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Molecular & Targeted therapy: THE PI3K/AKT/MTOR Pathway in cancer: New avenues for targeted therapy

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Abstract

The PI3K/AKT/mTOR signaling pathway interferes with cell proliferation, survival, metabolism, and angiogenesis. Overactivation of this signal transduction is one of the hallmarks of several human cancers, usually traceable to genetic alterations like PIK3CA mutation, PTEN loss, or AKT amplification. Inhibition of the pathway therefore opens attractive therapeutic windows currently applied or being tested in clinical trials with drugs ranging from PI3K isoform-specific inhibitors to dual PI3K/mTOR inhibitors. Drug resistance mechanisms, feedback activation of parallel pathways, and toxicity are some roadblocks limiting their long-term efficacy. However, these can increasingly be addressed by the advent of combination therapies, biomarker-based patient selection, and new drug delivery systems. This review dwells on a comprehensive assessment of the biological significance of the PI3K/AKT/mTOR pathway in cancer, therapeutics in development, mechanisms mediating resistance, and emerging concepts that may help improve and broaden the clinical interventions in target therapy for oncology.

Keywords: PI3K/AKT/mTOR pathway, cancer, targeted therapy, PI3K inhibitors, AKT inhibitors, mTOR inhibitors, resistance mechanisms, combination therapy, biomarkers.

Introduction

Basically, cancer is a disease of misregulated cellular signaling. Normally, cells depend on highly controlled signaling cascades for growth, proliferation, differentiation, and survival. In cancer, signaling pathways get altered through genetic and epigenetic changes, allowing the cells to proliferate uncontrollably, evade cell death, and become capable of metastasis. Aberrations in key signaling pathways implicated in tumorigenesis appear in the RAS/RAF/MEK/ERK pathway, JAK/STAT signaling, and PI3K/AKT/mTOR pathway. These cascades often converge or cross-talk, creating complex networks that lead to malignant transformation and tumor progression. The PI3K/AKT/mTOR pathway is one amongst those commonly dysregulated pathways across cancers.[1,2]

Traditional cancer treatments like chemotherapy and radiation therapy are non-selective and, affecting both healthy cells and cancer cells, are highly toxic. Targeted therapies, on the other hand, are aimed at targeting certain molecules or abnormalities that exist in cancer cells, thus affording more precision and better therapeutic results. Molecular targeted therapy has started a new era in oncology by allowing the creation of drugs that block important pathways or mutations critical for tumor growth. This paradigm shift has not just been about extended survival but also marked the beginnings of personalized medicine in which treatment is based upon the tumor's individual molecular profile.[3]

The PI3K/AKT/mTOR pathway controls cell metabolism, growth, proliferation, and survival. Generally altered in human cancers, and thus mentioned in the oncology studies, the aberrations of this axis are reported in breast cancers, ovarian, prostate, colorectal, and glioblastoma. Alterations or other changes that activate oncogenesis and confer therapy resistance include mutation of PIK3CA, loss of PTEN function, overexpression of AKT, or overexpression of mTOR. Because of its central role in the integration of extracellular growth signals and intracellular metabolic cues, it has been a recognized target that can be acted on for cancer therapy. It is evident about the therapeutic relevance of this pathway and the possible revolutionization that it might bring into cancer management due to the existence of specific inhibitors for this pathway and the clinical trials ongoing.[4]

The PI3K/AKT/mTOR Signaling pathway

PI3K/AKT/mTOR is a major cell signaling axis that regulates a wide range of cellular processes critical for growth, proliferation, metabolism, survival, angiogenesis, and protein synthesis. It is regulated by extracellular stimuli including growth factors, hormones, and cytokines received through upstream activators, including RTKs, GPCRs, and integrins, placing it right there as a strong nodal entity in physiological as well as pathological cell signaling. Any mishandling of this pathway is almost always documented in mundane cancer initiation and progression and incites resistance to conventional methodologies-onward toward a more aggressive tumor phenotype.[5]

Structural and functional components

PI3K: Classes and Isoforms

The phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases classified into three classes (I, II, and III) on the basis of their structural differences, substrate specificities, and mechanisms of activation. The Class I PI3Ks are mostly implicated in carcinogenesis and are subclassified into Class IA (activated by receptor tyrosine kinases) and Class IB (activated by G-protein-coupled receptors). The Class IA PI3Ks consist of a p110 catalytic subunit (with three isoforms: α, β, or δ) along with a regulatory subunit (most common is p85). The PIK3CA gene, which encodes p110α, is frequently mutated in solid tumors such as breast, endometrial, and colon cancers, thereby resulting in their constitutive activation. The p110β isoform has often been implicated in PTEN-deficient tumors, while p110δ and p110γ are being expressed at elevated levels in hematopoietic tissues and are of clinical importance in hematologic malignancies.

These enzymes phosphorylate PIP2 to form PIP3, thereby recruiting and activating downstream effectors, such as AKT.[6]

AKT: Isoforms and Substrates

Members of the AKT family are three serine-threonine kinases: AKT1, AKT2 and AKT3. They share a high degree of structural resemblance, but their tissue distribution patterns and biological function greatly differ.

- AKT1 is ubiquitously expressed and regulates cell proliferation and survival.
- AKT2 mainly regulates glucose metabolism and is mainly expressed in insulin-responsive tissues.
- AKT3 is predominantly expressed in the brain and testis and is involved in neurodevelopment.
-

Activation of AKT occurs at the plasma membrane by binding PIP3 through the PH domain of AKT. The phosphorylation of AKT by PDK1 at Thr308 and by mTORC2 at Ser473 leads to full activation. Active AKT thus phosphorylates a plethora of substrates including:

- BAD (inhibiting apoptosis)
- GSK3β (metabolism, proliferation)
- FOXO transcription factors (inhibiting pro-apoptotic gene expression)
- TSC2 (inhibiting mTORC1 activation)

Through the phosphorylation of these substrates, tumor cells come under further survival, metabolic adaptation, and cell cycle progression.[7]

mTOR: mTORC1 vs mTORC2

mTOR (mechanistic target of rapamycin) is an essential kinase that exists in two distinct complexes: mTORC1 and mTORC2, with distinctive regulatory and functional activities.

- mTORC1 contains mTOR, Raptor, mLST8, PRAS40, and DEPTOR. It shows sensitivity to rapamycin and mostly oversees protein synthesis through phosphorylation of downstream molecules including:
  - S6K1 (ribosomal protein S6 kinase)
  - 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein 1)

These substrates serve to promote processes that allow for cell growth and proliferation: ribosomal biogenesis and cap-dependent translation. mTORC1 is also implicated in the inhibition of autophagy by blocking ULK1.

- mTORC2 contains mTOR, Rictor, mLST8, SIN1, and PROTOR1/2, with acute rapamycin treatment generally not affecting it. It is required for cytoskeleton organization, metabolism, and cell survival. Of special interest is the ability of mTORC2 to phosphorylate AKT at Ser473, which is at least partially responsible for full AKT activation, also forming a positive feedback within the pathway.[8]

Downstream Effectors and Transcription Factors

The PI3K/AKT/mTOR pathway activates several downstream molecules, which in turn promote tumor formation:

- S6K1 and 4E-BP1: These increase protein synthesis to generate anabolic growth.
- FOXO family (FOXO1, FOXO3a): Transcription factors that induce apoptosis, cell cycle arrest, and oxidative stress response. Under phosphorylation by AKT, these factors are sequestered in the cytoplasm and inactivated.
- HIF-1α: Stabilized by PI3K/AKT/mTOR signaling, promotes angiogenesis and adaptation to hypoxia through upregulation of VEGF and glycolytic enzymes.
- Cyclin D1 and MYC: Upregulated downstream and allow for cell cycle progression and metabolic reprogramming.
- GSK3β: Inhibited by AKT and therefore stabilizes pro-survival proteins such as β-catenin.

Thus, these effectors divest into further avenues of tumor growth and dissemination and participate in therapy resistance, etching their

significance into the map of targeted treatment design.[9]

Activation and regulation of the PI3K/AKT/mTOR Pathway

The PI3K/Akt/mTOR pathway constitutes one of the major signaling cascades controlling fundamental cellular processes such as growth, survival, metabolism, and proliferation. Its activation is initiated by extracellular ligands, such as growth factors, insulin, and cytokines, which bind to receptors like receptor tyrosine kinases (RTKs) or G-protein-coupled receptors (GPCRs) on the cell surface. Upon ligand binding, these receptors autophosphorylate, thereby generating specific docking sites for the PI3K enzyme, which comprises a regulatory (p85) and catalytic (p110) subunit.[10]

Activated PI3K then phosphorylates lipid phosphatidylinositol-4,5-bisphosphate (PIP2) to yield phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 acts as a lipid second messenger that attracts AKT along with its upstream activator PDK1 to the plasma membrane. PDK1 subsequently phosphorylates AKT at Thr308, while mTORC2 finishes the kinase's activation through phosphorylation of Ser473.

Once fully activated, AKT phosphorylates diverse substrates that promote survival (through inhibition of pro-apoptotic factors such as BAD), cell growth (activation of mTORC1), glucose metabolism, and protein synthesis. mTORC1 also phosphorylates downstream targets, including S6 kinase and 4E-BP1, thus enhancing translation and biosynthesis.

Negative regulation of this pathway is essential for homeostasis. PTEN, the tumor suppressor, dephosphorylates PIP3 back to PIP2, counteracting PI3K and preventing AKT recruitment. Meanwhile, S6K inhibits IRS proteins in a feedback mechanism to modulate upstream signaling intensity. Several alterations (PIK3CA mutations, PTEN loss, AKT amplification) that result in constitutive activation of the pathway can often be observed in cancers, which makes it a prime target for the development of anticancer drugs.[11]

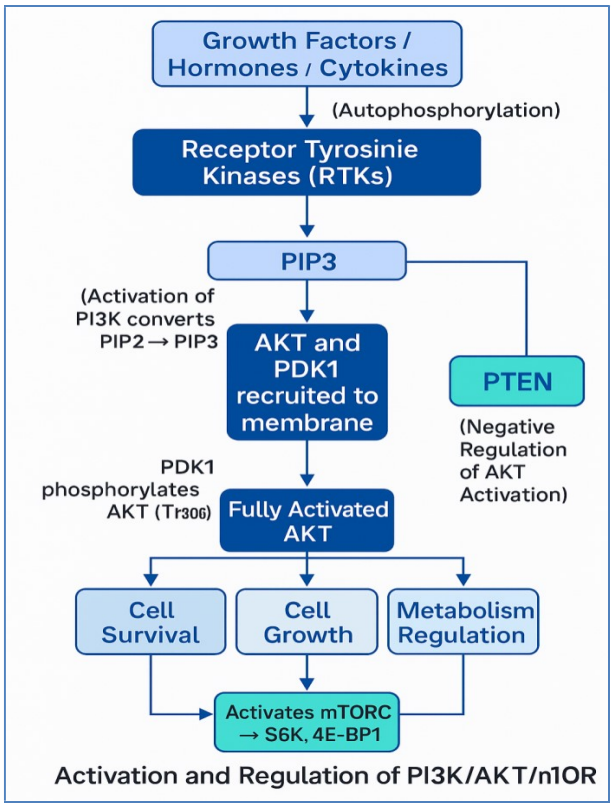

Figure 1 : Activation And Regulation Of The PI3K/AKT/mTOR Pathway

Role of the PI3K/AKT/mTOR Pathway in tumorigenesis

1. Enhanced Cell Proliferation and Growth

The PI3K/AKT/mTOR pathway represents a main driver of cell growth and proliferation, mostly via activation of mTORC1 downstream. In parallel, AKT activation phosphorylates TSC2, which normally suppresses mTORC1, thereby releasing this inhibition, and allowing mTORC1 to be activated. Activated mTORC1 enhances protein synthesis by phosphorylating S6 kinase (S6K1) and 4E-binding protein 1 (4E-BP1), resulting in increased translation of mRNA that encodes proteins involved in cell cycle progression and proliferation. Constitutive activation of this axis in cancers leads to unchecked cell division even in the absence of mitogenic stimuli, thus promoting tumorigenesis.[12].

2. Inhibition of Apoptosis and Promotion of Cell Survival

AKT acts as a mechanism against apoptosis, allowing cells harboring genetic mutations or damages to evade programmed cell death. It phosphorylates- hence, inactivates- BAD, which is pro-apoptotic in nature and belongs to the Bcl-2 family, and inhibits caspase-9, the primary executor of apoptosis. AKT inactivates FOXO transcription factors, which are involved in apoptotic gene expression like BIM and FasL. Cancer cells' survival under stress conditions such as DNA damage, hypoxia, or nutrient deprivation is ensured by this inhibition of apoptosis, accumulation of tumor cells as well as resistance to therapy.[13]

3. Angiogenesis and Vascularization

For tumor growth beyond a particular size, angiogenesis must happen. The PI3K/AKT/mTOR pathway drives this angiogenesis primarily via the upregulation of hypoxia-inducible factor-1α (HIF-1α), a transcription factor stabilized during hypoxia and further induced by mTOR signaling. HIF-1α then enhances the production of vascular endothelial growth factor (VEGF), which is essentially involved in stimulating endothelial cells for their proliferation and formation of new blood vessels. These new vessels will subsequently supply the nutrients and oxygen required by a tumor, thus supporting further tumor expansion and metastasis.[14]

4. Metabolic Reprogramming

Cancer cells have altered metabolism in order to sustain increased demands for biosynthesis and energy. These metabolic alterations, first characterized by Warburg, consist of enhanced glycolysis even in the presence of oxygen. AKT promotes this change by allowing the expression and localisation of glucose transporters (such as GLUT1) and activating glycolytic enzymes. In addition, AKT fosters lipid synthesis by activating ATP-citrate lyase (ACLY) and fatty acid synthase (FASN). Anabolic metabolism is even further activated by mTORC1, which drives nucleotide and protein synthesis while ensuring that necessary materials are provided to cancer cells for unabated growth and division.[15]

5. Cell Motility, Invasion, and Metastasis

PI3K/AKT/mTOR signaling renders cancer cells more adept at invasion and metastasis via cytoskeletal remodeling and stimulation of EMT. The phosphorylation and inhibition of GSK-3β by AKT stabilize Snail, a transcriptional repressor of E-cadherin. This repression results in less cell-cell adhesion, thereby causing motility. Matrix metalloproteinases (MMPs), which degrade extracellular matrix components and thus facilitate tissue invasion, are also activated by the pathway. AKT also induces actin cytoskeleton reorganization through Rho GTPases and other effectors, which subsequently promotes migration and colonization of cancer cells at distant sites.[16]

6. Immune Evasion and Microenvironment Modulation

Cancer progression promotes immune evading mechanisms, and the PI3K/AKT/mTOR pathway generates immune suppressive activities in the tumor microenvironment. This expression pathway induces PD-L1 expression, which binds

to PD-1 on T cells and inhibits their function, thereby allowing tumor cells to escape immune surveillance. Besides, this pathway affects the recruitment and polarization of TAMs and Tregs, which further suppress anti-tumor immune functions. On the other hand, mTOR signaling in immune cells affects their differentiation and functioning, tilting responses toward tumor tolerance and away from tumor elimination.[17]

Genetic alterations and dysregulation of the PI3K/AKT/mTOR Pathway in human cancers

PI3K/AKT/mTOR signaling pathway represent the most commonly deregulated systems in cancer biology. Alterations appear at many checkpoints of the pathway, which leads to constitutive activation. Likewise, this engenders oncogenesis, therapeutic resistance, and bad prognosis. Below is an elaborate description of the major genetic alterations leading to such dysregulation:

1. PIK3CA Mutations

The PIK3CA gene encodes for the p110α catalytic subunit of Class I PI3K. Somatic mutations in PIK3CA are common in cancers such as breast, colorectal, endometrial, and cervical cancer, the hotspots being those in exon 9 (E545K) and exon 20 (H1047R). These gain-of-function mutations activate PI3K constitutively, which in turn causes uncontrolled production of PIP3, thereby inducing AKT activation downstream and imparting growth and survival advantages to tumor cells. The presence of these mutations often presents actionability and serves as predictive biomarkers toward PI3K inhibitor treatments.[18]

2. PTEN Loss or Inactivation

PTEN (Phosphatase and Tensin Homolog) acts as a major tumor suppressor by dephosphorylating PIP3 back to PIP2, antagonizing PI3K activity. A mutation in coding sequence or deletion of PTEN, or promoter methylation so that it no longer functions, causes uncontrolled accumulation of PIP3, unchecked activation of AKT, and promote execution of downstream signaling pathways. PTEN is defective in various malignancies such as glioblastoma, prostate, breast, and endometrial cancers, aggressive behaviors being attributed to it along with poor therapeutic responses.[19]

3. AKT Amplification and Mutations

The mammalian serine/threonine kinase family AKT (AKT1, AKT2, AKT3) constitutes a direct downstream effector of PI3K. Oncogenic amplifications and mutations in these genes (e.g., AKT1 E17K) have been detected in breast, ovarian, and lung cancers. Normally, these mutations foster membrane localization and constitutive activation of AKT and thereby bypass the role of the upstream PI3K input. Hyperactivation of AKT boosts cell survival and proliferation, conditioning therapy resistance, and several inhibitors of AKT are under clinical development for reversion of such dysregulation.[20]

4. mTOR Hyperactivation

mTOR functions downstream of AKT as part of the mTORC1 and mTORC2 complexes in integrating nutrient and growth factor signals. Genetic alterations resulting in mTOR amplification, activating mutations, or dysregulation of mTOR regulators (e.g., TSC1/TSC2 loss or RHEB activation) lead to constitutive mTOR activity. This leads to constitutive protein synthesis and cell growth, favoring oncogenesis. Hyperactivation of the mTOR pathway is especially seen in cases of renal cell carcinoma, lymphomas, and tuberous sclerosis-associated tumors.[21]

5. Alterations in Upstream Receptors and Adaptor Proteins

The PI3K pathway can also be activated by mutation, amplification, or protein overexpression of receptor tyrosine kinases (RTKs) like EGFR, HER2, IGF-1R, and FGFRs, which initiate PI3K signaling. In addition, alterations in adaptor proteins such as IRS-1, GAB1, or PIK3R1 (the regulatory subunit of PI3K) can amplify signal transduction. These upstream alterations rarely stand alone and more often than not present alongside other mutations, thereby further

promoting oncogenic signaling output generated by the PI3K/AKT/mTOR axis.[22]

6. Crosstalk with Other Oncogenic Pathways

Most mutations that affect genes that are part of or interact with other pathways, such as RAS, RAF, or MAPK, act synergistically to activate the PI3K pathway. For example, KRAS mutations often co-occur with alterations in PI3K or PTEN in pancreatic and colorectal cancers, creating a more aggressive phenotype that adds to the difficulty of designing targeted therapies.[23]

Therapeutic targeting of the PI3K/AKT/mTOR Pathway

Being one of the central components of tumor growth, metabolism, survival, and therapeutic resistance, the PI3K/AKT/mTOR pathway represents an important proceeding path in precision oncology. Various classes of inhibitors are designed, operating on one or two targets and lie at different stages in clinical use and investigation.

1. PI3K Inhibitors

PI3K inhibitors block the enzymatic activity of PI3K, preventing the conversion of PIP2 to PIP3. This reduces AKT recruitment and activation, thereby halting downstream signaling that promotes growth and survival.

Types and Examples

a. Pan-PI3K Inhibitors

- **Examples:** Buparlisib (BKM120), Pictilisib
- **Activity:** Inhibit all four class I isoforms (α, β, δ, γ)
- **Clinical Trials:** Explored in solid tumors such as breast, lung, and glioblastoma.
- **Challenges:** Broad inhibition leads to off-target toxicities including psychiatric effects, hyperglycemia, and liver dysfunction. Clinical efficacy is modest due to limited tolerability.[24]

b. Isoform-Specific PI3K Inhibitors

- **Alpelisib (PIQRAY)**
  - **Target:** PI3Kα
  - **Approved Use:**HR+/HER2− advanced breast cancer with PIK3CA mutations, in combination with fulvestrant
  - **Benefits:** Improved specificity reduces toxicity; enhances endocrine therapy sensitivity.
  - **Adverse Effects:** Hyperglycemia, rash, diarrhea

- **Idelalisib**
  - **Target:** PI3Kδ
  - **Approved Use:** Chronic lymphocytic leukemia (CLL), follicular lymphoma
  - **Selectivity:** Effective in B-cell malignancies where PI3Kδ is predominant
  - **Adverse Effects:** Diarrhea, hepatotoxicity, colitis

c. Clinical Limitations

- Frequent dose-limiting toxicities
- Short-lived monotherapy effects
- Resistance via feedback reactivation or parallel signaling (MAPK)
- Need for biomarker-based selection (e.g., PIK3CA mutation testing).[25]

2. AKT Inhibitors

AKT inhibitors prevent phosphorylation and activation of AKT, blocking its interaction with substrates that control cell cycle, metabolism, and apoptosis.

Types and Examples

a. ATP-Competitive Inhibitors

- **Capivasertib (AZD5363)**
  - **Indications:** Breast cancer, prostate cancer, tumors with AKT1 mutations (e.g., E17K) or PTEN loss

- **Combination Trials:** With paclitaxel or fulvestrant
- **Efficacy:** Shown to improve PFS in PIK3CA/AKT1/PTEN-altered cancers
- **Toxicity:** Diarrhea, hyperglycemia, rash

- **Ipatasertib**
  - **Targets:** AKT1/2/3
  - **Use:** In TNBC and prostate cancer, often combined with paclitaxel or abiraterone
  - **Results:** Promising in PTEN-deficient tumors

b. Allosteric Inhibitors

- **MK-2206**
  - **Mechanism:** Binds AKT at a site distinct from the ATP-binding pocket
  - **Use:** Studied in NSCLC, breast, and ovarian cancer
  - **Limitations:** Requires combination with other therapies for efficacy

c. Challenges

- **Redundancy among AKT isoforms**
- Compensatory activation of **mTORC1 or MAPK**
- **Limited monotherapy response**, necessitating rational combinations.[26,27]

3. mTOR Inhibitors

mTOR inhibitors reduce protein synthesis, angiogenesis, and nutrient sensing by targeting the mTOR complexes.

Types and Examples

a. First-Generation Inhibitors (Rapalogs)

- **Everolimus (Afinitor)**
  - **Approved For:** Renal cell carcinoma, HR+ breast cancer, pancreatic NETs
  - **Mechanism:** Allosterically inhibits **mTORC1** via FKBP12 binding
  - **Limitations:** Incomplete inhibition of mTORC1 targets (e.g., 4E-BP1); **does not affect mTORC2**, leading to **AKT reactivation**

- **Temsirolimus**
  - **Indications:** Advanced RCC
  - **Benefits:** IV formulation with cytostatic effects

b. Second-Generation mTOR Kinase Inhibitors

- **Vistusertib, Sapanisertib (TAK-228)**
  - **Mechanism:** ATP-competitive inhibitors of **both mTORC1 and mTORC2**
  - **Benefits:** More complete pathway inhibition
  - **Clinical Trials:** Shown benefit in endometrial, breast, and lung cancers
  - **Challenges:** Systemic toxicity, such as mucositis, fatigue, metabolic issues.[28,29]

4. Dual PI3K/mTOR Inhibitors

These agents inhibit both PI3K (class I) and mTOR kinase domains simultaneously, offering comprehensive inhibition of the pathway and overcoming feedback loops.

Examples

- **Dactolisib (BEZ235)**
  - **Preclinical Data:** Potent antiproliferative activity in PIK3CA-mutant models
  - **Clinical Trials:** Early trials showed limited success due to **toxicity** (e.g., GI, liver)

- **Voxtalisib (XL765)**
  - **Use:** Glioblastoma, endometrial, breast cancers
  - **Issues:** Safety concerns and narrow therapeutic window
  -

Challenges

- Systemic toxicity due to broad target profile
- Poor therapeutic index in monotherapy
- Limited clinical success unless combined with chemotherapy or targeted agents.[30,31]

Combination therapy strategies targeting the PI3K/AKT/mTOR Pathway

Some limitations are faced by monotherapies acting along the PI3K/AKT/mTOR axis because of feedback activation, compensatory signaling, and heterogeneity of the tumor. Combination therapeutic regimens are thus being explored actively for various cancers to provide enhanced benefits in tumor suppression, increase time to resistance, and to get around the cross-pathway redundancies

1. PI3K/AKT/mTOR Inhibitors with Chemotherapy or Radiation

PI3K or mTOR inhibitors have been combined with chemotherapy or radiation to improve cancer cell response to treatment. By inhibition of survival pathways and DNA repair in tumor cells, these agents render tumor cells more susceptible to cytotoxic insult than they would ordinarily be. Everolimus, for example, can be used in combination with cisplatin or paclitaxel to good effect in breast and ovarian cancers, respectively. There may well be an amplification of adverse effects, such as cytopenia or gastrointestinal toxicity.

2. Combination with Hormonal (Endocrine) Therapy

In hormone receptor-positive tumors, such as breast and endometrial cancers, resistance to hormone therapy frequently happens upon activation of the PI3K/AKT/mTOR pathway. Disrupting this pathway by means of PI3K inhibitors (alpelisib) or mTOR inhibitors (everolimus) in concert with anti-estrogens (fulvestrant or exemestane) resensitizes the cancer cells to hormone therapy. This combination can delay progression in PIK3CA mutation-specific patients.[32]

3. Combination with Immune Checkpoint Inhibitors

The PI3K/AKT/mTOR pathway may allow immune suppression by upregulating PD-L1 and downregulating T-cell activity in tumors. Hence, by blocking PD-1/PD-L1 axes, the inhibitors of the PI3K can restore or enhance the recognition of the tumors by the immune system, thereby encouraging immune-dependent elimination of cancer. Combinational approaches with PI3K inhibitors and immune checkpoint inhibitors are currently under evaluation in TNBC and lung cancer.

4. Combination with Other Targeted Therapies

Targeting different signaling pathways sensitizes cancer cells, allowing them to circumvent drug action. For instance, the inhibition of CDK4/6 blocks growth signals while PI3K inhibitors block survival signals in breast cancer. Inhibitors of MEK are added to prevent compensation via the MAPK pathway, particularly in KRAS-mutant cancers. These combinations are being assessed in several solid tumors.[33]

5. Personalized (Biomarker-Based) Combinations

Biomarker testing via gene testing can identify those patients who benefit maximally from a combinational form of therapy. For example, for patients with PTEN loss, AKT inhibitors work better, whereas PIK3CA mutation is indicative of good response against PI3K inhibitors. Designing therapies against such markers would allow for combinations that are more effective, and less toxic, and thereby bring about the reality of precision oncology.

Challenges and resistance mechanisms

1. Intrinsic and Acquired Drug Resistance

PI3K/AKT/mTOR inhibitors often bring about therapeutic effects that are limited duration-wise, owing to intrinsic resistance or phenotypic barrier (some features of the tumor already present) or

acquired resistance, appearing during the course of the treatment. Tumor cells adopt compensatory survival pathways, such as the MAPK/ERK pathway, bypassing the silenced PI3K/AKT/mTOR axis and thus fostering cancer progression despite the initial positive response to treatment.

2. Feedback Loop Activation

Using mTORC1 inhibitors will relieve the reduction of insulin receptor substrate (IRS) proteins, thus rendering AKT capable of rebound activation via upstream receptors. This feedback reactivates the pathway that is the major target being studied, thus creating its limitations during single-agent use. Everolimus as well as temsirolimus are mTOR inhibitors.[34,35]

3. Tumor Heterogeneity

In many cases, cancers are mixtures of cell populations that are genetically heterogeneous and thus respond differently to treatment. One population of cells may be susceptible to a PI3K inhibitor, while others survive and repopulate the tumor. This intra-tumor heterogeneity is perhaps the principal cause of partial response or relapse after an initial success.

4. Toxicity and Narrow Therapeutic Window

The PI3K/AKT/mTOR pathway is involved in various physiological functions, including metabolism and immune regulation. As a result, inhibition of the pathway gives rise to side effects such as hyperglycemia, skin reactions, mucositis, diarrhea, and immunosuppression. These toxicities often prompt dose reduction or discontinuation of therapy and may compromise treatment effects.

5. Compensatory Pathway Activation

When PI3K/AKT/mTOR is blocked, other signaling pathways—such as **RAS/RAF/MEK/ERK**, **JAK/STAT**, or **Wnt/β-catenin**—can become upregulated and sustain tumor growth. This **crosstalk and redundancy** reduce the effectiveness of monotherapy, making combination therapies necessary but more complex to manage.

6. Lack of Robust Predictive Biomarkers

Although PIK3CA mutation or PTEN loss can help steer therapy, not all patients harboring these alterations seem to respond accordingly. The absence of a truly reliable biomarker that would predict which patients are going to really benefit from PI3K pathway inhibitors presents a major bottleneck in precision oncology.[36,37]

Trial Name	Intervention	Cancer Type	Key Outcomes
SOLAR-1 (NCT02437318)	Alpelisib + Fulvestrant	HR+/HER2− Breast Cancer (PIK3CA mutant)	Median PFS: 11.0 vs. 5.7 months (HR 0.65, $p<0.001$)
BOLERO-2 (NCT00863655)	Everolimus + Exemestane	HR+ Advanced Breast Cancer	Median PFS: 6.9 vs. 2.8 months (HR 0.43, $p<0.0001$)
CAPItello-291 (NCT04305496)	Capivasertib + Fulvestrant	HR+/HER2− Advanced Breast Cancer	PFS doubled in AKT1/PIK3CA/PTEN-altered tumors (HR 0.60, $p<0.001$)
FAKTION (NCT01992952)	Capivasertib + Fulvestrant	Endocrine-Resistant Breast Cancer	PFS: 10.3 vs. 4.8 months (HR 0.58, $p=0.004$)
BELLE-2 (NCT01610284)	Buparlisib + Fulvestrant	HR+/HER2− Breast Cancer	Modest PFS benefit in PIK3CA-mutant tumors, high toxicity
BEZ235 Trials (e.g., NCT01285466)	Dactolisib (dual PI3K/mTOR)	Advanced Solid Tumors	Limited clinical success due to toxicity

Future directions and novel targets

The complexity of the PI3K/AKT/mTOR signaling cascade, and its integration with various oncogenic pathways, has led to the need for much more complicated therapeutic strategies. Resistance, toxicity, and incomplete inhibition have been major manufacturing hindrances for many inhibitors that have been developed. Some emerging directions that could enhance the efficacy and specificity of targeting this pathway include:

1. Isoform-Selective and Mutation-Specific Inhibitors

Research is now headed toward future therapies where the inhibitors specifically block certain PI3K or AKT isoforms, particularly those mutated in cancer. A few such examples include PI3Kα inhibitors like alpelisib in the treatment of cancers with PIK3CA mutations or inhibitors against PI3Kβ that are being trialed in PTEN-deficient tumors, such as triple-negative breast cancer. By targeting the cancerous mutations so precisely, the drug is more able to avoid affecting normal cells, thus contributing highly to better therapeutic outcomes. It is a more mutation-specific approach with fewer side effects.

2. Dual- and Multi-Pathway Inhibition

Since more than one route can be triggered by the cancer cells, blockade of only one pathway-by the PI3K/AKT/mTOR, for example-may be insufficient. Combination strategies targeting PI3K and other pathways such as MEK, CDK4/6, or PARP could be more effective in shutting down cancer survival mechanisms. For instance, combined inhibition of PI3K and MEK is promising in KRAS-mutated cancers. These approaches seek to prevent resistance and elicit more durable responses.[38,39]

3. PROTACs (Proteolysis Targeting Chimeras)

PROTACs are a new type of drug that work by inducing the degradation of proteins rather than by inhibiting them. PROTACs against AKT or mTOR are under investigation and may provide a more complete and durable suppression of the signaling pathways. Unlike traditional inhibitors that simply block the action of the target protein, PROTACs actually eliminate the target protein from the cells, which also helps in eliminating the inactive form of the protein, thereby overcoming drug resistance.

4. Targeting Downstream Effectors and Feedback Regulators

While new therapies also try to target proteins downstream of mTOR such as S6 kinase or 4E-BP1, regulators of protein synthesis and tumor growth, downstream effectors can in fact continue activity if their upstream signal is blocked, so direct inhibition may be more efficacious. The downstream inhibitors that stop translation initiation or the regulators via the TSC1/TSC2 complex are being tested as a higher-level strategy.[40]

5. Immunomodulation via PI3K Pathway Inhibition

The PI3K/AKT/mTOR pathway stimulates tumor growth while at the same time suppressing, through a long list of molecules, immune system functioning. Inhibition of PI3Kδ and PI3Kγ helps in reprogramming the immune cells of the TME to endorse immune assault. Such drugs are presently combined with checkpoint inhibitors such as those against anti-PD-1 or anti-PD-L1 to stimulate immune responses along with their own to possibly bring better responses in certain tumors that seem to respond very little if any to immunotherapy alone.

6. AI-Guided Biomarker Discovery and Precision Oncology

Artificial intelligence and big data have been used to discover new biomarkers that predict tumor response to PI3K pathway inhibitors. By analyzing the genetic and protein expression profile of each patient, researchers attempt to associate treatment responses to the corresponding patient. This will facilitate adaptive designs for clinical trials and lead to the development of more personalized and effective treatments with fewer adverse effects.

7. Tumor Microenvironment and Metabolic Targeting

The PI3K/AKT/mTOR pathway also regulates the metabolism of tumor cells and their interaction with their microenvironment. Future therapies will inhibit metabolic enzymes involved in either glucose or lipid metabolism, or interfere with the proangiogenic signals in tumors. Such blocking strategies in concert with inhibitors of the pathway will nurture tumor cells to die and hence increase treatment response.[41,42]

Conclusion

The PI3K/AKT/mTOR pathway is a central signaling nexus involved in establishing, progressing, and resisting treatment of many cancers. It is considered an attractive molecular therapy target due to its central role in processes regulating growth, metabolism, angiogenesis, and survival. Despite several approvals by regulatory agencies, the development of inhibitors for clinical use is beset by low response rates, inherent or acquired resistance, and dose-limiting toxicities. Nonetheless, this brings hope with developments in isoform-specific inhibitors, combination therapies, along with other novel therapeutic venues such as PROTACs and immunomodulatory therapies. The future of an effective PI3K/AKT/mTOR-targeted therapy hinges on the integration of precision diagnostics, concrete biomarker-driven selection, and rational combinations. Continuous innovation in research and clinical application will advance the definition and elevation of targeted cancer treatment using the pathway.

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