MINI REVIEW

What a Tangled Web We Weave: Emerging Resistance Mechanisms to Inhibition of the Phosphoinositide 3-Kinase Pathway

Samuel J. Klempner¹, Andrea P. Myers²,³, and Lewis C. Cantley²,⁴

ABSTRACT

The phosphoinositide 3-kinase (PI3K) pathway is one of the most frequently mutated pathways in cancer, and is actively being pursued as a therapeutic target. Despite the importance of the PI3K pathway in cancer, durable responses to PI3K pathway-targeted therapies are uncommon with monotherapy. Several in vitro and xenograft models have elucidated compensatory signaling and genomic changes which may limit the therapeutic effectiveness of PI3K inhibitors in the clinic. Future clinical trials with prospective evaluation of tumor signaling and genomic changes are likely to identify novel resistance mechanisms as well as subsets of patients who may derive maximal benefit from PI3K pathway inhibitors.

Significance: There are multiple ongoing clinical trials targeting the PI3K pathway members in several malignancies. This review summarizes the known mechanisms of resistance to targeting the PI3K pathway. Understanding of resistance mechanisms will help to inform more rational clinical trial design to optimize the clinical impact of targeting the PI3K pathway in cancer.

INTRODUCTION

Sustained proliferative signaling is a major hallmark of malignancy and commonly occurs through transmembrane receptor tyrosine kinases (RTK) and their downstream effectors (1). One of the most important effectors of RTK signaling is phosphoinositide 3-kinase (PI3K). PI3K was initially implicated in cancer through identification of its physical association with the Rous sarcoma (Src) oncogene-encoded protein tyrosine kinase, pp60^src, and with the polyoma virus middle t protein (2, 3). Subsequent studies revealed that the PI3K pathway was central to multiple malignant hallmarks, including survival, growth, metabolism, motility, and progression. Activating mutations in key components of the PI3K pathway are common in numerous tumor types, and loss of the negative PI3K regulator phosphatase and tensin homolog (PTEN) is the second most common event in cancer after p53 mutations (4). The central importance of PI3K signaling and its downstream effects is now well established and previously reviewed (5–7). However, despite scientific rationale and in vitro and tumor xenograft data, PI3K/AKT/mTOR inhibitors have yet to achieve maximal clinical impact.

CANONICAL CLASS IA PI3K SIGNALING

To date, mainly the class IA PI3Ks are implicated in human cancers; therefore, this review will be restricted to the class IA PI3K isoforms. The class IA PI3Ks are composed of heterodimers of regulatory subunits (p85α, p85β, p50α, p55α, and p55γ) and catalytic subunits (p110α, p110β, and p110δ), and all share a similar five-domain structure (7). The association of the regulatory p85 subunit with various RTKs occurs via physical interaction between the SH domains of p85 and phosphotyrosines in the consensus YxxM sequence, which becomes autophosphorylated by RTK dimerization. RTKs can also phosphorylate YxxM motifs in adaptors such as insulin receptor substrate 1 and 2 (IRS1 and IRS2; ref. 7). Through binding of the regulatory subunit to RTKs or adaptors, PI3K is recruited to the plasma membrane where it phosphorylates the 3' position of its preferred in vivo

Authors' Affiliations: ¹Division of Hematology-Oncology, University of California Irvine Medical Center, Orange, California; ²Division of Signal Transduction, Beth Israel Deaconess Medical Center; ³Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; and ⁴Department of Medicine, Weill Cornell Medical College, New York, New York

Corresponding Author: Lewis C. Cantley, Weill Cornell Medical College, 1300 York Avenue, Box 8, New York, NY 10065. Phone: 646-962-2900; Fax: 617-667-0957; E-mail: LCantley@med.cornell.edu

doi: 10.1158/2159-8290.CD-13-0063

© 2013 American Association for Cancer Research.
substrate phosphatidylinositol-4,5-bisphosphate (PI-4,5-P₂) to generate the second messenger phosphatidylinositol (3,4,5) trisphosphate (PIP₃). PIP₃ generation recruits cytosolic proteins with PIP₃-binding pleckstrin homology (PH) domains and thereby localizes them to the plasma membrane. The serine/threonine kinase protein kinase B (AKT) is the most notable of the recruited proteins and a major effector of PI3K signaling (8). The extent and duration of PIP₃ elevation at the plasma membrane is primarily regulated by the tumor suppressor PTEN, whose lipid phosphatase activity converts PIP₃ to PIP₂.

The direct interaction between the PH domain of AKT and PIP₃ induces conformational changes, exposing the two important residues, threonine 308 (T308) and serine 473 (S473), for phosphorylation (9). A second PIP₃-binding protein kinase named phosphoinositide-dependent kinase 1 (PDK1) phosphorylates T308, which is located in the AKT activation loop. Full activation of AKT requires phosphorylation of S473 in the hydrophobic AKT motif by mTOR complex 2 (mTORC2).

Fully active AKT phosphorylates multiple targets containing the consensus RxRxxS/TΨΨ sequence (where Ψ is a hydrophobic residue; ref. 10). In turn, fully active AKT turns on mTOR complex 1 (mTORC1) activity via two main mechanisms; turning off the inhibitory protein, Tuberin [the protein product of the tuberous sclerosis complex 2 (TSC2) gene] by phosphorylation, and directly phosphorylating proline-rich AKT substrate of 40 kDa (PRAS40; refs. 11, 12). Active AKT, and extracellular regulated kinase regulated kinase 1 and 2 (ERK1/2), phosphorylate TSC2 which inhibits the GTPase activating protein (GAP) activity of the TSC1–TSC2 complex toward Ras homolog enriched in brain (RHEB). GTP-loaded RHEB is then able to activate mTORC1 (13–15). Concomitantly, active AKT phosphorylates PRAS40, causing it to release and bind to 14-3-3 proteins which prevent PRAS40 from inhibiting mTORC1 (16, 17).

Following activation, mTORC1 plays a major role in stimulating 5-cap-dependent protein translation through its substrates, ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1; refs. 7, 11). Phosphorylated 4EBP1, but not S6K, reappears is not known and may involve differential mTORC1-binding affinity for S6K and 4EBP1, binding of adaptor protein, and/or phosphorylation by a yet-to-be-identified kinase (38). Clinically, these findings raise the issue of biomarker readouts and suggest that S6 phosphorylation may not be the optimal biomarker of mTORC1 inhibition, as loss of S6 phosphorylation does not necessarily correlate with inhibition of all mTORC1 substrates. In fact, 4EBP1 phosphorylation status may correlate more tightly with cancer aggressiveness (39). The catalytic mTOR inhibitors, though improved over the rapalogs, are also subject to resistance via IRS-1–mediated feedback activation, particularly at suboptimal dosing (40, 41). These mTOR catalytic inhibitors also activate the RTK–PI3K–PDK1 cascade leading to AKT phosphorylation at T308 which can drive AKT signaling in the absence of S473 phosphorylation by mTORC2 (42). In addition, a recent report suggested that combined inhibition of both PI3K and mTOR may lead to feedback upregulation of JAK2 and its downstream target STAT5 via IRS-1 and insulin-like growth factor receptor 1 (IGF1R)-mediated activation, thereby decreasing sensitivity to p110-mTOR inhibitors (43). Combined targeting of IRS-1 AND IGFR-1

The mitogen-activated protein kinase (MAPK) and PI3K pathways converge at the regulation of protein synthesis through mTORC1 function, specifically, via modulation of TSC2 (31–33). Thereby, TSC2 can act as a sensor of both RAS–MAPK and PI3K–AKT pathway activation. Inhibition of mTORC1 with rapamycin has been shown to decrease insulin receptor substrate 1 (IRS-1) levels and induce AKT phosphorylation and downstream signaling (34). Inhibition of mTORC1, and the subsequent decrease in p70S6 kinase, decreases the basal inhibition (via p70/S6K-mediated S312, S636/639 phosphorylation) of IRS-1 and results in IRS-1 stabilization (Fig. 1A; refs. 35, 36). Furthermore, although the rapamycin analogs (referred to as rapalogs) initially inhibit both mTORC1 substrates, S6K and 4EBP1, phosphorylation of 4EBP1, and thus cap-dependent translation, reemerges 6 hours after rapamycin treatment and mediates rapalog resistance (Fig. 1B; ref. 37). The exact mechanism by which phosphorylated 4EBP1, but not S6K, reappears is not known and may involve differential mTORC1-binding affinity for S6K and 4EBP1, binding of adaptor protein, and/or phosphorylation by a yet-to-be-identified kinase (38). Clinically, these findings raise the issue of biomarker readouts and suggest that S6 phosphorylation may not be the optimal biomarker of mTORC1 inhibition, as loss of S6 phosphorylation does not necessarily correlate with inhibition of all mTORC1 substrates. In fact, 4EBP1 phosphorylation status may correlate more tightly with cancer aggressiveness (39). The catalytic mTOR inhibitors, though improved over the rapalogs, are also subject to resistance via IRS-1–mediated feedback activation, particularly at suboptimal dosing (40, 41). These mTOR catalytic inhibitors also activate the RTK–PI3K–PDK1 cascade leading to AKT phosphorylation at T308 which can drive AKT signaling in the absence of S473 phosphorylation by mTORC2 (42). In addition, a recent report suggested that combined inhibition of both PI3K and mTOR may lead to feedback upregulation of JAK2 and its downstream target STAT5 via IRS-1 and insulin-like growth factor receptor 1 (IGF1R)-mediated activation, thereby decreasing sensitivity to p110-mTOR inhibitors (43). Combined targeting of
Mechanisms of Resistance to PI3K/AKT/mTOR Inhibitors

MINI REVIEW

PI3K/mTOR and JAK/STAT signaling was able to abrogate the resistance, although this has not been shown clinically (43). Newer reports have also suggested a non–feedback inherent resistance pathway in which PI-4,5-P2 can directly activate signaling by the serine/threonine p21-activating kinase p21 protein (Cdc42/Rac)-activated kinase 1 (PAK1) to drive cell survival in lymphoma cell lines, and that PAK1 inhibition increases PI3K inhibitor sensitivity (44, 45).

An S6K-mediated feedback loop can also lead to MAPK activation reflected in ERK phosphorylation at threonine 202 and tyrosine 204, and this feedback is clinically relevant, occurring in up to 50% of everolimus-treated patients with breast cancer (46). The biologic and tumor-specific importance of feedback MAPK activation in response to PI3K inhibition has been highlighted in multiple studies. Our lab showed the importance of PI3K signaling in KrasG12D-driven murine lung cancers in which the concomitant inhibition of mitogen-activated protein kinase kinase (MEK) and PI3K had synergistic effects on inhibition of tumor growth (47).

IRS-1–mediated feedback activation of the PI3K, MAPK, and JAK/STAT pathways has led to the initiation of early-phase combination trials. However, emerging clinical data from combination trials such as MEK inhibitors combined with PI3K inhibitors suggest narrow therapeutic indices for combination therapy. Achieving combination targeting strategies may call for alternative dosing schedules such as sequential or alternating drugs to mitigate toxicity while minimizing the development of resistance.

FOXO-MEDIATED MECHANISMS

The FOXO family of transcription factors influences the expression of multiple proapoptotic proteins (19, 20). Activated AKT phosphorylates FOXO3a, thereby preventing its translocation to the nucleus and inhibiting the transcription of proapoptotic target genes. Several studies have now shown the importance of FOXO-mediated feedback loops in the development of resistance to PI3K inhibitors.

A subset of breast cancers are defined by HER2 (ErbB2) amplification, and the HER2/HER3 heterodimer potently activates PI3K signaling via six docking sites for the p85 subunit of PI3K (48–50). The success of HER2-directed therapies relies partly on their ability to inhibit downstream PI3K signaling, and inhibition of HER2 results in feedback HER3 upregulation, abrogating the effect of HER2 inhibition (51–53). The feedback HER3 upregulation seems to be
clinically relevant and has been shown in tumor samples from patients treated with the HER2 inhibitor lapatinib, and is the basis for the recent U.S. Food and Drug Administration approval of the HER3-directed antibody pertuzumab. Clinically, the combination of pertuzumab and the HER2 inhibitor trastuzumab is significant better than trastuzumab alone (54, 55). HER3 upregulation is mediated by PI3K–AKT-dependent phosphorylation of the AKT substrate FOXO3a in which HER2-induced PI3K–AKT signaling normally represses HER3 transcription (Fig. 2A; ref. 52). Thus, inhibition of either HER2 or PI3K–AKT results in decreased FOXO3a phosphorylation and increased nuclear FOXO3a where FOXO3a is free to bind the FOXO3a-binding sites (ATAAACA) upstream of the HER3 gene and induce mRNA and ultimately protein synthesis (Fig. 2B; refs. 52, 56, 57). The importance of FOXO-mediated feedback has also been shown in 3-dimensional ovarian cancer spheroids where treatment with BEZ-235, a dual PI3K/mTOR inhibitor, led to increased levels of Bcl-2, IGF-IRb, p-STAT3, p-STAT6, p-c-Jun, p-SMAD3, p-p90RSK, EGFR, and p-HER2 (58). Furthermore, Muranen and colleagues (58) showed that inhibition of the compensatory pathways abrogates the resistance to BEZ-235.

β-CATENIN

The wingless related MMTV integration site (Wnt)/β-catenin pathway regulates limb development in embryogenesis and has been implicated in several cancers. In colon cancer, increased β-catenin pathway activation through loss of function of adenomatosis polyposis coli (APC) is a common event in early tumorigenesis, and increased nuclear β-catenin has been well documented (59–61). At the convergence of the Wnt/β-catenin pathway and the PI3K signaling pathway is the AKT substrate FOXO3a, which is normally considered a tumor suppressor (62). In fact, the antitumoral effects of AKT inhibition are largely related to the resultant proapoptotic program induced by nuclear FOXO accumulation (63). Tenbaum and colleagues (64) recently highlighted the tumor-specific importance of AKT inhibition by showing that in the presence of a high nuclear level of β-catenin, AKT inhibition and the associated nuclear FOXO3a
Mechanisms of Resistance to PI3K/AKT/mTOR Inhibitors

MINI REVIEW

retention resulted in increased metastatic potential (Fig. 3A
and B). Mechanistically, the authors suggest that high nuclear
β-catenin and increased nuclear FOXO3a (due to AKT inhibi-
tion) cooperate to regulate a prometastatic genetic program
including IQ motif containing GTPase activating protein
2 (IQGAP2), which weakens E-cadherin junctions, result-
ing in increased cell scattering and motility (Fig. 3B; ref. 64).
Moreover, nuclear β-catenin content conferred inherent
resistance to AKT inhibition, possibly via reduction in the
proapoptotic FOXO3a target genes BCL2L11 and TNSF10.
The authors also suggest that high nuclear β-catenin results
in nuclear translocation of FAS-associated adaptor protein
(FADD) as well as inhibition of PARP1 cleavage normally
induced by FOXO3a. Thus, a high nuclear β-catenin level
creates an environment which is inherently less sensitive to
a nuclear FOXO-mediated antitumoral effect. Exposure to the
Wnt inhibitor XAV-939, and subsequent reduction in nuclear
β-catenin, was able to reverse AKT inhibitor resist-
ance (Fig. 3C; ref. 64). The work by Tenbaum and colleagues
(64) suggests the importance of identifying tumor biomark-
er that may select patients less likely to respond to PI3K/
AKT/mTOR inhibitors. It remains to be determined whether
or not the AKT/β-catenin interaction is limited to colon
cancer or whether this can be extended to other tumor types.

**ANDROGEN RECEPTOR FEEDBACK**

PI3K pathway activation through PTEN loss is common
to metastatic prostate cancer, with a frequency of up to 70%,
and PTEN loss promotes castrate resistance in cell line and
 xenograft models (65, 66). Despite the increase in PI3K path-
way readouts in prostate cancer, a phase II trial of the mTOR
inhibitor everolimus showed limited activity with only 2
of 36 patients showing a more than 50% decrease in serum
prostate-specific antigen (PSA; ref. 67). Carver and colleagues
(68) have recently shown that in PTEN-negative prostate can-
cers PI3K inhibition leads to androgen receptor (AR) pathway
activation via relieving basal AR inhibition through HER
kinases, specifically HER2/3. Conversely, AR inhibition led
to a feedback increase in AKT phosphorylation via a decrease
in the AR-dependent immunophosphin FKBP5, which is a chap-
erone for the AKT phosphatase PH domain and leucine-rich
repeat protein phosphatases (PHLPP; ref. 68). Thus, PTEN-
deficient prostate cancers are able to bypass the growth-sup-
pressive effects of PI3K inhibition via increased AR signaling.
The compensatory increase in AR signaling likely underlies
the poor clinical response rates to everolimus in combination
with the weak anti-androgen bicalutamide (67). This observa-
tion argues that combined PI3K blockade with effective AR
inhibition with abiraterone or enzalutamide may improve
responses in metastatic prostate cancer (68). This combina-
tion is currently being studied in early-phase clinical trials
(NCT01634061).

**C-MYC AND CAP-DEPENDENT TRANSLATION**

Up to 25% of breast cancers contain PIK3CA mutations in
the two oncogenic hotspot domains (E545 helical domain
and H1047R kinase domain), with H1047R being the most
common mutation (6, 69–72). Liu and colleagues have shown
that Phk3a induction can lead to mammary tumors in mice
and that sustained PI3K signaling was required to maintain
malignant mammary tumors (69). However, following with-
drawal of inducible Phk3aH1047R, a significant proportion of
mammary tumors resumed growth in PIK3CA-independent
manner and a single-nucleotide polymorphism array revealed
amplification of c-Myc and Mdm2 in the recurrent tumors
(69). Similarly, forced c-MYC expression confers resistance
to otherwise sensitive Phk3aH1047R-mutant mammary tumors
(69). As further validation, there are several human breast
cancer databases confirming increased c-MYC expression in
PIK3CA-mutant breast cancers with frequencies ranging from
27% to 47% (73–75). The importance of c-MYC as a regu-
lator of PI3K/AKT/mTOR resistance has been highlighted in
several other models.

NOTCH signaling is altered in a significant portion of
adult T-cell acute lymphoblastic leukemia (ALL; ref. 76).
c-MYC is a direct transcriptional target of NOTCH signal-
ing, and NOTCH inhibition results in reduced c-MYC levels
(76–79). c-MYC is also downstream of the PI3K–AKT path-
way in that AKT-mediated phosphorylation and inhibition
of GSK3 prevents the phosphorylation and degradation of
c-MYC protein (80, 81). In T-cell ALL lines the dual PI3K/
mTOR inhibitor PI-103 showed a predictable initial decrease
in c-MYC. However, subsequently c-MYC levels were rescued
by compensatory increased NOTCH signaling potentially
mediated by a decrease in SGK-enhanced FBXW7-mediated
degradation of active intracellular NOTCH (NICD; refs.
82–84). Using a chemical genetic screen, Mueller and colle-
agues (85) also identified NOTCH pathway alterations and
downstream MYC activation as a mechanism to override
to PI3K/AKT/mTOR-dependent proliferation in multiple
breast cancer cell lines.

The eukaryotic initiation factor 4E is a major medi-
ator of cap-dependent translation and tightly regulated
by the PI3K–AKT–mTOR pathway. Upon activation, mTORC1
phosphorylates 4EBP1 (PHAS-1), thereby disrupting its
interaction with eIF4E and allowing eIF4E to dissociate
from 4EBP1 and participate in the initiation of translation
after binding to the mRNA 5′ cap structure (86–88). Illic
and colleagues (89) recently showed that eIF4E gene ampli-
fication and protein increase developed as a compensatory
resistance mechanism in cells initially sensitive to the com-
bined PI3K/mTOR inhibitor BEZ-235. Considering that
the gene encoding eIF4E is a known MYC-regulated target,
cooperation between MYC and eIF4E in regulating resist-
ance is likely (89–92).

The internal ribosome entry site (IRES) is a conserved
nucleotide sequence targeting mRNA for 5′ cap-independent
translation (93–96). IRES-mediated cap-independent trans-
lation is seen in response to nutrient deprivation (analogous
to PI3K/mTOR inhibition) and oxidative stress in several
organisms, and serves as a method for producing proteins
required for cell survival (97–99). Several FOXO targets
can be translated via IRES-mediated mechanisms and the
ability of tumor cells to maintain translation in the face of
PI3K/AKT/mTOR-mediated inhibition of cap-dependent
translation may serve as a conserved resistance mecha-

Published OnlineFirst November 21, 2013; DOI: 10.1158/2159-8290.CD-13-0063

Downloaded from cancerdiscovery.aacrjournals.org on July 1, 2017. © 2013 American Association for Cancer Research.
Figure 3. High nuclear β-catenin levels confer resistance to AKT inhibition and coordinates with increased nuclear FOXO3a to promote metastasis in colon cancer. A, activation of the Wnt/β-catenin leads to nuclear accumulation of β-catenin, and activation of the PI3K–AKT pathway inhibits nuclear translocation of FOXO3a. B, the presence of high nuclear β-catenin and increased nuclear FOXO3a results in resistance to PI3K pathway inhibitors and promotes cell scattering and metastasis. C, reducing nuclear β-catenin through Wnt/β-catenin pathway inhibition reverses the metastatic potential and resistance to PI3K/AKT inhibitors, resulting in increased apoptosis. Dotted lines represent multiple steps not shown graphically, and line strength represents relative activation. LEF, lymphoid enhancer factor; TCF, T-cell factor.
Mechanisms of Resistance to PI3K/AKT/mTOR Inhibitors

The common theme to c-MYC- and eIF4E-related resistance mechanisms is the uncoupling of proliferation from dependence on the PI3K–AKT–mTOR pathway. Both c-MYC and eIF4E are likely to bypass clinically available inhibitors via exerting their action downstream of the commonly targeted signaling nodes (PI3K, AKT, and mTOR). Although it appears that c-MYC activation, either through increased NOTCH signaling or genomic alterations, may represent a conserved resistance mechanism, it is likely that multiple pathways capable of activating PI3K–AKT–mTOR components downstream of the commonly pharmacologically inhibited targets will confer varying degrees of resistance. As it will be difficult to inhibit redundantly regulated distal nodes (e.g., 5' cap-dependent translation) in the PI3K–AKT–mTOR pathway, improved responses to PI3K pathway-targeted therapies are more likely to result from improved patient selection based on patient tumor testing.

CLINICAL IMPLICATIONS

Several retrospective clinical studies have attempted to analyze the predictive and prognostic significance of mutations, amplifications, and protein loss in the PI3K/AKT/mTOR axis with varying results (100–103). Large genomic datasets coupled to phosphoproteomic and small-molecule screens will inform the interactions of oncogenic aberrations in the PI3K/AKT/mTOR axis with other commonly altered pathways in cancer. Simply incorporating genomic data into the selection of therapeutic options may be improving the response to PI3K/AKT/mTOR inhibitors in early-phase clinical trials (104–106). Although emerging preclinical work continues to inform resistance mechanisms, it will be important to obtain patient tumor samples during therapy (“on-treatment biopsies”) to validate preclinical observations. The importance of on-treatment biopsies is already being highlighted in preclinical models and informing treatment strategies such as discontinuous therapy to delay the emergence of resistance (26, 107). The incorporation of tumor signaling data using proteomic techniques such as reverse-phase protein array with genomic studies may further identify both patients likely to be resistant to PI3K pathway inhibitors as well as patients who may derive maximal benefit. Importantly, more work is needed to separate resistance mechanisms which develop under the selective pressure of drug exposure from those which are inherent prior to PI3K/AKT/mTOR-targeted therapy. Ultimately, prospective human trials are needed to determine whether or not knowledge of resistance mechanisms can affect hard clinical outcomes such as progression-free and overall survival.

CONCLUSIONS

Here, we have highlighted the central importance of the PI3K pathway in regulating multiple hallmarks of cancer, and known escape mechanisms that bypass PI3K/AKT/mTOR blockade. The ongoing observations of emerging resistance mechanisms highlight the paradigm for translational research. The flow of information obtained from bench studies to early-phase clinical trials is paramount, as is flow of patient-derived samples back to the bench. As more resistance mechanisms are elucidated, conserved patterns addressing compensatory signaling changes and genomic changes affecting targets downstream of pharmacologic inhibition are likely to emerge. Although the importance of the PI3K–AKT–mTOR pathway is well established in cancer, much remains to be determined about potential inherent and adaptive resistance mechanisms and their therapeutic potential.

Disclosure of Potential Conflicts of Interest

A.P. Myers is a Clinical Program Leader at Novartis and a consultant/advisory board member of Sanofi Aventis. L.C. Cantley has received a commercial research grant from GileadSmithKline, is a consultant/advisory board member of Novartis, Genentech, and Gilead, and has an immediate family member who is a consultant/advisory board member of Piramal. No potential conflicts of interest were disclosed by the other author.

The Editor-in-Chief of Cancer Discovery (L.C. Cantley) is an author of this article. In keeping with the AACR’s Editorial Policy, the paper was peer reviewed and a member of the AACR’s Publications Committee rendered the decision concerning acceptability.

Authors’ Contributions

Conception and design: S.J. Klempner, L.C. Cantley
Development of methodology: S.J. Klempner
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.J. Klempner
Writing, review, and/or revision of the manuscript: S.J. Klempner, A.P. Myers, L.C. Cantley
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.J. Klempner
Study supervision: S.J. Klempner, L.C. Cantley

Acknowledgments

The authors apologize to colleagues whose important contributions to the field could not be cited because of space limitations.

Grant Support

L.C. Cantley is supported by NIH Grant GM041890, Stand Up To Cancer Dream Team Translational Research Grant, a program of the Entertainment Industry Foundation (SU2C-AACR-DT0209), and the American Association for Cancer Research.

Received February 8, 2013; revised August 21, 2013; accepted August 22, 2013; published OnlineFirst November 21, 2013.

REFERENCES

8. Stephens L, Anderson K, Stokoe D, Erdjument-Bromage H, Painter GF, Holmes AB, et al. Protein kinase B kinases that mediate...

Downloaded from cancerdiscovery.aacrjournals.org on July 1, 2017. © 2013 American Association for Cancer Research.


Mechanisms of Resistance to PI3K/AKT/mTOR Inhibitors


What a Tangled Web We Weave: Emerging Resistance Mechanisms to Inhibition of the Phosphoinositide 3-Kinase Pathway

Samuel J. Klempner, Andrea P. Myers and Lewis C. Cantley


Updated version  Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-13-0063

Cited articles  This article cites 107 articles, 49 of which you can access for free at:
http://cancerdiscovery.aacrjournals.org/content/3/12/1345.full#ref-list-1

Citing articles  This article has been cited by 15 HighWire-hosted articles. Access the articles at:
http://cancerdiscovery.aacrjournals.org/content/3/12/1345.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.