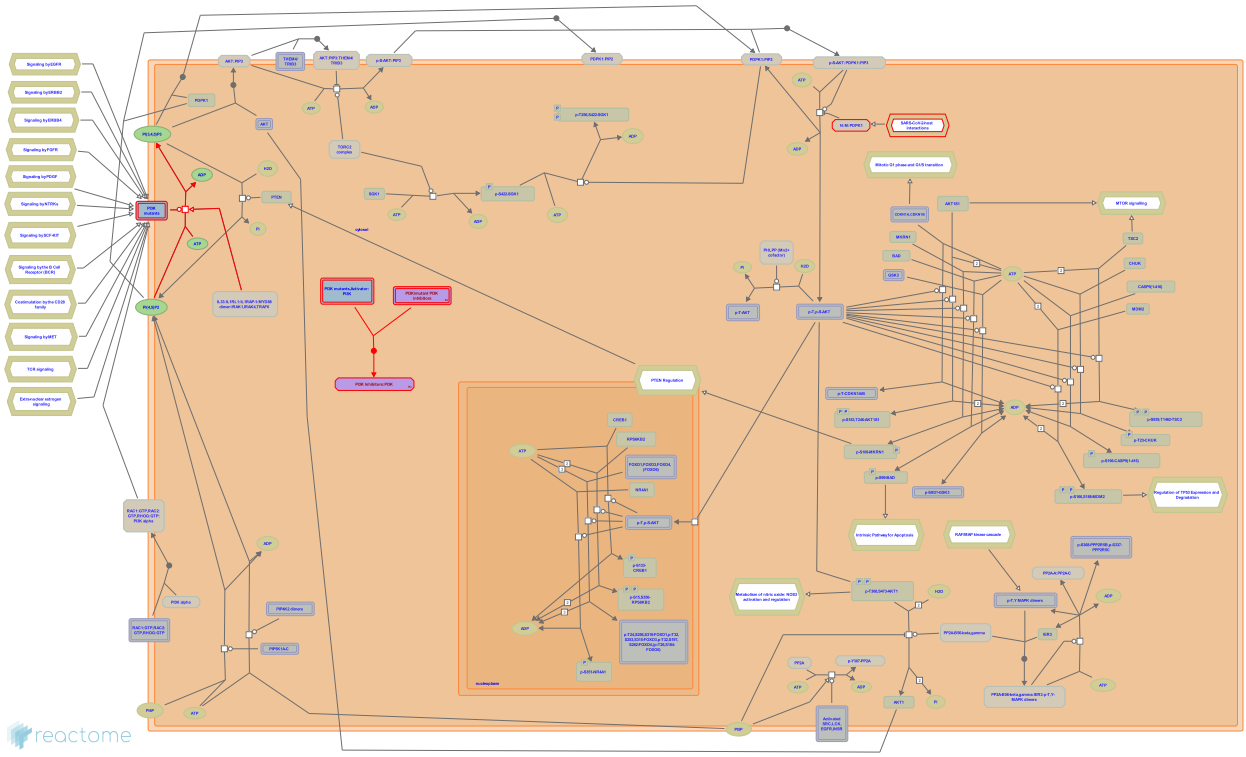
Constitutive Signaling by Aberrant PI3K in Cancer



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
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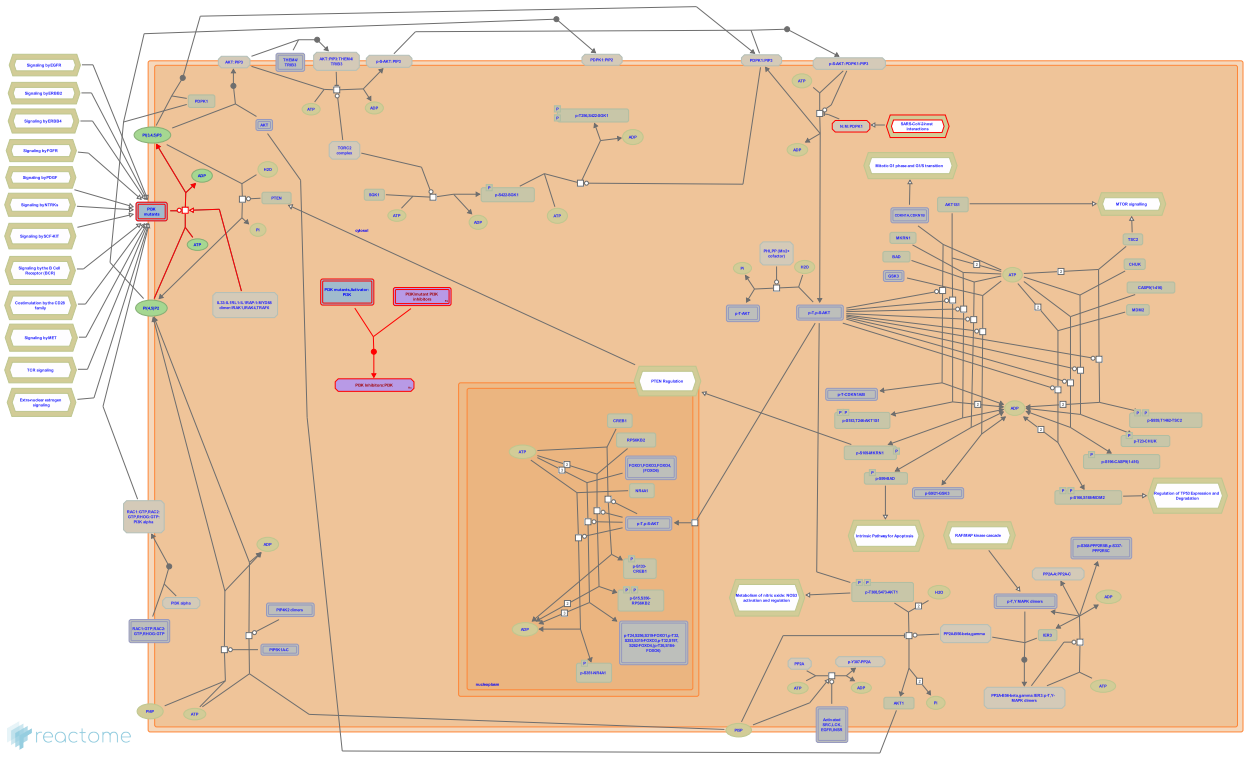
Constitutive Signaling by Aberrant PI3K in Cancer ↗

Stable identifier: R-HSA-2219530

Diseases: cancer



Signaling by PI3K/AKT is frequently constitutively activated in cancer via gain-of-function mutations in one of the two PI3K subunits - PI3KCA (encoding the catalytic subunit p110alpha) or PIK3R1 (encoding the regulatory subunit p85alpha). Gain-of-function mutations activate PI3K signaling by diverse mechanisms. Mutations affecting the helical domain of PIK3CA and mutations affecting nSH2 and iSH2 domains of PIK3R1 impair inhibitory interactions between these two subunits while preserving their association. Mutations in the catalytic domain of PIK3CA enable the kinase to achieve an active conformation. PI3K complexes with gain-of-function mutations therefore produce PIP3 and activate downstream AKT in the absence of growth factors (Huang et al. 2007, Zhao et al. 2005, Miled et al. 2007, Horn et al. 2008, Sun et al. 2010, Jaiswal et al. 2009, Zhao and Vogt 2010, Urick et al. 2011).

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Editions

2012-07-18	Authored	Orlic-Milacic, M.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.

PI3K gain of function mutants phosphorylate PIP2 to PIP3 ↗

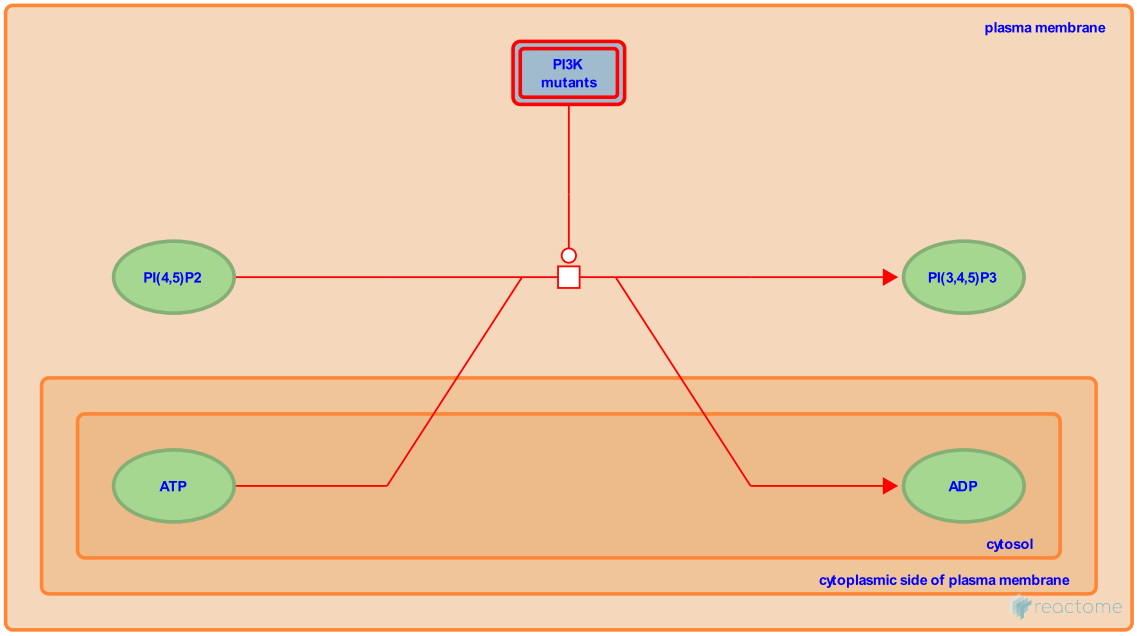
Location: Constitutive Signaling by Aberrant PI3K in Cancer

Stable identifier: R-HSA-2394007

Type: transition

Compartments: plasma membrane, cytosol

Diseases: cancer



Constitutively active PI3K complex produces PIP3 in the absence of growth stimuli, resulting in aberrant activation of downstream AKT signaling that positively regulates cell growth and survival. The PIK3CA gene, encoding the catalytic subunit of PI3K (p110alpha), is one of the most frequently mutated oncogenes in cancer. Hotspot mutations are found in the helical domain and kinase domain of PIK3CA, with the most frequent mutations being E545K substitution in the helical domain and H1047R substitution in the kinase domain.
The oncogenic PIK3CA mutants annotated here preserve their ability to bind PIK3R1 (p85alpha) regulatory subunit, but are constitutively active either because the inhibitory interactions with PIK3R1 are relieved, or because the conformation of the catalytic domain is changed. Missense mutations that result in substitution of amino acids at positions 542, 545 or 546 of PI3K disrupt an inhibitory interaction between the helical domain of PIK3CA and the nSH2 domain of PIK3R1. The effect of substitution of glutamic acid residue at position 545 has been studied in detail in PIK3CA E545K mutant, where glutamic acid is replaced with lysine (Miled et al. 2007, Huang et al. 2007, Zhao et al. 2005). The gain-of-function has been experimentally confirmed for PIK3CA E545A mutant (Horn et al. 2008), while PIK3CA E545G, PIK3CA E545Q and PIK3CA E545V mutants are assumed to behave similarly. The structural and functional consequences of glutamic acid to lysine substitution at position 542, in PIK3CA E542K mutant, have been established (Miled et al. 2007, Horn et al. 2008) and are extrapolated to PIK3CA E542Q and PIK3CA E542V mutants. A less frequent substitution of glutamine residue at position 546 follows the same mechanism, as shown for PIK3CA Q546K mutant (Miled et al. 2007) and extrapolated to PIK3CA Q546E, PIK3CA Q546H, PIK3CA Q546L, PIK3CA Q546P and PIK3CA Q546R mutants.
In the kinase domain of PIK3CA, substitution of histidine residue at position 1047 or methionine residue at position 1043, detected in PIK3CA H1047R, PIK3CA H1047L, PIK3CA H1047Y, PIK3CA M1043I, PIK3CA M1043T and PIK3CA M1043V mutants, is predicted to change the conformation of the activation loop (Huang et al. 2007) and was shown to confer constitutive activity, in the absence of growth factors, to PIK3CA H1047R, PIK3CA H1047L and PIK3CA M1043I mutants (Zhao et al. 2005, Horn et al. 2008). The catalytic activity of PIK3CA H1047R, PIK3CA H1047L and PIK3CA M1043I mutants may be further increased by binding of PIK3R1 regulatory subunit to phosphopeptides generated by activated receptor tyrosine kinases (Hon et al. 2011). PIK3CA H1047Y, PIK3CA M1043T and PIK3CA M1043V mutants are expected to behave similarly.
The arginine residue at position 38 of PIK3CA (R38) is located at a contact site between the ABD and kinase domains of PIK3CA. Substitution of this arginine residue with histidine in PIK3CA R38H mutant is likely to disrupt the interaction between the ABD domain and the kinase domain, causing a conformational change of the kinase domain that leads to increased enzymatic activity (Huang et al. 2007). PIK3CA R38H mutant shows reduced PIK3R1 binding and modestly increased catalytic activity (measured indirectly, via AKT1 phosphorylation) under

serum starved conditions (Zhao et al. 2005). PIK3CA R38C, PIK3CA R38G and PIK3CA R38S mutants are expected to behave similarly.
Mutations in other conserved domains of PIK3CA, such as membrane-binding C2 domain (Mandelker et al. 2009), have not been annotated as their mechanism of action needs to be further elucidated.
Although less common than mutations in PIK3CA, mutations in PIK3R1, encoding the regulatory subunit of PI3K (p85alpha) have been recently described. Mutations mapping to iSH2 and nSH2 domains, the two domains of PIK3R1 involved in the inhibition of PIK3CA, which were shown to result in constitutive activity of PIK3R1 complex, are annotated here. An experimentally studied nSH2 domain mutant is PIK3R1 G376R (Sun et al. 2010). PIK3R1 iSH2 domain mutants, affected by amino acid substitutions and small inframe deletions, PIK3R1 D560Y (Jaiswal et al. 2009), PIK3R1 N564D (Jaiswal et al. 2009), PIK3R1 N564K (Sun et al. 2010), PIK3R1 H450_E451del (Urick et al. 2011), PIK3R1 K459del (Urick et al. 2011), PIK3R1 R574_T576del (Urick et al. 2011) and PIK3R1 Y463_L466del (Urick et al. 2011), were all shown to bind PIK3CA and confer constitutive activity to PI3K complex. PIK3R1 D560H, PIK3R1 R574I and PIK3R1 R574T mutants are expected to behave similarly to functionally characterized D560 and R574 substitution mutants.
Co-occurrence of PIK3CA and PIK3R1 mutations has been documented in some tumors, but since it is rare and the exact clinical combinations of PIK3CA and PIK3R1 mutants have not been studied, complexes of PIK3CA mutants with PIK3R1 mutants are not shown (Urick et al. 2011).
Although rare, perturbations in genes encoding other isoforms of PI3K subunits have also been reported in cancers. Mutations in PIK3R2, encoding PI3K regulatory subunit isoform p85beta, are found infrequently in endometrial cancers, but have not been functionally studied (Cheung et al. 2011). They are not shown in this context. PIK3CB, encoding PI3K catalytic subunit isoform p110beta, can be overexpressed in cancer, mainly due to genomic gain. Several studies have shown that PTEN deficient cancer cell lines depend on PIK3CB (p110beta) for AKT activation and sustained growth (Wee et al. 2008, Jiang et al. 2010, Chen et al. 2011). PIK3CB activation synergizes with PTEN loss in mouse prostate cancer model (Jia et al. 2008). Mutations in PIK3CB are very rare, have not been functionally studied, and are therefore not shown. Structural studies indicate that, in comparison with PIK3CA (p110alpha), PIK3CB (p110beta) and PIK3CD (p110delta) form additional inhibitory contacts with the regulatory subunit p85alpha, and are therefore probably less prone to mutational activation (Burke et al. 2011).
For more information, please refer to recent reviews by Liu et al. 2009 and Vogt et al. 2009.

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Editions

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2012-08-03	Edited	Matthews, L.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.

PI3K inhibitors block PI3K catalytic activity ↗

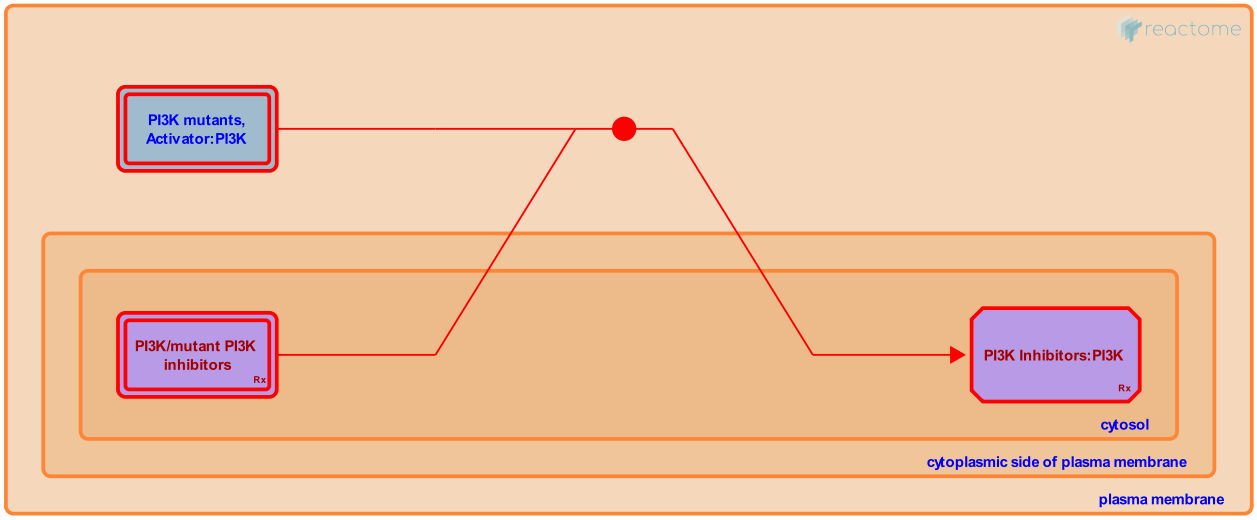
Location: Constitutive Signaling by Aberrant PI3K in Cancer

Stable identifier: R-HSA-2400009

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cancer



A variety of inhibitors capable of blocking the phosphoinositide kinase activity of PI3K have been developed. These inhibitors display differential selectivity and inhibit kinase activity of their substrates by distinct mechanisms. For example, the first-generation PI3K inhibitor wortmannin (Wymann et al. 1996) covalently and irreversibly binds all classes of PI3K enzymes, as well as other kinases including mTOR, at a residue critical for catalytic activity. Although wortmannin is precluded from in vivo and clinical use due to its toxicity, it has proven to be a useful tool for in vitro laboratory studies. Newer inhibitors, such as BEZ235, are currently being investigated in Phase I clinical trials. BEZ235 is a dual pan-class I PI3K/mTOR inhibitor that blocks kinase activity by binding competitively to the ATP-binding pocket of these enzymes (Serra et al. 2008, Maira et al. 2008). BGT226 (Chang et al. 2011) and XL765 (Prasad et al. 2011) also inhibits both PI3K class I enzymes and mTOR. Other inhibitors in clinical trials, such as BKM120 (Maira et al. 2012), GDC0941 (Folkes et al. 2008, Junttila et al. 2009) and XL147 (Chakrabarty et al. 2012), are specific for class I PI3Ks and exhibit no activity against mTOR. Current research aims to identify isoform-specific PI3K inhibitors. Small molecule inhibitors that selectively inhibit PIK3CA (p110alpha), e.g. PIK-75 and A66, were used to study the role of p110alpha in signaling and growth of tumor cells (Knight et al. 2006, Sun et al. 2010, Jamieson et al. 2011, Utermark et al. 2012). The PIK3CB (p110beta) specific inhibitor TGX221 has been used in in vitro models of vascular injury (Jackson et al. 2005), and the TGX221 derivative KIN-193 has been shown to block AKT activity and tumor growth in mice with p110beta activation or PTEN loss (Ni et al. 2012). CAL-101 is a PIK3CD (p110delta) specific inhibitor that is being clinically investigated as a therapeutic for lymphoid malignancies (Herman et al. 2010). It is hoped that, in the future, more specific inhibitors, such as those targeting selective PI3K isoforms, will provide optimum treatment while minimizing unwanted side effects. For a recent review, please refer to Liu et al. 2009.

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