Emerging therapeutics for targeting Akt in cancer

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Regulation of Akt isoforms
   3.1. Phosphorylation/dephosphorylation
      3.1.1. Phosphorylation
      3.1.2. Dephosphorylation
   3.2. MicroRNA
4. Involvement of Akt isoforms in chemoresistance
   4.1. Akt1 isoform
   4.2. Akt2 isoform
   4.3. Akt3 isoform
5. Akt isoforms as targets for cancer therapy
   5.1. General considerations for Akt inhibition
   5.2. Akt inhibitors in clinical trials
      5.2.1. Akt inhibitors targeting the PH domain
         5.2.1.1. Perifosine
         5.2.1.2. Triciribine
      5.2.2. Akt inhibitors targeting the kinase domain
         5.2.2.1. AZD5363
         5.2.2.2. Ipatasertib
         5.2.2.3. GSK2110183 (Afuresertib)
         5.2.2.4. GSK2141795
         5.2.2.5. LY2780301
         5.2.2.6. MK2206
      5.2.3. Other inhibitors
         5.2.3.1. Archexin
6. Conclusion
7. Acknowledgments
8. References

1. ABSTRACT

The ultimate goal of cancer therapeutic research is to develop effective, targeted therapeutics that exploit the vulnerabilities of cancer cells. The three isoforms of Akt, also known as protein kinase B (PKB), are important mediators of various pathways that transmit mitogenic signals from the cell's exterior to the effector proteins of the cell's interior. Due to Akt's importance in cell functions such as growth, proliferation and cell survival, many cancer cells rely on this pathway to aid in their survival. This dependence can lead to chemoresistance and selection of more adapted populations of cancer cells. Thus, it is important to understand the functional significance of isoform specificity and its relation to chemoresistance. In this review, we have summarized recent studies on Akt isoform specific regulation as well as each isoform's role in chemoresistance, emphasizing their potential as targets for cancer therapy. We have also condensed ongoing clinical studies involving various types of Akt inhibitors while highlighting the type of study, rationale and co-therapies involved in identifying Akt isoforms as promising therapeutic targets.

2. INTRODUCTION

Akt, is a serine/threonine kinase of the AGC family of kinases that is normally activated in response to mitogenic signaling through receptor tyrosine kinases. Akt has three different isoforms Akt1, Akt2 and Akt3 encoded by distinct genes on chromosomes 14, 19 and 1, respectively (1). The overall structure of each
Emerging therapeutics for targeting Akt in cancer

isoform is consistent with a catalytic domain linked to an N-terminal pleckstrin homology (PH) domain and a C-terminal regulatory domain (1). While there is considerable sequence homology among the three Akt isoforms with regard to the PH, catalytic, and regulatory domains, the linker region, which tethers the PH domain to the catalytic domain, is divergent (1,2). The PH domain binds the phosphorylated membrane lipid phosphatidylinositol 3,4,5 triphosphate (PIP3), mainly through interaction with the 3'-phosphate group (3). This membrane lipid is produced in response to mitogenic stimulation following activation of phosphatidylinositol 3-kinase (PI3K), which adds the aforementioned 3'-phosphate group to function as a second messenger. Once Akt proteins have been recruited to the plasma membrane through PH domain docking, they can be fully activated by phosphorylation of threonine and serine residues in the catalytic and regulatory domains respectively (1). Phosphoinositide-dependent kinase 1 (PDK1) is responsible for phosphorylating a central threonine residue, while mechanistic target of rapamycin complex 2 (mTORC2) is one of several proteins that are able to phosphorylate a distal serine residue (4-7). Deactivation of Akt signaling occurs through both upstream dephosphorylation of 3'-phosphate groups on PIP3 by the protein/lipid phosphatase PHLPP (phosphatase and tensin homolog deleted on chromosome 10) as well as dephosphorylation of Akt itself through the activity of other protein phosphatases (8,9).

Akt's function as an activator of growth, proliferation and cell survival gives reason for cancer cells to preferentially activate this kinase. While many other oncogenes show high mutation rates to confer hyperactivation, the majority of increased activity of Akt kinases can instead be attributed to mutations in other members of the pathway, such as PI3K and PTEN. These mutations result in an increased ability to produce PIP3 and thus increased activation and phosphorylation of Akt. In those cancers, which do not employ an activating mutation or amplification of PI3K to stimulate Akt function, PTEN mutation can eliminate its capability to shut off PI3K signaling (10,11). PTEN mutations are extremely detrimental to its ability to regulate PI3K/Akt signaling as even a single mutation in one allele can result in haploinsufficiency (12). Interestingly, mutations rarely occur in both PI3K and PTEN as both mutations accomplish the same outcome of increased Akt activation (13).

The PI3K/Akt/mTOR pathway is among the most frequently altered pathways in cancer (14-16), thus targeting this pathway has broad implications for various types of cancer. Consequently, Akt has been pursued as a favorable clinical target. In this review article, we summarized recent studies on Akt as a potential target for cancer therapy.

3. REGULATION OF AKT ISOFORMS

3.1. Phosphorylation/dephosphorylation

3.1.1. Phosphorylation

Recent studies suggest that post-translational modifications (PTMs) of Akt isoforms could be distinct. This would allow for differential regulation of Akt isoforms and explain observed isoform specific functions. Cyclin-dependent kinase 2 (CDK2)/cyclin A complexes were shown to promote phosphorylation of the canonical activating C-terminal serine residues (ACTS) in Akt1 (S473) and Akt2 (S474) by directly phosphorylating additional serine and threonine residues in their regulatory domains (S477/T479 in Akt1) (17). No mention was made with regard to influence of CDK2/cyclin A complexes on Akt3’s ACTS (S472). Akt1 hyperactivation has been reported due to the phosphorylation of S129 located at the linker region of the protein by casein kinase 2 (CK2) (18). This group later went on to show that CK2 phosphorylation of Akt is confined to the Akt1 isoform as the corresponding serine residue in Akt2 (S131) failed to exhibit phosphorylation, despite the presence of the correct consensus sequence required for CK2-mediated phosphorylation (19). This isoform specificity assigned to the linker domain is confirmed by the determination that it was required for Akt1 phosphorylation of palladin, an Akt1-specific substrate, which plays a role in actin cytoskeleton organization (20).

3.1.2. Dephosphorylation

As previously mentioned, protein phosphatases are required to stop Akt signaling. Due to the differences in Akt isoform sequence homology, this deactivation provides another level of isoform-specific regulation as phosphatases may have high affinity for one or two Akt isoforms, while failing to recognize the other(s). PH domain leucine-rich repeat protein phosphatase (PHLPP) is a phosphatase that was shown to directly dephosphorylate Akt, and thus reduce its function (21). There are two PHLPP isoforms that recognize specific isoforms of Akt (9). PHLPP1 was shown to regulate phosphorylation status of the ACTS of Akt1 and Akt3, while PHLPP2 selectively dephosphorylates the ACTS of Akt2 and Akt3 (9). Also, Akt1-specific phosphorylation by CK2 prolongs Akt1 activation by recruiting Hsp90, which blocks the phosphatase activity of protein phosphatase 2A (PP2A) on phosphorylated T308 (22). The complete picture of isoform specific post-translational modifications remains unknown, but studies indicate that this is indeed one mechanism of regulating isoform function.

3.2. MicroRNA

MicroRNAs (miRNAs) play a key role in cellular processes, such as cell proliferation and apoptosis, and may function as tumor suppressors or oncogenes. The small nucleotide molecules can bind to the 3’-untranslated region of their target mRNAs, and repress or destabilize the target mRNA (23). A number of microRNAs have
Emerging therapeutics for targeting Akt in cancer

been implicated in the regulation of Akt (24-27). PHLPP isoforms themselves have recently been shown to be regulated by a number of miRNAs, adding yet another mechanism of Akt isoform specific activation (28-31). Cancer cells are able to exploit this mechanism to facilitate tumorigenesis by upregulating these miRNAs. MiR-205 in particular has been shown in non-small cell lung cancer (NSCLC) to regulate both PHLPP2 as well as PTEN to ensure continued Akt activation by retaining stimulatory signaling in addition to increased longevity of activated Akt (29). Polytarchou et al. showed that during hypoxia Akt2 upregulates miR-21 through activation and binding of CREB/CBP and NF-κB to the miR-21 enhancer, which downregulates PTEN and leads to activation of all three Akt isoforms (32). Similarly, in esophageal cancer, miR-200c directly targets and downregulates PPP2R1B, a subunit of protein phosphatase 2A (PP2A) that dephosphorylates Akt (24). Conversely, miR-302b in hepatocellular carcinoma, and both miR-203 and miR-194 in colon cancer cells function to suppress Akt2 expression and inhibit cell proliferation and survival (25-27).

While it is clear that PTMs and microRNAs play important roles in Akt isoform specific function, the complete picture of the roles they play in pathway regulation is still unclear. Yet another piece of the puzzle that remains to be seen is the relation of these regulatory mechanisms to the specific tissue/cancer type. More information in these areas will aid in our understanding of Akt isoform contribution to chemoresistance and lead to development of more targeted therapeutics.

4. INVOLVEMENT OF AKT ISOFORMS IN CHEMOSERESISTANCE

The development of chemoresistance in cancer cells presents a major challenge to the treatment of many malignancies (33-35). Cancer cells may exhibit intrinsic and/or extrinsic resistance. Intrinsic resistance is evident prior to the first course of chemotherapy treatment while extrinsic resistance develops during treatment (36,37). Hence, it is important to understand the underlying mechanisms of chemoresistance and ways to prevent and overcome this resistance (38,39). One of the main causes of drug resistance is the efflux of drugs from the cell by ATP binding cassette transporters (33,38). Another mechanism of drug resistance involves cellular changes, such as increased DNA damage repair, decreased apoptosis, and altered cell cycle (40). It is well known that Akt plays a critical role in cell survival, cell proliferation, migration, and metabolism (41). Thus, it follows that deregulation of the Akt signaling pathways can lead to increased cell survival, reduced apoptosis, and eventually chemoresistance (42,43). In this section, we will focus on the recently identified mechanisms by which Akt mediates the development of chemoresistance.

As a crucial mediator of many important signaling cascades, perturbations in Akt activity, specifically hyperactivation of Akt plays a major role in many human cancers (44,45). Breast carcinoma cells with elevated AKT upregulated the expression of ribonucleotide reductase M2 (RRM2), leading to enhanced DNA damage repair and protection from tamoxifen-induced apoptosis (46). Additionally, Akt promoted cisplatin resistance in ovarian and cervical cancers by inhibiting the proteasomal degradation of protein phosphatase magnesium-dependent 1 D (PPM1D), which directly dephosphorylates ATM, checkpoint kinase 2 (Chk2), and p53 (47). Ali et al. showed that Akt augments the DNA damage response to promote cell survival and chemoresistance via regulation of its effector, PPM1D (47). The forkhead transcription factor, FOXO1, promoted cisplatin resistance in human gastric cancer cells by triggering Akt activity through PI3K activation (48).

The specific expression patterns of various Akt isoforms (Akt1, Akt2, and Akt3) provide insight into the Akt isoform-specific resistance. For example, AKT1 and AKT3 expression levels are significantly elevated in breast tumors. Additionally, the expression level of AKT3 was notably increased with recurrence and estrogen receptor (ER)-negative status in breast cancer patients (46,47). In the following paragraphs, we will discuss the implications of the various Akt isoforms on chemoresistance.

4.1. Akt1 isoform

Recent studies indicate that in both chemoresistant (KLE) and chemosensitive (HEC-1-A) endometrial cancer cells, downregulation of Akt1 and Akt2 lead to death of the cell and caspase cleavage after treatment with either doxorubicin, taxol, or cisplatin (49). Downregulation of Akt1 reduces MEK/ERK1/2 activity, which normally leads to the activation of NF-κB, whereas downregulation of Akt2 results in Mcl-1 cleavage, mitochondrial membrane potential breakdown, cytochrome c release, and caspase cascade activation (50). Downregulation of Akt3 in KLE and HEC-1-A endometrial cells had an impact on doxorubicin resistance, but no effect on cisplatin resistance (49). This indicates that Akt isoforms have a specific influence on resistance to a particular drug in endometrial cancer cells. Furthermore, AKT1 expression along with Notch1 and PTEN expression was increased in gastric cancer cells after treatment with doxorubicin (51). Additionally, inhibition of AKT1 expression increased the sensitivity of gastric cancer cells both in vitro and in vivo to doxorubicin treatment (51). This data suggests that the Akt1/NF-κB/Notch/PTEN axis plays a significant role in gastric cancer chemoresistance.

4.2. Akt2 isoform

Akt2 confers resistance to chemotherapeutic drugs such as paclitaxel (52), doxorubicin (49), cisplatin (49), and gemcitabine (53). In fact, knockdown
of Akt2 decreased the expression of MDR1 and MRP1 protein in HCT116 human colorectal cancer cells (52) and the expression of MRP1 protein in U87 glioma cells (54), sensitizing these cells to paclitaxel and VM-26 (teniposide), respectively. This suggests that overexpression of MDR1 and MRP1 is via an Akt2-dependent mechanism and decreased Akt2 signaling may reduce the efflux of these drugs through these ABC transporters via downregulation of MDR1 and MRP1 (52,54). Moreover, inhibition of Akt2 expression in A549 lung cancer cells resulted in significant inhibition of cell growth, proliferation, and invasion, and this was accompanied by reduced nucleophosmin/B23 protein (55). In addition, overexpression of Akt1, but not Akt2, restored growth of the A549 cells upon B23 knockdown, suggesting that Akt2 requires B23 to promote lung cancer cell proliferation (55). Overexpression of B23 promoted proliferation in cells in which Akt2 was inhibited (55). Taken together, these findings suggest that Akt2 enhances tumor growth and development via the stabilization of the nuclear anti-apoptotic regulator B23 (55).

4.3. Akt3 isoform
The Akt3 isoform also contributes to chemoresistance in cancer cells. Using a mouse model of low-grade glioma, Turner et al. investigated the tendency of Akt1, Akt2, and Akt3 to promote glioma progression. The results showed that constitutively-active Akt2 and Akt3, but not Akt1, showed a strong likelihood of tumor progression (56). Through gene ontology enrichment analysis, this research group found that Akt3 promoted both nonhomologous end joining and homologous recombination DNA repair (56). This enhanced DNA repair promoted the survival of glioblastoma cells after treatment with radiation or the chemotherapeutic agent temozolomide (56). Thus, Akt3 activation in glioma contributes to chemoresistance through enhanced DNA repair. Given the wide variety of cancers in which Akt3 is amplified (e.g., breast cancer), it is plausible that Akt3 may serve as a major resistance factor (56,57). Furthermore, a study by Grabinski et al. indicated that Akt3 regulated the expression of human epidermal growth factor receptor 2 (ErbB2), human epidermal growth factor receptor 3 (ErbB3), and estrogen receptor alpha in mice breast cancer cells (58). Knockdown of Akt3 restored sensitivity of ErbB2-positive breast cancer cells to the selective estrogen receptor modulator, tamoxifen (58).

5. AKT ISOFORMS AS TARGETS FOR CANCER THERAPY

5.1. General considerations for Akt inhibition
Considerable progress has been made in understanding the nuanced signaling mechanisms that regulate the Akt pathway, and this knowledge is starting to translate into clinically approved targeted treatments. The following sections will give an overview of the rationale for designing small molecule inhibitors against Akt, general considerations for selecting agents for combination chemotherapy with Akt inhibitors, and the molecules that have shown promise in translating to clinically approved Akt inhibitors. Due to the number of compounds that fail phase I clinical trials, particular emphasis has been placed on emerging Akt inhibitors that are currently in ongoing phase II clinical trials as denoted by their status on clinicaltrials.gov.

One of the greatest battles with administration of chemotherapeutics is the eventual development of resistance. This problem is often magnified when utilizing targeted therapies because cancer cells can activate alternative survival signaling cascades when challenged with targeted inhibitors. Thus, rational strategies have been developed in an attempt to overcome resistance by treating patients with a combination of drugs that target multiple entities at once. One approach that has been tested in clinical trials is to inhibit molecules that lie in the same pathway as Akt while at the same time targeting Akt itself. These target molecules can be either proximal in the pathway, such as receptor tyrosine kinase and PI3K, or downstream such as mTORC1 (mechanistic target of rapamycin complex 1). This combinatorial scheme is important in clinical trial design because of the potential for monotherapy inhibitors against downstream targets to cause feedback activation of the pathway and result in suboptimal outcomes for patients. A second strategy that has been incorporated into clinical trial designs is inhibiting pathways that are parallel in function to the PI3K/Akt/mTOR pathway such as the Ras/Raf/Mek/Erk pathway. This particular strategy is intended to prevent redundant survival pathways from becoming hyperactive and compensating when Akt is inhibited. A final strategy that can be utilized is administration of an Akt inhibitor along with other targeted drugs and/or cytotoxic agents that act at less related sites. These might include: microtubule inhibitors, proteasomal inhibitors, or HDAC inhibitors (59).

5.2. Akt inhibitors in clinical trials
As mentioned in the introduction, the three isoforms of Akt have specific domains that contribute to Akt’s functioning: the PH domain, the hinge region, and the kinase domain. Each of these domains has been used to develop targeted treatments against Akt with the most clinically mature drugs targeted against the PH domain and the kinase domain. The variation of the domain sequence among the different Akt isoforms has implications for drug development, target specificity, and the ability to inhibit either a certain isoform use as a pan-Akt inhibitor. A general principle is that drugs that target a domain with high homology between the isoforms generally result in pan-Akt inhibitors while those designed to target regions where the Akt isoforms have more diversity are likely to result in drugs that are more isoform specific in vitro. This isoform specificity may
break down when dealing with the higher drug dosages that are seen in clinically relevant situations. Thus, in this section, we have categorized different Akt inhibitors that are in clinical trials based on their ability to target different domains of Akt (Table 1).

5.2.1. Akt inhibitors targeting the PH Domain

5.2.1.1. Perifosine
Perifosine is a third generation alkylphospholipid that inhibits Akt activation by binding to the PH domain of Akt and inhibiting its ability to localize to the plasma membrane, which is required for its activation (60). Notably, perifosine has advanced the furthest in clinical trials out of all the Akt inhibitors. Perifosine had shown favorable results in phase II clinical trials and progressed to phase III trials for metastatic colorectal cancer and multiple myeloma with combination treatment with capecitabine and bortezomib, respectively, but failed due to lack of efficacy (61). Other phase II clinical trials are currently utilizing this drug in combination with the mTOR inhibitor, temsirolimus, for recurrent/progressive malignant gliomas (62).

5.2.1.2. Triciribine
Like perifosine, triciribine’s target is the PH domain of Akt, and upon entering the cell, it is converted to the active drug metabolite by phosphorylation from adenosine kinase (63). Currently, this molecule is in phase II trials for breast cancer in combination with paclitaxel, doxorubicin, or cyclophosphamide (64).

5.2.2. Akt inhibitors targeting the kinase domain

5.2.2.1. AZD5363
The orally available pyrrolopyrimidine derivative AZD5363 is a potent ATP-competitive pan-Akt inhibitor that is currently in phase I and phase II trials for various cancers (65). As a treatment for breast cancer, it is in a variety of clinical trial designs. In NCT02077569, AZD5363 is being given to estrogen receptor-positive breast cancer patients to primarily study pharmacodynamics with primary outcome measures being alteration of biomarkers in the Akt pathway such as: pPRAS40, pGSK3b, and Ki67. Other studies are investigating AZD536 as part of a combination chemotherapy regimen in addition to the estrogen receptor antagonist, fulvestrant (66), or in combination with the microtubule stabilizer, paclitaxel (67). Another trial is investigating its use in patients with metastatic castration resistant prostate cancer in combination with docetaxel and prednisone (68). One example of a trial, which utilizes the design of inhibiting proximal and distal molecules in the Akt pathway, is NCT02208375 for recurrent endothelial and ovarian cancer by combining AZD5363 with the mTORC1/2 inhibitor AZD2014 (69).

In addition to traditional clinical trial designs, AZD5363 has been incorporated into trials developed to test a particular therapeutic agent on a particular molecular or genetic abnormality. These genomic-guided trials are particularly helpful in testing targeted therapeutics such as the various Akt inhibitors discussed in this paper. Two separate examples of this kind of trial are NCT02299999 and NCT02117167 in which breast or lung cancer patients, respectively, are treated with a targeted agent plus standard chemotherapy according to the molecular abnormalities of their tumor as determined by high throughput genome sequencing (70,71). The design of this type of study is called an umbrella study and is designed to assess the effect of different drugs on various mutations in a single cancer type.

5.2.2.2. Ipatasertib
Ipatasertib is an ATP-competitive pan-Akt inhibitor that is currently in phase II clinical trials as a
Emerging therapeutics for targeting Akt in cancer

combination treatment for breast cancer patients. It is being studied as a neoadjuvant with paclitaxel for stage Ia-Ila triple-negative breast cancer patients (72) and in locally advanced or metastatic triple negative breast cancer (73).

5.2.2.3. GSK2110183 (Afuresertib)
GSK2110183 is a reversible, ATP-competitive, pan-Akt inhibitor. It is in phase II clinical trials for chronic lymphocytic leukemia as both a monotherapy and in combination with other chemotherapeutics. NCT01532700 is studying this agent in combination with the anti-CD20 antibody, ofatumumab, for relapsed and refractory CLL (74).

5.2.2.4. GSK2141795
Another ATP-competitive inhibitor of Akt that has progressed to a number of phase II clinical trials is GSK2141795. The goal of the majority of current ongoing phase II clinical trials with GSK2141795 is to determine if there is a benefit in combining this Akt inhibitor with the MEK inhibitor, trametinib, for the following cancers: cervical, multiple myeloma, metastatic uveal melanoma, acute myeloid leukemia, persistent endometrial cancer, metastatic triple-negative breast cancer, and cervical cancer (75-82). In addition, GSK2141795 is part of a basket study design for treatment of BRAF mutant cancers (83). In contrast to an umbrella study, the basket study design seeks to test a targeted drug on multiple cancer types that exhibit a particular molecular abnormality, in this case, the BRAF mutation. Patients are grouped into different “baskets” for analysis based on what type of cancer they have.

5.2.2.5. LY2780301
LY2780301 is an ATP-competitive inhibitor of pan-Akt. It is currently in a trial for HER2-negative, inoperable locally advanced or metastatic breast cancer in combination with paclitaxel (84).

5.2.2.6. MK2206
MK2206, an allosteric inhibitor of Akt, has progressed to a number of clinical trials. MK2206 is about 5-fold more specific for inhibiting Akt isoforms 1 and 2 than it is for inhibiting Akt 3 in in vitro experiments (85). It is being studied as a monotherapy in relapsed or refractory diffuse large B-cell lymphoma (86). MK2206 is also being studied as a monotherapy in previously treated metastatic colorectal cancer patients. Secondary objectives in this study include analyzing the response rate of patients that have PTEN loss or PIK3CA mutations (87). In another study, breast cancer patients positive for PIK3CA mutations are given MK2206 as a neoadjuvant in combination with anastrozole and goserelin acetat (88). MK2206 is one of the targeted agents being tested in the umbrella study: BATTLE-2 Program. This study is a biomarker-integrated study for targeted therapies in non-small cell lung cancer (NSCLC) patients who have been previously treated with other agents. The other targeted agents in this study are erlotinib, AZD6244, and sorafenib (89). Another umbrella design study that has incorporated MK2206 into the design is the I-SPY 2 Trial for breast cancer patients (90). Finally, NCT01306045 is a trial for NSCLC, small cell lung cancer (SCLC), and thymic malignancies and incorporated MK2206 into the treatment regimen for those patients who have PIK3CA, AKT, or PTEN mutation (91).

5.2.3. Other inhibitors
5.2.3.1. Archexin
Archexin is a first in class 20-mer antisense oligonucleotide complementary to Akt1 (92). A phase Ila clinical trial was started in January 2014 for patients with metastatic renal cell carcinoma in combination with the mTOR inhibitor, everolimus. Future generations of this drug may benefit from the polymeric nanoparticle and lipid coated albumin nanoparticle preparations for improved stability.

6. CONCLUSION

The crucial role of Akt signaling in many different types of cancer has been well established in both the basic science and clinical literature. Moreover, specific expression patterns of various Akt isoforms provide critical insight into Akt isoform-specific function. Complete elucidation of the isoform-specific mechanisms and crosstalk that occurs between Akt and other signal transduction pathways as well as its role in the development of chemotherapy resistance are still works in progress. An enhanced understanding of Akt-mediated chemoresistance will aid in the development of more effective chemotherapeutic agents. However, the advances that have been made in developing clinically targeted Akt drugs in patient trials is an example of what the future holds for targeted cancer therapeutics.

7. ACKNOWLEDGMENTS

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Emerging therapeutics for targeting Akt in cancer


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Emerging therapeutics for targeting Akt in cancer


Abbreviations: PKB: Protein kinase B; PH: Pleckstrin homology; PIP3: phosphatidylinositol (3,4,5) triphosphate; P3K: phosphatidylinositol 3-kinase; PDK1: Phosphoinositide-dependent kinase 1; mTORC1: mechanistic target of rapamycin (also known as mammalian target of rapamycin) complex 1; mTORC2: mechanistic target of rapamycin complex 2; PTEN: phosphatase and tensin homolog deleted on chromosome 10; PTMs: post-translational modifications; CDK2: cyclin-dependent kinase 2; ACTS: activating C-terminal serine residues; CK2: casein kinase 2; PHLPP: PH domain leucine-rich repeat protein phosphatase;
Emerging therapeutics for targeting Akt in cancer

PP2A: protein phosphatase 2A; miRNA: microRNA; NSCLC: non-small cell lung cancer; RRM2: ribonucleotide reductase M2; PPM1D: Protein Phosphatase Magnesium-dependent 1 D; Chk2: checkpoint kinase 2; ER: estrogen receptor; ErbB2: human epidermal growth factor receptor 2; ErbB3: human epidermal growth factor receptor 3; CLL: chronic lymphocytic leukemia; SCLC: small cell lung cancer

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