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The role of PI-3 kinase in cancer biology and approaches to the therapeutics of cancer

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Abstract
Many types of immune cellular stimulation or toxic insults activate the generalized systemic PI3K/AKT pathway and it regulates the basic cellular functions such as transcription, proliferation, growth and survival. The modified and disturbed activation of these pathway result in development of major disease such as cancer, diabetes mellitus and autoimmune disorders. Especially, PI3K/AKT mediated signal transduction molecules and effects on gene expression that contribute to tumorigenesis. Current evidence has suggested that the PI3K/AKT pathway is visible target for novel antitherapeutic drugs. Importantly, the main objectives of the signal transduction based research are to develop effective, low cost chemotherapeutic drugs that target very dangerous cancerous cells without affecting the normal cells. Small interfering RNA (siRNA) is one of the very effective therapeutic models in cancerous gene to inhibit or mimic the PI3K/AKT pathway for anticancer treatment. Many biological, active chemotherapeutic drugs have developed to inhibit the PI3K/AKT signaling pathways. This review will focus on the PI3K/AKT pathways, its alteration in cancer progression and different chemotherapeutic drugs have been used to inhibit the different types of cancer.

Keywords: PI3K/AKT, Cellular stimulation, Transcription, Proliferation, Small interfering RNA, Signal transduction, Tumorigenesis, Chemotherapeutic drugs.

Introduction

Phosphoinositide 3 kinase (PI3K) family members act as cellular sensor to relay mitogenic signals to internal cellular effectors. In this way, this signaling kinase influence several cellular activities such as proliferation, motility and survival. Genetic changes of the respective genes, through DNA amplification, somatic mutations or chromosomal rearrangements are commonly found in many human tumors and results in the uncontrolled activation of the PI3K signaling pathway. The enzymes of the PI3K family are divided into three cases based primarily on substrate specificity and sequence homology. Specifically, the class IA PI3K sub family has been the most extensively studied in the context of tumorigenesis. ClassIA PI3K is lipid kinases comprised of three p110 subunits (alpha, beta, and gamma) and are activated by growth factor receptor tyrosine kinases. The activity of the three catalytic p110 subunits is regulated through a heterodimeric interaction with a regulatory subunit of 85, 55 or 50 KDa. Following receptor tyrosine kinase activation, the p110 subunit is brought to the lipid membrane where it then proceeds to phosphorylate phosphatidylinositol 4, 5 biphosphate PIP2 to produce phosphatidylinositol 3, 4, 5 triphosphate PIP3. In turn ,PIP3 serves as a key second messenger that controls a range of cellular functions through the recruitment of AKT ,and a number of pleckstrin homology (PH) FYVE (Fab 1p,YOTB,VACLP AND EEA1)and other proteins containing lipid–binding domains, to the membrane (Cantley LC, 2002).

The PI3K-AKT signaling pathway is activated by many types of cellular stimuli or toxic insults and regulates fundamental cellular functions such as transcription, translation, proliferation, growth and survival (Datta SR *et al.,* 1999) Serine/threonine kinase AKT/PKB is a crucial kinase in this pathway (Vivanco I and Sawyers CL, 2002) as shown in Fig.1. A disturbed activation of the PI3K-AKT has been also associated with development of diseases such as cancer, diabetes mellitus and autoimmunity (Dicristofano A *et al.,* 1999). Actually, PI3K-AKT signaling is associated with both of these events, and plays a major role not only in tumor growth but also in the potential response of a tumor to cancer treatment(Testa JR and Balacosa A, 2001).Recent evidence has

suggested that the PI3K-AKT pathway is a visible target for novel anti-neoplastic drugs. The ultimate goal of signal-transduction based research is to develop chemotherapeutic drugs that target cancerous cells without affecting non cancerous form cells (McCubrey JA *et al.,* 2001)

Signaling pathways of PI3K-AKT and its functions

PI3K is responsible for the phosphorylation of 3 position of the inositol ring of PI (4, 5) P2, to generate PI (3, 45) P3, a potent second messenger required for survival signaling and insulin action (Fruman DA et *al.,* 1998.) The PI3K are heterodimers composed of a catalytic subunit (p110) and an adapter/regulatory subunit (p85) which is activated by receptors with protein tyrosine kinase activity (receptor tyrosine,RTK) and by G protein coupled receptor (GPCR) (Katso R *et al.,* 2001).The activated PI3K converts plasma membrane lipid PI (4,5) P2 to PI (3,4,5) P3 in seconds (Vanhaesebroect B and Waterfield MD,1999.).The effects of PI(3,4,5)P3 on cells are mediated through specific to at least two distinct protein–lipid binding domain namely FYVE and pleckstrin homology (PH) domains(Pawson T and ,Nash P,2000).The activated PI3K converts phosphatidylinositol (4,5) phosphate(P1(4,5)P2) into phosphatidylinositol (3,4,5)-phosphate(PI(3,4,5)P3) which results in membrane localization of phosphatidylinositol-dependent kinase-19PDK1) via its pleckstrin homology(PH) domain (Vazquez F and Sellers WR ,2000). AKT is also recruited by the lipid plasma membrane by its PH domain and phosphorylated at residues T308 AND S473 by PDK1 and unidentified kinase respectively (Wux *et al.,* 1998).AKT is the primary mediator of PIK3-initiated signaling and has a number of downstream substrates that may contribute to malignant transformation. Some of these substrates are Bad, Procaspase-9, 1-KB kinase (IKK), CREB, the fork head family of transcription factors (FKHR/AFX/FOX), glycogen synthase kinase-3(GSK-3), p21 CIP1,AND RAF18,IKK and CREB are activated by AKT phosphorylation, where as Raf ,Bad, procaspase-9,FKHR and GSK-3 are inactivated (Sakki A *et al.,*1998) as shown in Fig.2. Activity of the PIK3/AKT pathway is negatively regulated by phosphatase. Phophatase and tensin homologue deleted on chromosome 10(PTEN), which also know as mutated in multiple advanced cancer-1(MMAC-1), as well as Src homology2 (SH2) containing phosphatase 1 and 2 SHIP-1 and SHIP-2 remove phosphates from PI (3, 4, 5) P3 (Taylor V *et al.,* 2000).Mutation in these phosphatases that eliminate their activity can lead to tumor progression. Consequently, genes encoding these phosphatases are referred to as anti-oncogenes (or) tumor suppressor genes. (Muraille E *et al.,* 1999)

PI3K pathway deregulation in cancer

PI3K is tightly regulated in normal tissues but it is estimated to be constitutively active in up to 50% of human cancers. Alteration or upregulation of PI3K or Akt isoforms and inactivation/silencing of PTEN, all of these processes result in hyperactivation of the pathway (Forgacs E *et al.,* 1998). Genetic analyses have identified other PI3K pathway components and this is used by cancer cells to enhance signaling through the PI3K network. PTEN is either deleted or silenced through promoter methylation in a significant proportion of solid tumors (Goel A *et al.,* 2004).Germ line mutations in PTEN are the primary genetic event in cowden's disease, a breast, thyroid and endometrial cancer predisposition syndrome (Liauo D et al., 1997). Its generally accepted that the PI3K pathway relies on its major downstream effector kinase AKT to propagate and amplify its growth promoting signals. Constitutively active membrane localized AKT1,2 & 3 enzymes are highly tumorigenic in experimental models of cancer (Sun M *et al.,* 2001).Frequent genomic amplification of AKT have been identified in pancreatic ,breast and ovarian human tumors(Cheng JR *et al.,* 1992).While over expression of AKT3 has been detected in a subset of breast and prostate cancer (Cheng JR *et al.,* 1996).Recently Carpten *et al* identified a subset of human tumors harboring an oncogenic mutation in the pleckstrin homology domain of AKT1, which result in constitutively active membrane-localized enzyme. Collectively these results demonstrate that the key downstream effector of PI3K signaling, Akt is central to tumorigenesis (Carpten JD et al., 2007).Recent evidence suggest that tumor with activated PI3K pathway also depend on intact mTOR signaling for their tumorigenic effects (Klendel HG *et al.,* 2004).Activation of mTOR by AKT serves to integrate external growth factor and nutrient cues,resulting in enhanced protein translation, increased cell size, and suppression of autophagy (Guertin DA and Sabatine DM,2007). In addition, somatic mutations in the mTOR gene

(FRAP1) have recently been identified in human tumors (Greenman C *et al.,* 2007).

Further compelling evidence for a central role of the PI3K pathway in cancer comes from a genomic study sequencing multiple PI3K pathway members in colorectal cancer and out of the 146 tumors examined 58,or 40% contained somatic mutations in members of the PI3K pathway. Strikingly of the 58 tumors with PI3K pathway alterations only two contained mutations in more than one component of the pathway (Parsons DW *et al.,* 2005).PI3K –AKT Signaling is activated as a result of the ligand dependent activation of RTKs and/or G-protein-coupled receptors. Since cell surface receptors are commonly over-expressed or constitutively activated in a large number of lungs cancer downstream signal pathways are often activated as a result .One of the most extensively studied examples is the erbB2 tyrosine kinase receptor, which is over expressed as a result of gene amplification in breast and other cancers.(Blume-jenson and P,Hunter T, 2001). ErbB2 dimerizes with other members containing erbB2 are potent activators of multiple signaling pathways involved in cell growth, antiapoptosis and invasion (Olayioe MA *et al.,* 2000).Zhae *et al.,* have demonstrated that erbB2-erbB3 dimers strongly activate the PI3k-AKT pathway in tumor cells (Zhou BP *et al.,* 2000),because erbB3 possesses seven phosphorylatable tyrosine residues able to bind the SH2 domain of the P85 regulatory subunit of PI3K (Prigent SA and Gullick KIJ 1994).

Cell survival and proliferation

Cancer cells have devised mechanism to inhibit apoptosis and increase their chances of survival. This is particularly important in anoikis, a specialized from of programmed cell death which normal epithelial cells undergo when they are deprived of attachment to (and survival signals from) physiological substrates. Metastatic carcinoma cells are able to over-ride this restraint during dissemination. One of the consequences of PI3K or AKT activation is engagement of an anti apoptotic pathway. This involves a variety of substrates downstream of AKT that are inhibited or activated to prevent apoptosis. For example,AKT prevents release of cytochrome c from mitochondria and inactivate forehead(FKHR) transcription factors preventing their nuclear translocation and subsequent activation of downstream pro-apoptotic proteins, including Bim and FAs ligands.AKT phosphorylates and inactivates a prodeath protease, caspase 9,and the anti-apoptotic factor BAD.AKT via IKK induces nuclear translocation of the survival protein NF-KB AND MDM2 and targets the tumor suppressor gene P53 for degradation by the proteosome (Mayo LD and Donner DB 2001).Angiogenesis can be considered to have both afferent induction and efferent (response) elements The former includes the production of angiogenic cytokines by tumor and/or host cell due to oncogenic activation or hypoxia and the later the functional responses of vascular and lymphatic endothelial cells to these stimuli, which include cell proliferation, migration, invasion of the ECM and differentiation into new capillaries Interestingly, many of the signaling pathways and processes used by activated endothelial cells mimic those used by invading tumor cells ,and the PI3K pathway plays a key role in both.

In many cancer vascular endothelial growth factors(S)(VEGF) are the most powerful and selective angiogenic cytokines. VEGF transcription is induced by hypoxia-inducible factor alpha (H1F12)(Mazyre NM *et al.,* 1997).Loss of PTEN upregulates this afferent angiogenic pathway and reintroduction of PTEN in to prostate carcinoma cell lines decreased VEGF production and their angiogenic potential (Koul D *et al.,* 2002). Induction of angiogenic cytokines such VEGF and IL-8 by a variety of growth factors including PDGF,EGF,HGF and HRG is PI3K dependent (Dong G *et al.,* 2001).VEGF is an important survival factor in newly normal vasculature, and this process is mediated via PI3K/AKT and induction of bcl-2 .It has been reported that VEGF activation of PI3K is mediated via focal adhesion kinase (FAK)(Qi JH and Claesson- Welsh L 2001). And both are implicated in VEGF –mediated endothelial cell migration.PI3K is also involved in endothelial cell survival and migration mediated by angiopoietin 1(Fujikawa K *et al.,* 1999).

Recently, it has been shown that topotecan inhibits both VEGF and bFGF – induced endothelial cell migration via down regulation of PI3K/AKT pathway(Nakashio A *et al.,* 2002).In addition,a third important angiogenic mediator nitric oxide synthase (eNOs), has also been shown to be an Akt substrate (Dimmeler S *et al.,* 1999).The PI3K signal transduction is implicated in multiple key angiogenic pathways at both afferent and efferent levels, and may therefore represent an excellent pivotal point for therapeutic intervention. This has been exemplified by the finding that the mTOR inhibitor Rapamycin can reduce both (a)

induction of VEGF and b)endothelial cell proliferation and tube formation in response to this cytokines, resulting in significant inhibition of angiogenesis, tumor growth and metastasis *in vivo* (Guba M *et al.,* 2002).

Inhibition of PI3 Kinase and its effectivity in treatment of cancer

A number of naturally occurring compounds exist that inhibit PI3K, e.g. wortmannin and demethoxyvirdin originally isolated from soil bacteria and a bioflavonoid, quercetin(Woscholski R *et al.,* 1994).A chromenone analogue of quercetin, LY294002 was developed in 1994 and was found to be three times more active against PI3K(.Vlahos CJ *et al.,* 1994).Wortmannin is a fungal metabolite and a potent inhibitor of type 1 PI3K(Cross MJ *et al.,*1995).Wortmannin irreversibly inhibits PI3K by binding to the p110 catalytic subunit when tested in large panel of protein kinases, wortmannin was found to have high selectivity for inhibiting PI3K (Powis G *et al.,* 1994).Wortmannin has anti-tumor activity *in vitro*/*in vivo* with an IC50 for the inhibition of PI3K ranging from 2 to 4 nm (Davies SP *et al.,* 2000).Wortmannin was found to inhibit the phosphorylation of AKT by 50% or more relative to the vehicle control (Schultz RM *et al.,* 1995: Lemke LE *et al.,* 1999).Blocking the PI3K-AKT pathway with Wortmannin might be a valuable approach to treating cancer ,an important disadvantage of using Wortmannin is that the compound is soluble in organic solvents but not in the water, which may limit its use in clinical trials.Vatricovski *et al*., have developed a modified water soluble Wortmannin ,but its ability to inhibit PI3K activity was reduced (Ng SS *et al.,* 2000).LY294002 is also a potent inhibitor of PI3K. LY 294002 a flavonoid derivative is a competitive and reversible inhibitor of the ATP binding site of PI3K with an IC50 of 4 micromolars which is about 500 fold higher than that of wortmannin (Sanchez-Margalet V *et al.,* 1994). In pancreatic cancer cell line LY294002 treatment also caused G1 arrest which was associated with increased P27/Kip levels and decrease cyclin D and E levels, followed by inhibition of Rb protein hyperphosphorylation (Takeda A *et al.,* 2004).Semba *et al.,* reported that daily administration of LY294002 suppressed tumor growth and induced apoptosis in human colon cancer cells xenografted in SCID mice (Semba S *et al.,* 2002). Wortmannin or LY294002 alone may inhibit cell proliferation and induce apoptosis in cancer cells via inhibition of the PI3K-AKT pathway their effect may be further enhanced by radio or chemotherapy (Hul *et al.,* 2000).

AKT pathway as a target for cancer treatment

Castilo *et al.,* reported that phosphatidyl inositol ether lipid analogue (PIAS) inhibited AKT activity (IC50,<5 micro liter) by interacting with the phosphoinositide-binding site in the PH domain of akt.The PIAS down regulate the phosphorylation of many downstream targets of AKT without affecting upstream kinases,such as PI3K and PDK (Castilo SS *et al.,* 2004). Full activation of AKT requires phosphorylation on Thr 308 and ser 473. Reduction of PDK-1 levels using antisense oligonucleotides inhibits AKT activity, with a con-comitant decrease in phosphorylation of Thr308 and ser 473 on akt. inhibition of PDK-1 would also block the activity of other PDK-1 target such as the AGC kinase family and in particular P70S6K.Blockade of PDK-1 expression decreased cell cycle progression and increased apoptosis .Strangely, in the same cells, inhibition of PI3K with LY294002 induced cell cycle arrest without inducing apoptosis (Flynn P *et al.,* 2000).ILK act as a PDK-2 Phos-Phorylating AKT on Ser 473. In addition to blocking akt activation, inhibition of ILK may attenuate the effect of integrin signaling thus potentially limiting tumor invasion and metastasis. ILK inhibitors abolish phosphorylation on ser473 but not Thr308, in PTEN mutant cells. This effect decreases the growth of multiple tumor lineages both *in vitro* and *in vivo* through inhibition of proliferation migration and survival (Persad S *et al.,* 2000). PI3K-AKT pathway may also be targeted by several bioactive compounds derived from natural products that prevent cancer in different model systems, such as inositol hexa phosphate (IP6), inositol-3-carbinol (IC3), green black tea, polyphenols, triterpenoids and various dietary flavonoids compounds. The possibility that non-toxic natural compounds modulate PI3K –AKT pathway makes it an alternative target for tumor prevention as well as cancer therapy (West KA *et al.,* 2002).

Wortmannin is a fungal metabolite with a value of 5nm (Arcaro A and Wymann MP, 1993). AKT inhibitors have been recently discoverd.one is IL-6-hydroxy methyl-chiro-inositol 2-®-O-methyl-3-octadecyl-carbonate, It has been reported to inhibit selectively akt with an IC50 value of 5 micro molar, which is much less than its IC50 value of 90 micromolar for PI3K inhibition (Hu Y *et al.,* 2000).Additionally, it was recently reported that the tyrosine

phosphorylation inhibitor (tyrphostin) AG957, which is also named NSC 654705, caused dephosphorylation of AKT(Urbano A *et al.,* 2002). p70S6K is another viable target for chemotherapeutic intervention within the PI3K/AKT pathway. Rapamycin is commonly used to inhibit p70S6K activity. Its macrolide antibiotic produced by the filamentous bacterium streptomyces hygroscopicus (Dumont H *et al.,* 1996).Rapamycin is used as a powerful immunosuppressant, which has been effective in a variety of clinical settings such as organ transplantation. Rapamycin dephosphorylates p70S6K at sites different from those with activation. As a consequence, phosphorylation of the S6 ribosomal protein necessary for cell growth does not occur (Ferrari S *et al.,* 1993) Skorski *et al*., showed that expression of antisense cDNA or treatment with antisense oligonucleotides downregulated p85 gene expression and abrogated PI3K signaling (Skorski T *et al.,* 1995).Antisense oligonucleotides targeted to akt1 had several effects on a variety of cancer cell lines, including-reduced ability to grow on soft agar, induction of apoptosis and enhanced susceptibility to various chemotherapeutic agents (Liu X *et al.,* 2001). PI3K is known downstream substrate of the GTPase Ras. Disruption of Ras activity may also be effective for inhibition of the PI3K /AKT pathway. Three approaches that have been taken to inhibit Ras signaling include prevention of Ras membrane localization, antisense strategies, and ectopic expression of DN proteins.

Membrane localization of Ras has been inhibited with farenesyltransferase inhibitors (FTIs). Arglabin-DMA is a recently discovered FTI that is derived from a species of wormwood endemic to central asia (Shaikenov TE *et al.,* 2001).There are currently four FTIs undergoing clinical trials R115777, SCH66336, L-778, 123, and BMS-214662 (Johnson SR ,2001).

Antisense strategies have also been used to disrupt Ras. Expression of antisense K-Ras cDNA suppressed the malignant phenotype of large lung cancer carcinomas (Zhang Y *et al.,* 1993) and inhibited growth of H460a lung cancer cells nearly three fold (Mukhopadhyay T *et al.,* 1991).ISIS2503 is a 20-base antisense phosphorothioate oligodeoxyribonucleotide targeting H-Ras that is currently in phase2 clinical trials (Cunningham CC *et al.,* 2001).

DN proteins

DN proteins have been used to inhibit Ras signaling.DN proteins bind and inhibit function of endogenous proteins. Two DN forms of Ras have been described. The first, Ras 17N ,blocks endogenous Ras GTPase activity ,which is essential for signal transduction (Feig LA *et al.,* 1998).Ras17N has been described to inhibit akt activation elicited by the v-Crk oncogene (Akagi T *et al.,* 2002). Another DN mutant binds endogenous Ras to form inactive complexes localized to the cytoplasm. Signals from the plasma membrane are not transduced by Ras because its localization to the membrane is disrupted (Fiodalisi J *et al.,* 2002).

Inhibition of both PI3K and AKT has also been achieved with DN proteins. Expression of a P85,Δp85,decreased cell growth in Bcr-Abl-transformed cells(Sonoyama J *et al.,* 2002).Another report described use of a DN form of p110,the catalytic subunit of PI3K(Takuwa N *et al.,* 1999).Furthermore, Mabuchi *et al.* reported that ovarian cancer cells become sensitized to paclitaxel by DN Akt expression (Mabuchi S *et al.,* 2000). Lastly, PI3K signaling can be abrogated through the activity of two known phosphatase. SHIP-2 over expression has been observed to cause Akt inactivation and cell cycle arrest in glioblastoma cell (Taylor V *et al.,* 2000). Overexpression of PTEN inhibits proliferation and malignant progression of prostate cancer cells (Murillo H *et al.,* 2001).Taken together, these data indicate that phosphatase may have therapeutic promise by abrogating signaling transduced through PI3K.Strategies for inhibiting the PI3K/AKT pathway are outlined in Fig 3.

siRNA and its approaches in effective cancer therapeutics

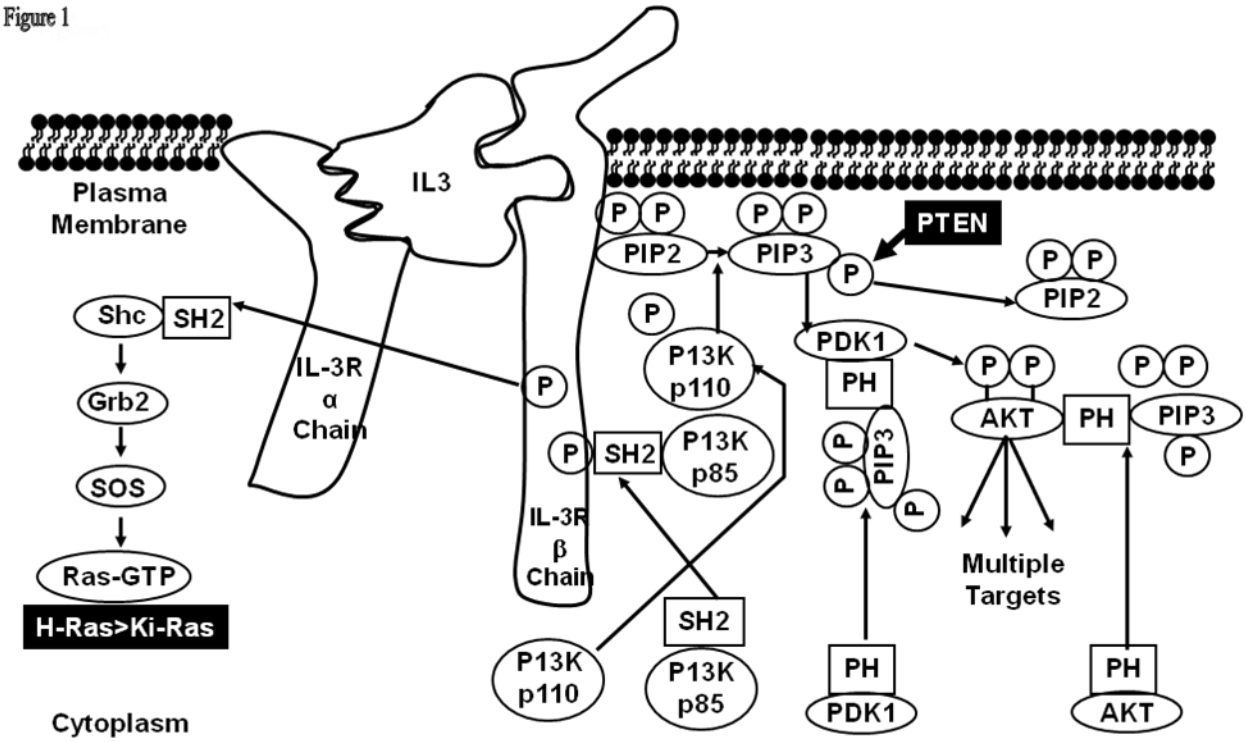
An alternative approach to therapeutic targeting of the PI3K-AKT pathway is to specifically inhibit the expression of important pathway proteins by RNA interference (RNAi). RNAi is an evolutionary conserved mechanism that is operative in insects, nematodes, plants, and mammalian cells. In this process, sequence specific post transcriptional silencing is initiated by the introduction in to cells of double stranded annealed sense and antisense RNAs that are homologues to the sequence of the silenced gene(Matzte MA and Birchler JA,2005).Small interfering RNAs (siRNAs) can be targeted to tumors and several recent studies indicate the potential for application of this technique in the therapy for various cancers (Yin JQ, *et al.,* 2003;

Tateshita F *et al.,* 2005).siRNA targeting VEGF effectively inhibits growth of malignant melanoma and squamous cell carcinoma of head and neck cancers both *in vitro* and *in vivo* (Zang X et al., 2005). Also, down regulation of antiapoptotic gene expression (eg.survivin) by *in vivo* siRNA can decrease the radio resistance of breast cancer cells (Uchida H *et al.,* 2004).RNAi has the potential to be more selective and as a result, more effective and less toxic than traditional approach. Two major obstacles must be overcome for this potential to be realized, first, drug delivery techniques must be refined to provide more specific uptake in cancer cells. Viral delivery methods are efficient but cause serious side effects (Lundstrom K *et al.,* 2003).Cationic lipid complexes are effective siRNA delivery agents. A draw back of cationic lipid reagents is that in some instance, they can be specifically toxic and induce immune response *in vivo* (Sioud M *et al.,* 2003).Secondly the ability to modify RNA oligonucleotides so that they are more stable *in vivo* will be necessary before applying this techniques for *in vivo* therapy. Secondly the ability to modify RNA oligonucleotides so that they are more stable *in vivo* will be necessary before applying this techniques for *in vivo* therapy. Proprietary chemical modifications have been developed that dramatically enhance both the stability and silencing longevity of siRNA while improving its potency and decreasing cellular toxicity (Chie Y L and Rana, 2003).

Examples of human cancers where the PI3K pathway has been shown to be abundantly upregulated

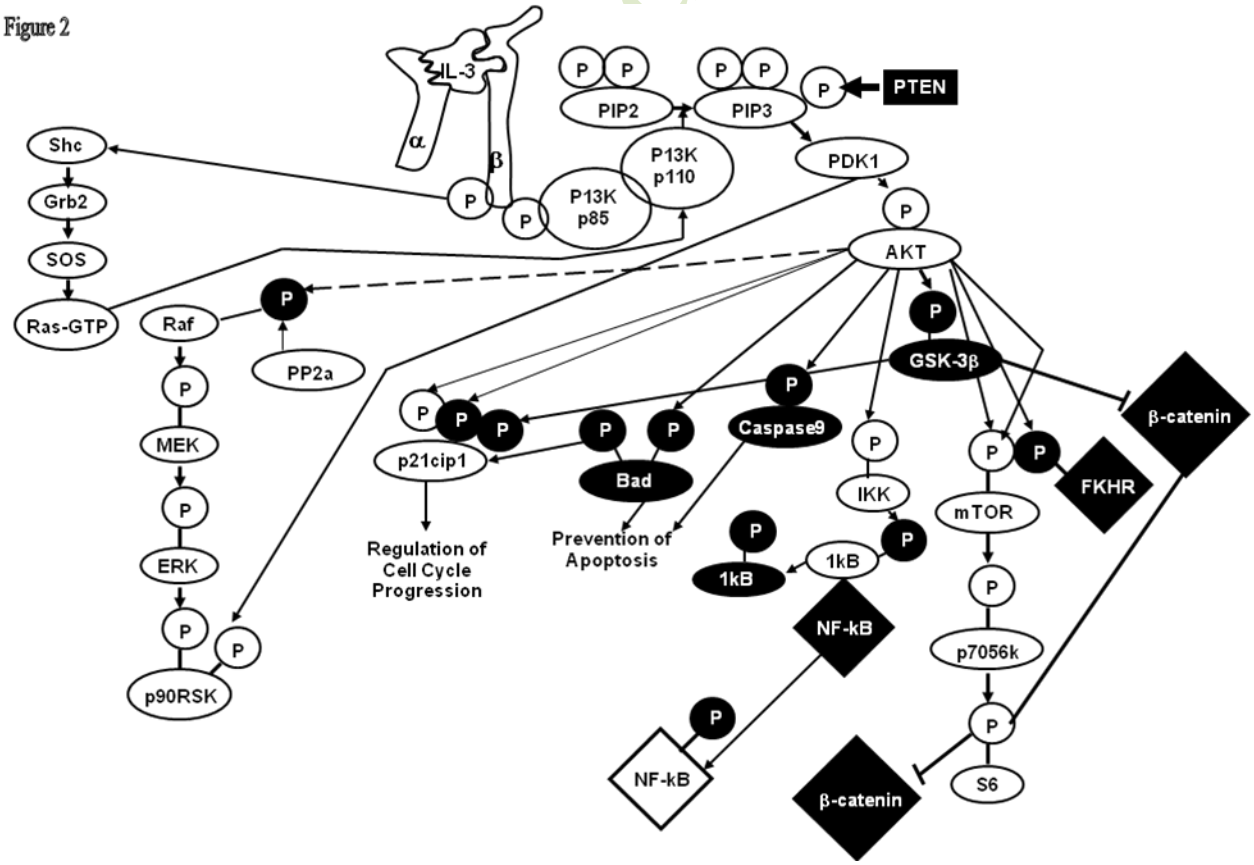
Cancer type	Alteration in PI3K pathway	Reference
Ovarian	Amplification of p110 alpha gene	Shayesteh L *et al.,*1999
	PI3K p85alpha Mutation	Philip AJ *et al.,* 2001
	Elevated AKT1 kinase activity	Sun M,Wang G *et al.,* 2001
	AKT2 amplification	Bellacosa A *et al.,* 1995
	PTEN Mutation	Ali IU *et al.,* 1999
	Loss of PTEN hetrozygosity and silencing of remaining alleles	Saito M *et al.,* 2000
	PI3K CA associated with VEGF expression,Microvessel invasion	Zhang L *et al.,* 2003
Cervical	Amplification of p110 alpha gene	Ma YY *et al.,* 2000
Colorectal	Over expression of PI3K Class 1a	Phillips WA *et al.,* 1998
	Protein PI3K P85 alpha mutation	Philip AJ *et al.,* 2001
	PTEN mutation in tumors with microsatellite Instability	Guanti G *et al.,* 2000
Breast	Elevated akt1 kinase activity	Sun M *et al.,* 2001
	AKT2 amplification	Bellacosa A *et al.,* 1995
	Loss of PTEN hetrozygosity	Garcia JM *et al.,* 1999
	AKT3 mRNA over expression and high Enzyme activity in ER negative cancer	Nakatani K *et al.,* 1999
Pancreatic	AKT2 amplification	Cheng JQ *et al.,* 1996
Glioblastoma	PTEN mutation in 70% of advanced tumors	Wang SI *et al.,* 1997
	PTEN mutation in high grab tumors	Rasheed BK *et al.,*1997
Melanoma	PTEN mutation	Celebi JT *et al.,* 2000
	PTEN silencing	Zhou XP *et al.,* 2000
Prostate	AKT1 amplification	Sun M *et al.,* 2001
	PTEN mutation	Ali IU *et al.,* 1999
	Loss of PTEN heterozygosity and silencing of remaining alleles	Whang YE *et al.,* 1998
Leukemia	PTEN activation	Marsh DJ *et al.,* 1995
Lymphoma	PTEN inactivation	Nakahara Y *et al.,* 1998
Gastric	AKT 1 amplification	Philip AJ *et al.,* 2001
	Activation of PI3K via erbB-associated with De-differentiation	Taal SP , 1987
Lung	PTEN inactivation	Forgacs E *et al.,* 1998

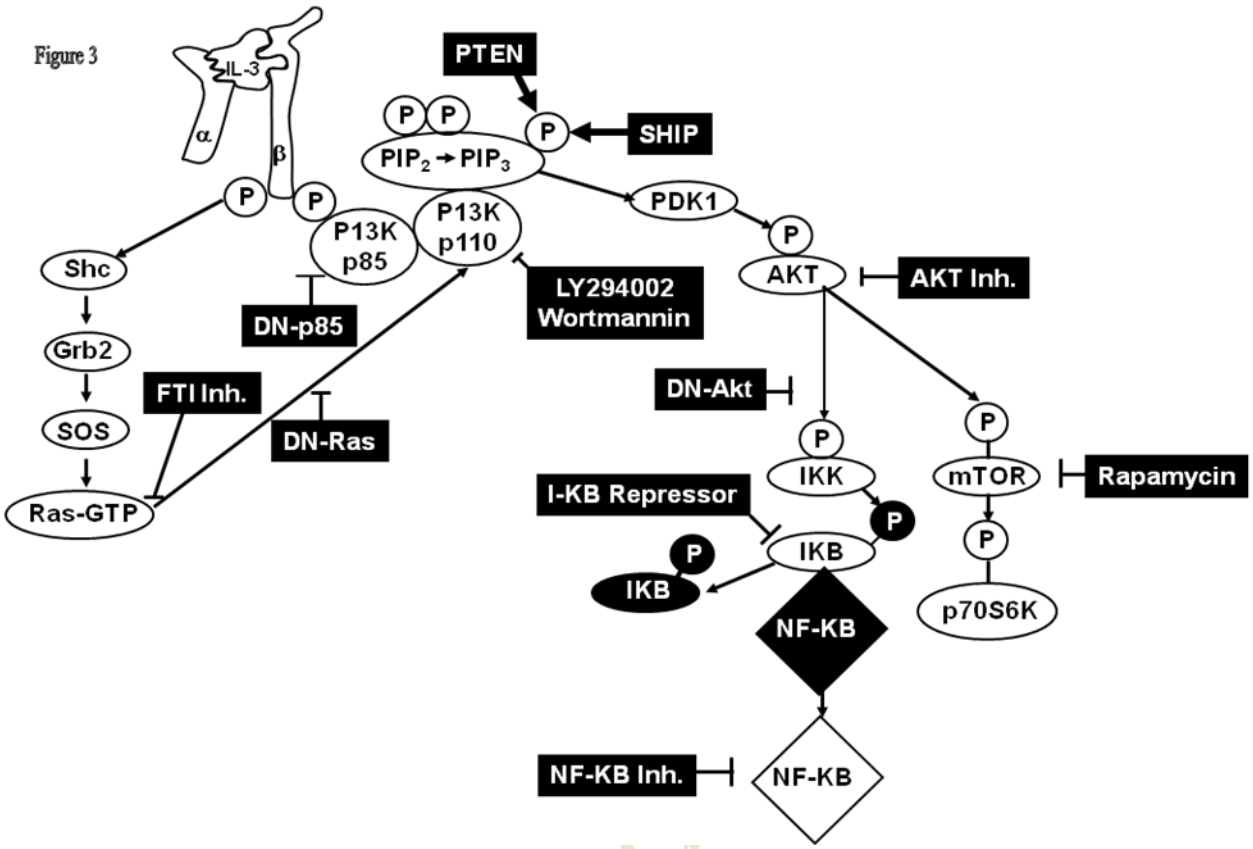
Figure 1



Inactive P13K, PDK and AKT

Figure 2





Conclusion

Many potential chemotherapeutic drugs are widely used to inhibit the altered PI3K/AKT signaling pathways. So, the levels of cancer progression were ultimately reduced. Especially PI3K/AKT mediated signal transduction molecules and effects on gene expression that contribute to tumorigenesis. Current evidence has suggested that the PI3K/AKT pathway is visible target for novel antitherapeutic drugs. Currently the small interfering RNA mediated inhibition is systematically developed because it is more selective, more effective and less toxic compared with existing methods.

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