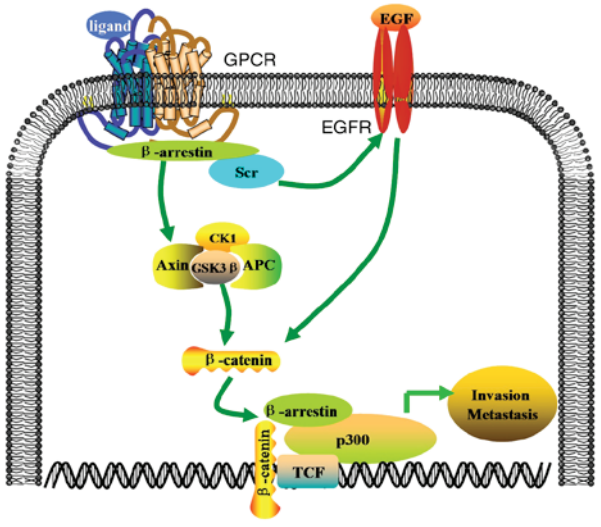

Figure 3. β-arrestin-Src complex induces the direct activation of Wnt/β-catenin and EGFR transactivation, indirectly leading to β-catenin phosphorylation by promoting the formation of a nuclear β-catenin/TCF complex and recruiting p300 acetyltransferase on these promoter genes, consequently promoting cell migration. EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; GPCR, G protein-coupled receptor; Ck1, casein kinase 1; APC, adenomatous polyposis coli; GSK3β, glycogen synthase kinase 3β; 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-κB activity (16). Bedini *et al* (96) demonstrated that lipopolysaccharide (LPS)-induced cell migration and increased interleukin-1β mRNA levels were consistently counteracted by nociceptin/orphanin FQ via β-arrestin2 and resulted in the decreased transcriptional activity of NF-κB 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 phosphatidyl-(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

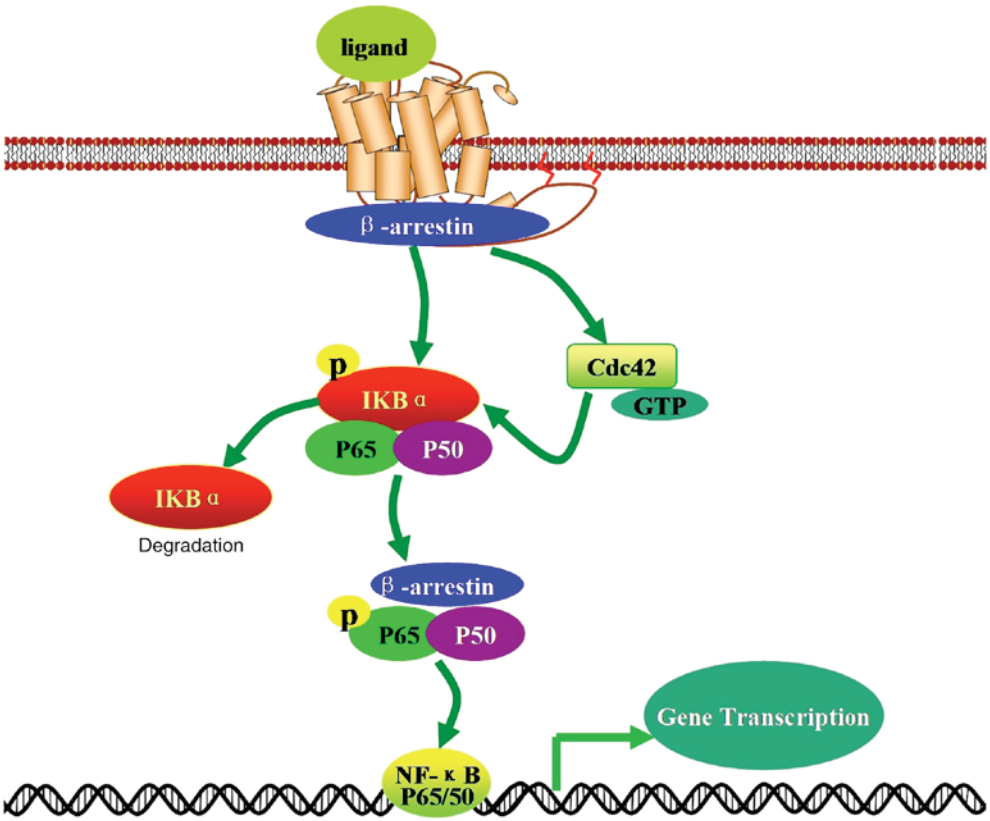

Figure 4. G protein-coupled receptor-mediated β-arrestin activation promotes p65 and IκB-α phosphorylation and translocation and increases NF-κB p65 signaling and transcription. Cdc42 regulates the interaction of β-arrestins with GTPases and promotes NF-κB signaling. IκBα, NF-κB inhibitor; NF-κB, nuclear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

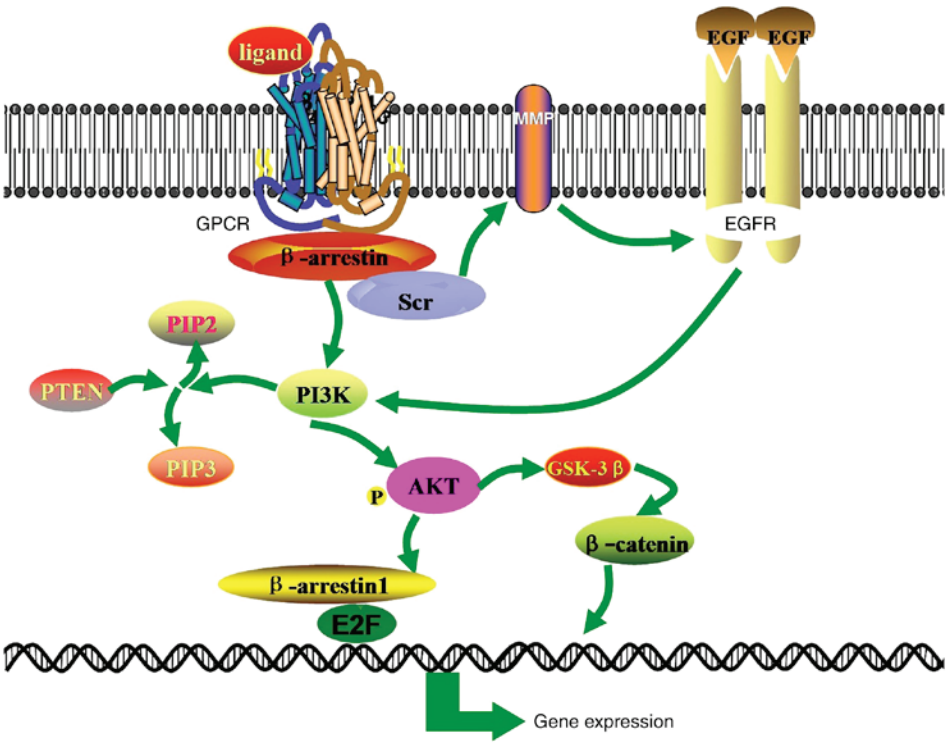

Figure 5. β-arrestin-induced PI3K activation increases membrane PI (3-5)P3 accumulation and activates Akt by inducing its phosphorylation. Activation of PTEN leads to the transformation of PIP3 to PIP2 and the suppression of PI3K/Akt signaling. The β-arrestin-Scr complex causes the transactivation of 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; GSK3β, glycogen synthase kinase 3β; 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.

Acknowledgements

The present review was supported by the International Cooperation Key Project of National Natural Science Foundation of China (grant no. 81520108031), the National Natural Science Foundation of China (grant no. 81573749), the Science Foundation of Shanghai Committee of Science Project (grant no. 14430722900) and the Program for Outstanding Medical Academic Leader and Shanghai Academic Research Leader (grant no. 16XD1403600).

References

1. Gimenez LE, Kook S, Vishnivetskiy SA, Ahmed MR, Gurevich EV and Gurevich VV: Role of receptor-attached phosphates in binding of visual and non-visual arrestins to G protein-coupled receptors. J Biol Chem 287: 9028-9040, 2012.
2. Sharma D and Parameswaran N: Multifaceted role of β-arrestins in inflammation and disease. Genes Immun 16: 576, 2015.
3. Smith JS and Rajagopal S: The β-arrestins: Multifunctional regulators of G protein-coupled receptors. J Biol Chem 291: 8969-8977, 2016.
4. Hu S, Wang D, Wu J, Jin J, Wei W and Sun W: Involvement of β-arrestins in cancer progression. Mol Biol Rep 40: 1065-1071, 2013.
5. Gurevich EV and Gurevich VV: Arrestins: Ubiquitous regulators of cellular signaling pathways. Genome Biol 7: 236, 2006.
6. Ranjan R, Gupta P and Shukla AK: Gpcr signaling: β-arrestins kiss and remember. Curr Biol 26: R285-R288, 2016.
7. Kohout TA, Lin FS, Perry SJ, Conner DA and Lefkowitz RJ: Beta-arrestin 1 and 2 differentially regulate heptahelical receptor signaling and trafficking. Proc Natl Acad Sci USA 98: 1601-1606, 2001.
8. Enslen H, Lima-Fernandes E and Scott MG: Arrestins as regulatory hubs in cancer signalling pathways. Handb Exp Pharmacol 219: 405-425, 2014.
9. Rosanò L, Cianfrocca R, Masi S, Spinella F, Di Castro V, Biroccio A, Salvati E, Nicotra MR, Natali PG and Bagnato A: Beta-arrestin links endothelin a receptor to beta-catenin signaling to induce ovarian cancer cell invasion and metastasis. Proc Natl Acad Sci USA 106: 2806-2811, 2009.
10. Rosanò L, Cianfrocca R, Tocci P, Spinella F, Di Castro V, Caprara V, Semprucci E, Ferrandina G, Natali PG and Bagnato A: Endothelin a receptor/β-arrestin signaling to the wnt pathway renders ovarian cancer cells resistant to chemotherapy. Cancer Res 74: 7453-7464, 2014.
11. Spinella F, Caprara V, Di Castro V, Rosanò L, Cianfrocca R, Natali PG and Bagnato A: Endothelin-1 induces the transactivation of vascular endothelial growth factor receptor-3 and modulates cell migration and vasculogenic mimicry in melanoma cells. J Mol Med (Berl) 91: 395-405, 2013.
12. Eichel K, Jullié D and von Zastrow M: β-arrestin drives map kinase signalling from clathrin-coated structures after GPCR dissociation. Nature Cell Biol 18: 303-310, 2016.

13. Bourquard T, Landomiel F, Reiter E, Crépieux P, Ritchie DW, Azé J and Poupon A: Unraveling the molecular architecture of a G protein-coupled receptor/β-arrestin/erk module complex. Sci Rep 5: 10760, 2015.
14. Sun WY, Hu SS, Wu JJ, Huang Q, Ma Y, Wang QT, Chen JY and Wei W: Down-regulation of β-arrestin2 promotes tumour invasion and indicates poor prognosis of hepatocellular carcinoma. Sci Rep 6: 35609, 2016.
15. Kim M, Suh YA, Oh JH, Lee BR, Kim J and Jang SJ: Corrigendum: KIF3A binds to β-arrestin for suppressing wnt/β-catenin signalling independently of primary cilia in lung cancer. Sci Rep 7: 46773, 2017.
16. Lee SU, Ahn KS, Sung MH, Park JW, Ryu HW, Lee HJ, Hong ST and Oh SR: Indacaterol inhibits tumor cell invasiveness and mmp-9 expression by suppressing IKK/NF-κB activation. Mol Cells 37: 585-591, 2014.
17. Conner DA, Mathier MA, Mortensen RM, Christe M, Vatner SF, Seidman CE and Seidman JG: Beta-arrestin1 knockout mice appear normal but demonstrate altered cardiac responses to beta-adrenergic stimulation. Circ Res 81: 1021-1026, 1997.
18. Bohn LM, Lefkowitz RJ, Gainetdinov RR, Peppel K, Caron MG and Lin FT: Enhanced morphine analgesia in mice lacking beta-arrestin 2. Science 286: 2495-2498, 1999.
19. Gu YJ, Sun WY, Zhang S, Wu JJ and Wei W: The emerging roles of β-arrestins in fibrotic diseases. Acta Pharmacol Sin 36: 1277-1287, 2015.
20. Philipp M, Evron T and Caron MG: The role of arrestins in development. Prog Mol Biol Transl Sci 118: 225-242, 2013.
21. Bayburt TH, Vishnivetskiy SA, McLean MA, Morizumi T, Huang CC, Tesmer JJ, Ernst OP, Sligar SG and Gurevich VV: Monomeric rhodopsin is sufficient for normal rhodopsin kinase (grk1) phosphorylation and arrestin-1 binding. J Biol Chem 286: 1420-1428, 2011.
22. Hamdan FF, Rochdi MD, Breton B, Fessart D, Michaud DE, Charest PG, Laporte SA and Bouvier M: Unraveling G protein-coupled receptor endocytosis pathways using real-time monitoring of agonist-promoted interaction between beta-arrestins and AP-2. J Biol Chem 282: 29089-29100, 2007.
23. Han M, Gurevich VV, Vishnivetskiy SA, Sigler PB and Schubert C: Crystal structure of beta-arrestin at 1.9 A: Possible mechanism of receptor binding and membrane translocation. Structure 9: 869-880, 2001.
24. Fan H, Liao Y, Tang Q, Liang L and Chen XY: Role of β-arrestins in the pathogenesis of inflammatory bowel disease. World Chinese J Digestol 18: 3114-3120, 2010.
25. Nobles KN, Guan Z, Xiao K, Oas TG and Lefkowitz RJ: The active conformation of beta-arrestin1: Direct evidence for the phosphate sensor in the n-domain and conformational differences in the active states of beta-arrestins1 and -2. J Biol Chem 282: 21370-21381, 2007.
26. Seo J, Tsakem EL, Breitman M and Gurevich VV: Identification of arrestin-3-specific residues necessary for JNK3 kinase activation. J Biol Chem 286: 27894-27901, 2011.
27. Lin FT, Miller WE, Luttrell LM and Lefkowitz RJ: Feedback regulation of beta-arrestin1 function by extracellular signal-regulated kinases. J Biol Chem 274: 15971-15974, 1999.
28. Johnson GL and Lapadat R: Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science 298: 1911-1912, 2002.
29. Morrison DK: Map kinase pathways. Cold Spring Harb Perspect Biol 4: pii: a011254, 2012
30. Sebolt-Leopold JS and Herrera R: Targeting the mitogen-activated protein kinase cascade to treat cancer. Nat Rev Cancer 4: 937-947, 2004.
31. Zhou H, Li XM, Meinkoth J and Pittman RN: Akt regulates cell survival and apoptosis at a postmitochondrial level. J Cell Biol 151: 483-494, 2000.
32. Okada T, Sinha S, Esposito I, Schiavon G, López-Lago MA, Su W, Pratilas CA, Abele C, Hernandez JM, Ohara M, *et al*: The Rho GTPase Rnd1 suppresses mammary tumorigenesis and EMT by restraining RAS-MAPK signalling. Nat Cell Biol 17: 81-94, 2015.
33. Gu Y, Wang Q, Guo, K, Qin W, Liao W, Wang S, Ding Y and Lin J: TUSC3 promotes colorectal cancer progression and epithelial-mesenchymal transition (EMT) through WNT/β-catenin and MAPK signalling. J Pathol 239: 60-71, 2016.
34. Kaufhold S and Bonavida B: Central role of snail1 in the regulation of EMT and resistance in cancer: A target for therapeutic intervention. J Exp Clin Cancer Res 33: 62, 2014.
35. Mulholland DJ, Kobayashi N, Ruscetti M, Zhi A, Tran LM, Huang J, Gleave M and Wu H: Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. Cancer Res 72: 1878-1889, 2012.
36. Zhou G, Peng F, Zhong Y, Chen Y, Tang M and Li D: Rhein suppresses matrix metalloproteinase production by regulating the Rac1/ROS/MAPK/AP-1 pathway in human ovarian carcinoma cells. Int J Onco 50: 933-941, 2017.
37. Sangpairoj K, Vivithanaporn P, Apisawetakan S, Chongthammakun S, Sobhon P and Chaithirayanon K: RUNX1 regulates migration, invasion, and angiogenesis via p38 MAPK pathway in human glioblastoma. Cell Mol Neurobiol, 2016 (Epub ahead of print).
38. Cepeda MA, Evered CL, Pelling JJH and Damjanovski S: Inhibition of MT1-MMP proteolytic function and ERK1/2 signalling influences cell migration and invasion through changes in MMP-2 and MMP-9 levels. J Cell Commun Signal 11: 167-179, 2017.
39. Suyama K, Shapiro I, Guttman M and Hazan RB: A signaling pathway leading to metastasis is controlled by N-cadherin and the FGF receptor. Cancer Cell 2: 301-314, 2002.
40. Luttrell LM, Roudabush FL, Choy EW, Miller WE, Field ME, Pierce KL and Lefkowitz RJ: Activation and targeting of extracellular signal-regulated kinases by beta-arrestin scaffolds. Proc Natl Acad Sci USA 98: 2449-2454, 2001.
41. Fong AM, Premont RT, Richardson RM, Yu YR, Lefkowitz RJ and Patel DD: Defective lymphocyte chemotaxis in beta-arrestin2- and GRK6-deficient mice. Proc Natl Acad Sci USA 99: 7478-7483, 2002.
42. Décaillot FM, Kazmi MA, Lin Y, Ray-Saha S, Sakmar TP and Sachdev P: Cxcr7/cxcr4 heterodimer constitutively recruits beta-arrestin to enhance cell migration. J Biol Chem 286: 32188-32197, 2011.
43. Xu D, Li R, Wu J, Jiang L and Zhong HA: Drug design targeting the cxcr4/cxcr7/cxcl12 pathway. Curr Top Med Chem 16: 1441-1451, 2016.
44. Coggins NL, Trakimas D, Chang SL, Ehrlich A, Ray P, Luker KE, Linderman JJ and Luker GD: Cxcr7 controls competition for recruitment of β-arrestin 2 in cells expressing both cxcr4 and cxcr7. PLoS One 9: e98328, 2014.
45. Zhang P, He X, Tan J, Zhou X and Zou L: β-arrestin2 mediates β-2 adrenergic receptor signaling inducing prostate cancer cell progression. Oncol Rep 26: 1471-1477, 2011.
46. Buchanan FG, Gorden DL, Matta P, Shi Q, Matrisian LM and DuBois RN: Role of beta-arrestin 1 in the metastatic progression of colorectal cancer. Proc Natl Acad Sci USA 103: 1492-1497, 2006.
47. Lan T, Wang H, Zhang Z, Zhang M, Qu Y, Zhao Z, Fan X, Zhan Q, Song Y and Yu C: Downregulation of β-arrestin 1 suppresses glioblastoma cell malignant progression vis inhibition of src signaling. Exp Cell Res 357: 51-58, 2017.
48. Ge L, Shenoy SK, Lefkowitz RJ and DeFea K: Constitutive protease-activated receptor-2-mediated migration of MDA MB-231 breast cancer cells requires both beta-arrestin-1 and -2. J Biol Chem 279: 55419-55424, 2004.
49. Parisis N, Metodieva G and Metodiev MV: Pseudopodial and β-arrestin-interacting proteomes from migrating breast cancer cells upon PAR2 activation. J Proteomics 80: 91-106, 2013.
50. Girnita L, Shenoy SK, Sehat B, Vasilcanu R, Vasilcanu D, Girnita A, Lefkowitz RJ and Larsson O: Beta-arrestin and Mdm2 mediate IGF-1 receptor-stimulated ERK activation and cell cycle progression. J Biol Chem 282: 11329-11338, 2007.
51. Schaal C and Chellappan SP: Nicotine-mediated cell proliferation and tumor progression in smoking-related cancers. Mol Cancer Res 12: 14-23, 2014.
52. Liu H, Zhang Q, Li K, Gong Z, Liu Z, Xu Y, Swaney MH, Xiao K and Chen Y: Prognostic significance of USP33 in advanced colorectal cancer patients: New insights into β-arrestin-dependent ERK signaling. Oncotarget 7: 81223-81240, 2016.
53. Li XX, Zheng HT, Huang LY, Shi DB, Peng JJ, Liang L and Cai SJ: Silencing of CXCR7 gene represses growth and invasion and induces apoptosis in colorectal cancer through ERK and β-arrestin pathways. Int J Oncol 45: 1649-1657, 2016.
54. Goertzen CG, Dragan M, Turley E, Babwah AV and Bhattacharya M: KISS1R signaling promotes invadopodia formation in human breast cancer cell via β-arrestin2/ERK. Cell Signal 28: 165-176, 2016.
55. Dasgupta P, Rizwani W, Pillai S, Davis R, Banerjee S, Hug K, Lloyd M, Coppola D, Haura E and Chellappan SP: Arrb1-mediated regulation of E2F target genes in nicotine-induced growth of lung tumors. J Natl Cancer Inst 103: 317-333, 2011.

56. Korinek V, Barker N, Willert K, Molenaar M, Roose J, Wagenaar G, Markman M, Lamers W, Destree O and Clevers H: Two members of the tcf family implicated in wnt/beta-catenin signaling during embryogenesis in the mouse. Mol Cell Biol 18: 1248-1256, 1998.
57. Mythreye K and Blobe GC: The type iii TGF-beta receptor regulates epithelial and cancer cell migration through beta-arrestin2-mediated activation of Cdc42. Proc Natl Acad Sci USA 106: 8221-8226, 2009.
58. Kim GH, Her JH and Han JK: Ryk cooperates with frizzled 7 to promote wnt11-mediated endocytosis and is essential for xenopus laevis convergent extension movements. J Cell Biol 182: 1073-1082, 2008.
59. Habas R, Dawid IB and He X: Coactivation of Rac and Rho by Wnt/Frizzled signaling is required for vertebrate gastrulation. Genes Dev 17: 295-309, 2008.
60. Kypta RM and Waxman J: Wnt/β-catenin signalling in prostate cancer. Nat Rev Urol 9: 418-428, 2012.
61. Meng X, Zhu D, Yang S, Wang X, Xiong Z, Zhang Y, Brachova P and Leslie KK: Cytoplasmic metadherin (MTDH) provides survival advantage under conditions of stress by acting as RNA-binding protein. J Biol Chem 287: 4485-4491, 2012.
62. Clevers H and Nusse R: Wnt/β-catenin signaling and disease. Cell 149: 1192-1205, 2012.
63. Xu Q, Krause M, Samoylenko A and Vainio S: Wnt signaling in renal cell carcinoma. Cancers (Basel) 8: pii: E57, 2016.
64. Chen Z, He X, Jia M, Liu Y, Qu D, Wu D, Wu P, Ni C, Zhang Z, Ye J, *et al*: β-catenin overexpression in the nucleus predicts progress disease and unfavourable survival in colorectal cancer: A meta-analysis. PLoS One 8: e63854, 2013.
65. Aminuddin A and Ng PY: Promising druggable target in head and neck squamous cell carcinoma: Wnt signaling. Front Pharmacol 7: 244, 2016.
66. Liang S, Zhang S, Wang P, Yang C, Shang C, Yang J and Wang J: Lncrna, TUG1 regulates the oral squamous cell carcinoma progression possibly via interacting with Wnt/beta-catenin signaling. Gene 608: 49-57, 2017.
67. Liang J, Liang L, Ouyang K, Li Z and Yi X: MALAT1 induces tongue cancer cells' EMT and inhibits apoptosis through wnt/β-catenin signaling pathway. J Oral Pathol Med 46: 98-105, 2017.
68. Kalluri R and Weinberg RA: The basics of epithelial-mesenchymal transition. J Clin Invest 119: 1420-1428, 2009.
69. Howard S, Deroo T, Fujita Y and Itasaki N: A positive role of cadherin in Wnt/β-catenin signalling during epithelial-mesenchymal transition. PLoS One 6: e23899, 2011.
70. Huber MA, Kraut N and Beug H: Molecular requirements for epithelial-mesenchymal transition during tumor progression. Curr Opin Cell Biol 17: 548-558, 2005.
71. Felipe Lima J, Nofech-Mozes S, Bayani J and Bartlett JM: Emt in breast carcinoma-a review. J Clin Med 5: pii: E65, 2016.
72. Grant CM and Kyprianou N: Epithelial mesenchymal transition (EMT) in prostate growth and tumor progression. Transl Androl Urol 2: 202-211, 2003.
73. Ko CJ, Huang CC, Lin HY, Juan CP, Lan SW, Shyu HY, Wu SR, Hsiao PW, Huang HP, Shun CT and Lee MS: Androgen-induced TMPRSS2 activates matriptase and promotes extracellular matrix degradation, prostate cancer cell invasion, tumor growth, and metastasis. Cancer Res 75: 2949-2960, 2015.
74. Liao X, Thrasher JB, Pelling J, Holzbeierlein J, Sang QX and Li B: Androgen stimulates matrix metalloproteinase-2 expression in human prostate cancer. Endocrinology 144: 1656-1663, 2003.
75. Yang Y, Jiao L, Hou J, Xu C, Wang L, Yu Y, Li Y, Yang C, Wang X and Sun Y: Dishevelled-2 silencing reduces androgen-dependent prostate tumor cell proliferation and migration and expression of Wnt-3a and matrix metalloproteinases. Mol Biol Rep 40: 4241-4250, 2013.
76. Sun L, Liu T, Zhang S, Guo K and Liu Y: Oct4 induces EMT through LEF1/β-catenin dependent WNT signaling pathway in hepatocellular carcinoma. Oncol Lett 13: 2599-2606, 2017.
77. Zhang Y: Ganodermalucidum (Reishi) suppresses proliferation and migration of breast cancer cells via inhibiting Wnt/β-catenin signaling. Biochem Biophys Res Commun 488: 679-684, 2017.
78. Rosanò L, Cianfrocca R, Tocci P, Spinella F, Di Castro V, Spadaro F, Salvati E, Biroccio AM, Natali PG and Bagnato A: β-arrestin-1 is a nuclear transcriptional regulator of endothelin-1-induced β-catenin signaling. Oncogene 32: 5066-5077, 2013.
79. Turm H, Maoz M, Katz V, Yin YJ, Offermanns S and Bar-Shavit R: Protease-activated receptor-1 (PAR1) acts via a novel galpha13-dishevelled axis to stabilize beta-catenin levels. J Biol Chem 285: 15137-15148, 2010.
80. Bonnans C, Flaceliere M, Grillet F, Dantec C, Desvignes JP, Pannequin J, Severac D, Dubois E, Bibeau F, Escriou V, *et al*: Essential requirement for β-arrestin2 in mouse intestinal tumors with elevated wnt signaling. Proc Natl Acad Sci USA 109: 3047-3052, 2012.
81. Duan X, Zhang T, Kong Z, Mai X, Lan C, Chen D, Liu Y, Zeng Z, Cai C, Deng T, *et al*: β-arrestin1 promotes epithelial-mesenchymal transition via modulating GSK-3β/β-catenin pathway in prostate cancer cells. Biochem Biophys Res Commun 479: 204-210, 2016.
82. Witherow DS, Garrison TR, Miller WE and Lefkowitz RJ: Beta-arrestin inhibits NF-kappaB activity by means of its interaction with the Nf-KappaB inhibitor IkappaBalpha. Proc Natl Acad Sci USA 101: 8603-8607, 2004.
83. Kim YR, Kim IJ, Kang TW, Choi C, Kim KK, Kim MS, Nam KI and Jung C: HOXB13 downregulates intracellular zinc and increases NF-κB signaling to promote prostate cancer metastasis. Oncogene 33: 4558-4567, 2014.
84. Jiang L, Lin C, Song L, Wu J, Chen B, Ying Z, Fang L, Yan X, He M, Li J and Li M: Microrna-30e* promotes human glioma cell invasiveness in an orthotopic xenotransplantation model by disrupting the NF-κB/IκBα negative feedback loop. J Clin Invest 122: 33-47, 2012.
85. Karin M: Nuclear factor-kappab in cancer development and progression. Nature 441: 431-436, 2006.
86. Karin M, Cao Y, Greten FR and Li ZW: Nf-kappaB in cancer: From innocent bystander to major culprit. Nat Rev Cancer 2: 301-310, 2002.
87. Liu B, Han M and Wen JK: Acetylbritannilactone inhibits neointimal hyperplasia after balloon injury of rat artery by suppressing nuclear factor-{kappa}B activation. J Pharmacol Exp Ther 324: 292-298, 2008.
88. Ghosh S and Karin M: Missing pieces in the NF-kappaB puzzle. Cell 109 (Suppl) S81-S96, 2002.
89. Kong D, Li Y, Wang Z, Banerjee S and Sarkar FH: Inhibition of angiogenesis and invasion by 3,3'-diindolylmethane is mediated by the nuclear factor-kappaB downstream target genes MMP-9 and uPA that regulated bioavailability of vascular endothelial growth factor in prostate cancer. Cancer Res 67: 3310-3319, 2002.
90. Liao D, Zhong L, Duan T, Zhang RH, Wang X, Wang G, Hu K, Lv X and Kang T: Aspirin suppresses the growth and metastasis of osteosarcoma through the NF-κB pathway. Clin Cancer Res 21: 5349-5359, 2015.
91. Cianfrocca R, Tocci P, Semprucci E, Spinella F, Di Castro V, Bagnato A and Rosanò L: β-arrestin 1 is required for endothelin-1-induced NF-κB activation in ovarian cancer cells. Life Sci 118: 179-184, 2014.
92. Raghuwanshi SK, Nasser MW, Chen X, Strieter RM and Richardson RM: Depletion of beta-arrestin-2 promotes tumor growth and angiogenesis in a murine model of lung cancer. J Immunol 180: 5699-5706, 2008.
93. Gao H, Sun Y, Wu Y, Luan B, Wang Y, Qu B and Pei G: Identification of beta-arrestin2 as a G protein-coupled receptor-stimulated regulator of NF-kappaB pathways. Mol Cell 14: 303-317, 2004.
94. Wang Y, Tang Y, Teng L, Wu Y, Zhao X and Pei G: Association of beta-arrestin and TRAF6 negatively regulates toll-like receptor-interleukin 1 receptor signaling. Nat Immunol 7: 139-147, 2006.
95. Dranoff G: Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer 4: 11-22, 2004.
96. Bedini A, Baiula M, Vincelli G, Formaggio F, Lombardi S, Caprini M and Spampinato S: Nociceptin/orphanin FQ antagonizes lipopolysaccharide-stimulated proliferation, migration and inflammatory signaling in human glioblastoma U87 cells. Biochem Pharmacol 140: 89-104, 2017.
97. Lino MM and Merlo A: PI3Kinase signaling in glioblastoma. J Neurooncol 103: 417-427, 2011.
98. Chalhoub N and Baker SJ: PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol 4: 127-150, 2017.
99. Wang H, Wu Q, Liu Z, Luo X, Fan Y, Liu Y, Zhang Y, Hua S, Fu Q, Zhao M, *et al*: Downregulation of FAP suppresses cell proliferation and metastasis through PTEN/PI3K/AKT and RAS-ERK signaling in oral squamous cell carcinoma. Cell Death Dis 5: e1155, 2014.
100. Han M, Liu M, Wang Y, Chen X, Xu J, Sun Y, Zhao L, Qu H, Fan Y and Wu C: Antagonism of miR-21 reverses epithelial-mesenchymal transition and cancer stem cell phenotype through AKT/ERK1/2 inactivation by targeting PTEN. PLoS One 7: e39520, 2012.

101. Jensen RL: Brain tumor hypoxia: Tumorigenesis, angiogenesis, imaging, pseudoprogression, and as a therapeutic target. J Neurooncol 92: 317-335, 2009.
102. Chen B, Zeng X, He Y, Wang X, Liang Z, Liu J, Zhang P, Zhu H, Xu N and Liang S: STC2 promotes the epithelial-mesenchymal transition of colorectal cancer cells through AKT-ERK signaling pathways. Oncotarget 7: 71400-71416, 2016.
103. Wang Z, Qu L, Deng B, Sun X, Wu S, Liao J, Fan J and Peng Z: Styk1 promotes epithelial-mesenchymal transition and tumor metastasis in human hepatocellular carcinoma through Mek/Erk and PI3K/AKT signaling. Sci Rep 6: 33205, 2016.
104. Zhang Y, Yang CQ, Gao Y, Wang C, Zhang CL and Zhou XH: Knockdown of CXCR7 inhibits proliferation and invasion of osteosarcoma cells through inhibition of the PI3K/AKT and β-arrestin pathways. Oncol Rep 32: 965-972, 2014.
105. Zou L, Yang R, Chai J and Pei G: Rapid xenograft tumor progression in beta-arrestin1 transgenic mice due to enhanced tumor angiogenesis. FASEB J 22: 355-364, 2008.
106. Alvarez CJ, Lodeiro M, Theodoropoulou M, Camiña JP, Casanueva FF and Pazos Y: Obestatin stimulates aktsignalling in gastric cancer cells through beta-arrestin-mediated epidermal growth factor receptor transactivation. Endocr Relat Cancer 16: 599-611, 2009.
107. Nawaz Z, Patil V, Paul Y, Hegde AS, Arivazhagan A, Santosh V and Somasundaram K: Pi3 kinase pathway regulated mirnome in glioblastoma: Identification of mir-326 as a tumour suppressor miRNA. Mol Cancer 15: 74: 2016.
108. Lima-Fernandes E, Enslen H, Camand E, Kotelevets L, Boularan C, Achour L, Benmerah A, Gibson LC, Baillie GS, Pitcher JA, *et al*: Distinct functional outputs of PTEN signalling are controlled by dynamic association with β-arrestins. EMBO J 30: 2557-2568, 2011.
109. Li Y, Guo G, Song J, Cai Z, Yang J, Chen Z, Wang Y, Huang Y and Gao Q: B7-H3 promotes the migration and invasion of human bladder cancer cells via the PI3K/AKT/STAT3 signaling pathway. J Cancer 8: 816-824, 2017.
110. Tayeh M, Nilwarangoon S, Mahabusarakum W and Watanapokasin R: Anti-metastatic effect of rhodomyrtone from rhodomyrtus tomentosa on human skin cancer cells. Int J Oncol 50: 1035-1043, 2017.
111. Scott MG, Le Rouzic E, Périanin A, Pierotti V, Enslen H, Benichou S, Marullo S and Benmerah A: Differential nucleocytoplasmic shuttling of beta-arrestins. Characterization of a leucine-rich nuclear export signal in beta-arrestin2. J Biol Chem 277: 37693-37701, 2002.
112. Kang J, Shi Y, Xiang B, Qu B, Su W, Zhu M, Zhang M, Bao G, Wang F, Zhang X, *et al*: A nuclear function of beta-arrestin1 in GPCR signaling: Regulation of histone acetylation and gene transcription. Cell 123: 833-847, 2005.
113. Kim JI, Lakshmikanthan V, Frilot N and Daaka Y: Prostaglandin E2 promotes lung cancer cell migration via EP4-betaArrestin1-c-src signalsome. Mol Cancer Res 8: 569-577, 2010.
114. Lin EW, Karakasheva TA, Hicks PD, Bass AJ and Rustgi AK: The tumor microenvironment in esophageal cancer. Oncogene 35: 5337-5349, 2016.
115. Clark AG and Vignjevic DM: Modes of cancer cell invasion and the role of the microenvironment. Curr Opin Cell Biol 36: 13-22, 2015.
116. Ji RC: Hypoxia and lymphangiogenesis in tumor microenvironment and metastasis. Cancer Lett 346: 6-16, 2014.
117. Whalen EJ, Rajagopal S and Lefkowitz RJ: Therapeutic potential of β-arrestin- and G protein-biased agonists. Trends Mol Med 17: 126-139, 2011.
118. Bologna Z, Teoh JP, Bayoumi AS, Tang Y and Kim IM: Biased G protein-coupled receptor signaling: New player in modulating physiology and pathology. Biomol Ther (Seoul) 25: 12-25, 2017.