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A REVIEW ON PI3K/AKT- AN SIGNALLING PATHWAY FOR THE CANCER TREATMENT

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Abstract

The PI3K/Akt pathway, which is abnormally activated in the phosphatidylinositol 3-kinase (PI3K) malignancies and essential for many cellular functions, promotes the growth and development of tumours. It may be possible to fully understand the role of this pathway by looking at its upstream and downstream nodes. The development of new cancer drugs may benefit from techniques that target the pathway's primary constituents in light of mounting evidence.

Therefore, approaches combining pathway inhibitors and additional cancer therapies may be able to address the therapeutic conundrum. In this review, we cover the functions of the PI3K/Akt pathway in different cancer phenotypes, a status report on several PI3K/Akt inhibitors, and an introduction to combination therapies that combine signalling inhibitors with traditional cancer treatments. The evidence presented here demonstrates that the most successful approach to treating cancer involves cascade inhibitors of the PI3K/Akt signalling pathway, either alone or in conjunction with other medicines.

Keywords Cancer, Immune escape, Inflammation, Metastasis, Targeted therapy, PI3K/Akt pathway

Introduction

The phosphoinositide 3-kinase (PI3K)/Akt Signaling pathway is discovered to be the main signalling pathway in various types of cancer [1]. This intercellular pathway, which regulates angiogenesis, cell motility, survival, metabolism, and growth, is also regarded as one of the most significant ones [2][3].

During times of cellular stress, the PI3K/Akt pathway is a crucial survival regulator [4]. The PI3K/Akt pathway functions in angiogenesis and the recruitment of inflammatory factors, two additional critical functions in the tumour environment. Different genetic modifications, including mutations in PIK3CA, phosphatase and tensin homolog (PTEN), Akt, TSC1, and mechanistic target of rapamycin, might cause the PI3K/Akt pathway to be abnormally active [5]. PIP3 recruits oncogenic signalling proteins, such as the serine and threonine kinase Akt, by phosphorylating phosphatidylinositol-4,5-bisphosphate (PIP2) to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3) [6].

When Akt is activated, it phosphorylates several substrates. One of Akt's most prevalent downstream effectors, mTOR, integrates a variety of proteins to advance the development of cancer. In cancer, the PI3K/Akt/mTOR pathway is frequently mutated and activated [7][8]. Since practically all human cancers, including breast cancer, colorectal cancer, and hematologic malignancies, have been identified to have dysregulated activity in the PI3K/AKT/mTOR pathway, it is important to target this pathway as a potential therapeutic avenue in the fight against cancer [9]. Inhibition of PI3K can cause both an increase in cellular mortality and a decrease in cellular growth [10].

PI3K/mTOR inhibitors, pan-PI3K inhibitors, and isoform-selective PI3K inhibitors are examples of small molecule PI3K inhibitors. Numerous preclinical and clinical studies have examined the safety and effectiveness of various therapeutic strategies, and it is becoming more and more obvious that PI3K inhibitors are successful at slowing the growth of tumours. For instance, the PI3K delta-specific inhibitor idelalisib is the first PI3Ki drug to receive FDA approval in the United States and has been successfully used to treat cancer [11]. In this review, we discuss the role and focus on the therapeutic potential of drugs targeting the PI3K signaling in tumor progression.

PI3K STRUCTURE AND FUNCTIONS

The lipid kinase family known as phosphatidyl-inositol-3-kinases (PI3Ks) is characterised by its ability to phosphorylate the 30 -OH group on the inositol ring in inositol phospholipids [12]. Class I PI3Ks are heterodimers made up of a catalytic (CAT) subunit and an adaptor/regulatory (p110) subunit (i.e., p85).

This class is further divided into subclass IA (PI3K, PI3K, and PI3K), which is triggered by receptors with protein tyrosine kinase activity, and subclass IB (PI3y), which is triggered by receptors linked to G protein [13].

Tyrosine kinases of the growth factor receptor protein are activated, which causes tyrosine residues to undergo autophosphorylation. Then, by directly binding to the phosphotyrosine consensus residues of growth factor receptors or adaptors, PI3K is recruited to the membrane through one of the two SH2 domains of the adaptor subunit. As a result, the CAT component is allosterically activated. When PI3K is activated, the second messenger phosphatidylinositol-3,4,5-triphosphate (PI3,4,5-P3) is quickly produced from the substrate phosphatidylinositol-4,4-bisphosphate (PI-4,5-P2).

Then, PI3,4,5-P3 (PKB) recruits a collection of signalling proteins with pleckstrin homology (PH) domains to the membrane, including Akt/protein kinase B and protein serine/threonine kinase-30-phosphoinositide-dependent kinase 1 (PDK1) [14,15]. A number of cellular processes necessary for cell survival and cell cycle progression are independently regulated by Akt/PKB [16].

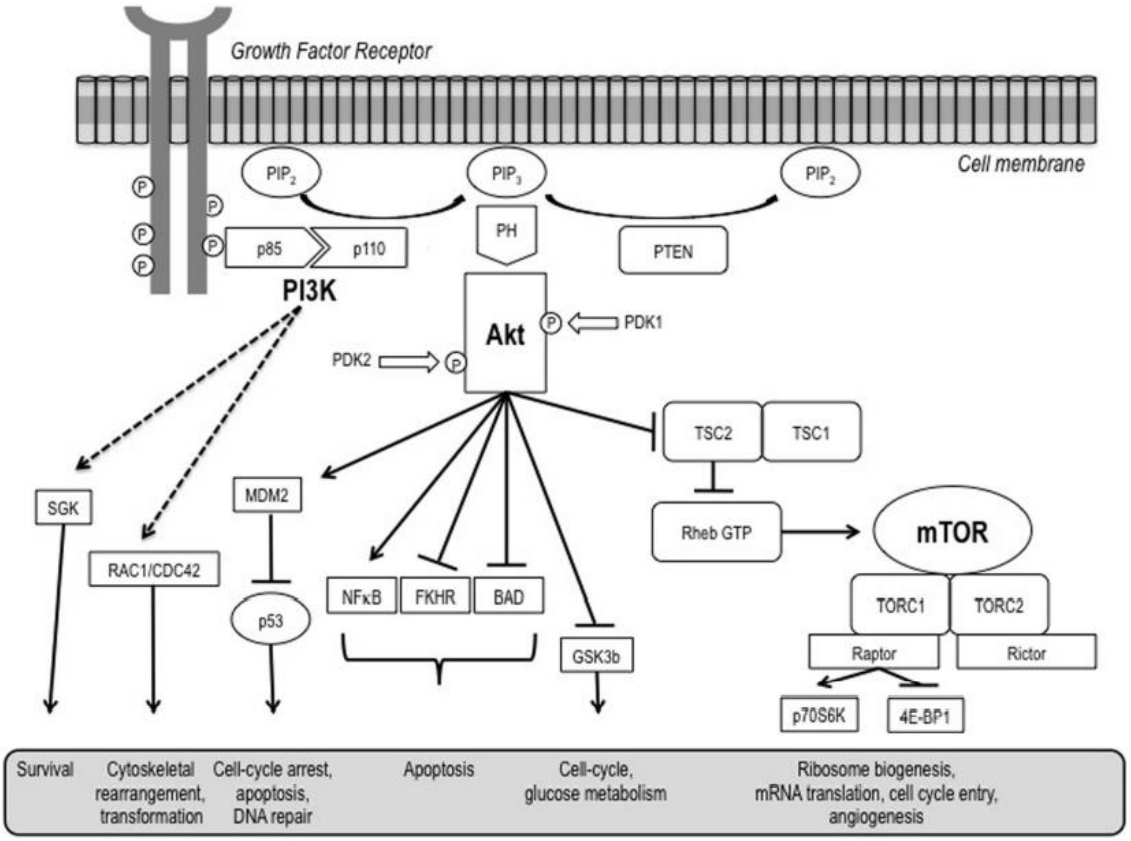

Figure 1: An illustration of the PI3K/Akt/mTOR pathway

Activation of PI3K signaling

The p110 catalytic subunit is stabilised by dimerization with the regulatory p85 subunit under basal circumstances. PI3K is often triggered under physiological settings by a number of extracellular stimuli, including growth factors, cytokines, and hormones [17].

PtdIns(3,4,5) P3 (PIP3), a second messenger that binds and attracts to the cell membrane a subset of pleckstrin-homology (PH), FYVE, Phox (PX), C1, C2, or other lipid-binding domains of downstream targets. is produced when PI3K is activated. Numerous signalling proteins, including the kinases AKT and PDK1, can bind to PI3lipid K's byproducts and localise to the cell membrane, where they can activate pathways for cell growth and cell survival [18]. By dephosphorylating PIP3 to PIP2, the phosphohatase and tensin homologue deleted on chromosome 10 (PTEN) regulates the pathway and suppresses the activation of downstream kinases [19]. Around a decade ago, ncRNAs began to be recognised as significant regulators of a variety of genes including the PI3K/AKT/mTOR pathway [20,21].

In order to influence the activities of the PI3K pathway, ncRNAs operate as both upstream mediators and downstream effectors. It is significant that ncRNAs have been shown to either directly or indirectly target various important PI3K pathway constituents, including AKT, PTEN, PI3K, and mTOR. The precise methods by which lncRNAs influence PI3K directly or indirectly have not yet been thoroughly investigated [22].

Major PI3K/AKT signalling pathway upstream activators

The PI3K/Akt signalling pathway must be activated upstream in order to function in cancer and other disorders that are connected to it. Numerous variables, including the RTK family, Toll-like receptors (TLRs), and B-cell antigen receptors, are connected to the activation of this pathway (BCRs). The PI3K/Akt signalling pathway's key upstream elements are explained below **(Figure 2)**.

RTKs

Epidermal growth factor receptors (EGFRs), vascular endothelial growth factor receptors (VEGFRs), and fibroblast growth factor receptors are the key members of the transmembrane protein family known as RTKs (FGFRs). Before being activated by ligands, RTKs are dormant in the plasma membrane [23]. By turning on RTKs, ligands like hormones, cytokines, and homologous growth factors stimulate PI3K signalling pathways [24].

EGFRs

EGFRs are 170-kDa RTKs that, upon binding to ligands and creating homodimers or heterodimers, phosphorylate tyrosine residues to activate class I PI3K and class II PI3K signal transduction [25][26]. EGFRs are a member of the RTK ErbB family, along with ErbB-3, ErbB-4, and HER2. Together with EGFR, HER2 generates HER2/EGFR heterodimers that have higher signal transduction capability than EGFR homodimers [27].

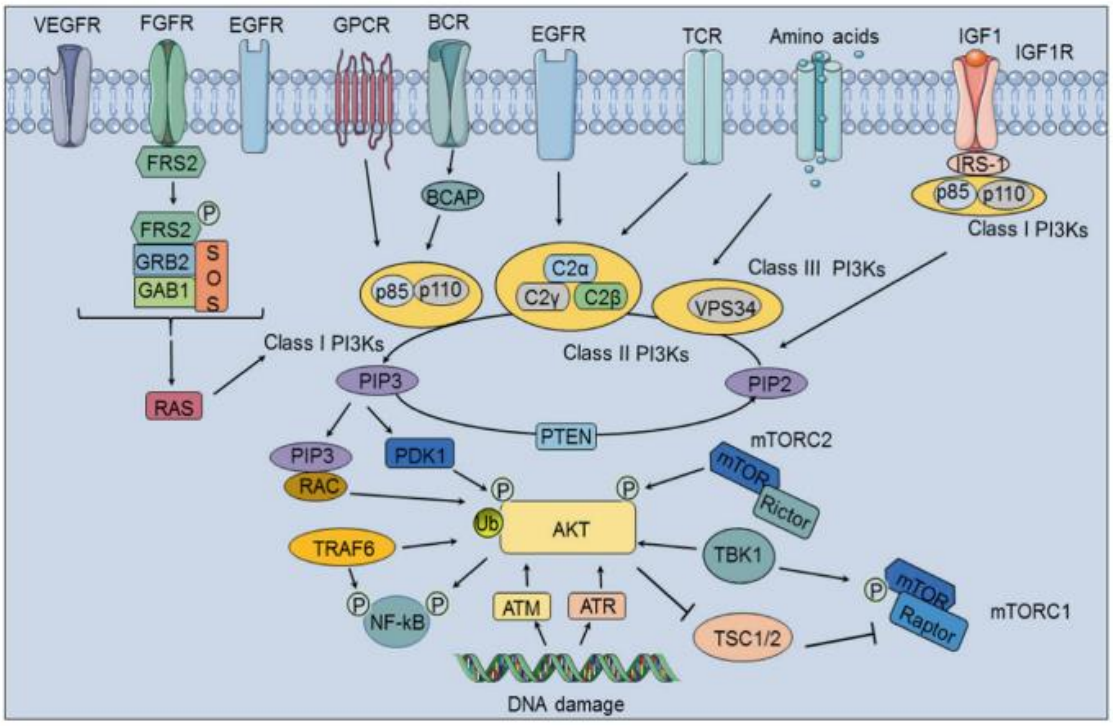

Figure 2: Akt/PI3K signalling pathway upstream activation.

VEGFRs

RTKs known as VEGFRs are divided into three primary subtypes: VEGFR-1 (Flt-1), VEGFR-2 (KDR, Flk-1) and VEGFR-3 (Flt-4). VEGFR-1 and VEGFR-2 are mostly active in endothelial cells, but VEGFR-3 is found in the lymphatic endothelium [28].

In response to VEGF binding, the VEGFR extracellular domain dimersizes, phosphorylates the intracellular tyrosine kinase domain, and activates downstream proteins. VEGFRs are therefore essential for maintaining neovascularization and encouraging cell survival and migration [29].

Furthermore, using the siRNA technique, it was demonstrated that VEGFR-1 and VEGFR-2 interact. VEGFR-1 siRNA-mediated deletion in endothelial cells decreased the activity of the VEGFR-2 promoter, indicating that VEGFR1 is crucial for triggering and regulating a variety of signalling pathways [30].

FGFRs

For cancer metastasis and angiogenesis, FGFRs are crucial [31]. The PI3K/Akt pathway is activated by high FGFR levels and is involved in the development of tumours.

Additional research demonstrated that modifications to the FGFR pathway have an impact on tumour cells and modify the tumour microenvironment [32].

Additionally, gene reprogramming might happen as a result of FGFR suppression [33].

TLRs

TLRs are expressed in immune and non-immune cells and are crucial for the development of cancer [34][35]. TLRs can recognise conserved microbial patterns in single- or double-stranded RNA and bacterial lipopolysaccharides (recognised by TLR4) (identified by TLR3) [36]. Additionally, 57 TLRs recognise and bind endogenous ligands, triggering the signalling cascade [37].

In a similar way, TLR4 activation shields cells from chemotherapy, which results in drug resistance in head and neck squamous cell cancer [38]. Renal cell carcinoma and melanoma are both susceptible to the anticancer effects of TLR3 activation, which causes cancer cells to undergo apoptosis [39].

GPCRs

GPCRs are the biggest family of cell surface proteins and are crucial for cell signalling; they are also frequently targets of the PI3K/Akt signalling pathway [40]. By interacting with numerous small G proteins that bind directly to GPCRs and take part in the control of signalling networks, GPCRs regulate downstream effector pathways and convey signals via heterotrimeric G proteins. GPCRs have the ability to recognise and react to ligands with varying chemical compositions, successfully activating PI3K/Akt signalling in various cells [41][42].

Numerous GPCR ligands, including as sphingosine 1-phosphate, activate PI3Ks, with the most common pathways being tissue-specific. GPCRs stimulate Ras, which then activates class I PI3Ks, which control cancer and many other disorders [43].

This process initiates PI3K/Akt signalling. By regulating PI3K/Akt signalling, small GTPases also assist tumour spread [44].

BCRs

B cell growth, activation, and differentiation depend heavily on the signalling pathways that BCRs trigger [45]. The PI3K/Akt pathway is one of them that is crucial. Class I PI3Ks in B cells are activated by BCRs through the B-cell receptor associated protein (BCAP), which is a crucial step in the synthesis of PIP3 and the activation of Akt [46].

Activation of the PI3K/Akt signalling pathway is significantly influenced by BCRs and cytoplasmic adapters, and Akt is not activated in the absence of BCRs in B cells [47].

BCR research has primarily addressed CLL up to this point. According to earlier research, p110 or the suppression of BTK downregulate BCR signalling, which is essential for maintaining cancer cell viability [48].

PTEN

PTEN was first discovered as a gene susceptible to alterations in a variety of sporadic tumour forms. PTEN is a tumour suppressor that is essential for maintaining normal physiological activity [49]. The preservation of chromosomal integrity and centromere stability depends on nuclear PTEN [50].

This phosphatase, which has the ability to act on both lipids and proteins, inhibits cell development and increases cellular sensitivity to apoptosis and anoikis, a kind of apoptosis exclusive to epithelial cells that is brought on by changes in integrin-extracellular matrix interactions [51].

Several advanced human malignancies typically have mutations in the phosphohatase and tensin homolog gene. Additionally, PTEN mutations in germ cell lines cause Cowden's disease, a rare genetic illness that raises the risk of several malignancies, including breast, thyroid, and endometrial cancers [52]. PTEN's primary lipid substrate is PI3,4,5-P3, and it does function as a suppressor of PI3K/Akt signalling. As a result, persistent activation of the PI3K/Akt pathway results from PTEN activity reduction [53].

Major PI3K/AKT signalling pathway Downstream activators

A serine/threonine protein kinase called Akt controls a number of cellular processes, including food metabolism, cell development, apoptosis, and survival. It plays crucial roles in signalling pathways in response to growth hormones and other external stimuli [54]. By activating its downstream effectors, Akt signalling supports tumour cell survival, proliferation, growth, and metabolism [55].

Following the PI3K/Akt signalling cascade, we now cover the main targets **(Figure 3)**.

mTOR

Although not all of them have been verified, more than 100 Akt substrates have been found [56]. The downstream consequences of Akt signalling are wide-ranging as a result of its simultaneous control of several substrates. According to reports, mTOR controls the metabolism, immunity, growth, and survival of tumours. mTOR is a protein kinase that is thought to be an atypical member of the PI3K-related kinase family. It typically forms complexes, such as mTORC1 and mTOR complex 2 (mTORC2,) which function as essential components in a variety of biological processes [57].

Normal circumstances result in basal PI3K activity. Signals are sent to PI3K after growth factor stimulation. The subsequent generation of PIP3, which binds to the PH domain of Akt, is catalysed by PI3K. A PTEN-related mTOR negative regulator places restrictions on this

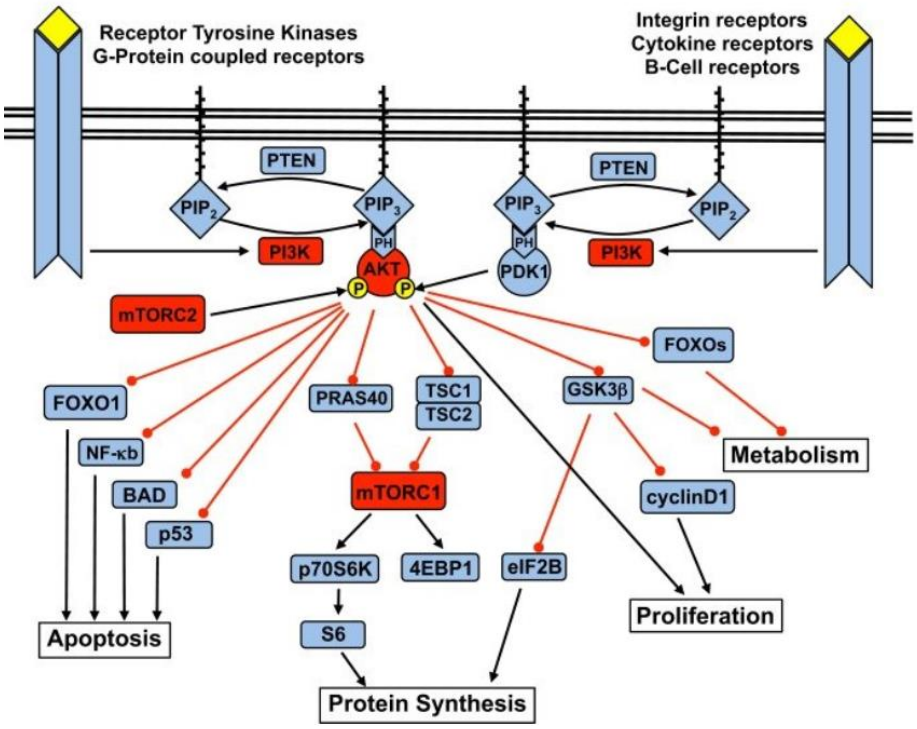

Figure 3: Akt/PI3K signalling pathway Downstream activation.

action [58]. Since Akt was demonstrated to activate mTOR through the phosphorylation of tuberous sclerosis complex 2, it is believed that Akt and mTOR interact (TSC2) [59].

The three proteins mTOR, mLST8, raptor, and PRAS40 make up the mTORC1 complex. S6 kinase 1 (S6K1) and eIF-4E-binding protein 1 (4EBP1), recognised regulators of protein synthesis, are phosphorylated by the mTORC1 protein, which in turn regulates cell growth in part [60]. Additionally, signalling from mTORC1 to HIF1 and LIPIN1 boosts lipid synthesis and glucose metabolism, respectively. mTOR, mLST8, SIN1, and rictor make up mTORC2. In order to create mTORC2, activated mTOR interacts with its protein subunits [61]. Akt is phosphorylated by mTORC2 in response to growth factor stimulation. In conclusion, mTOR inhibition has tremendous promise for clinical cancer treatment [62].

GSK3

The first Akt substrate identified was the multifunctional serine and threonine protein kinase glycogen synthase kinase 3 (GSK3) [63]. There are two different subtypes of GSK3, GSH3α and GSK3β.

These two subtypes were initially shown to be connected to the glycogen synthesis response to insulin because they share 85% sequence homology [64]. Studies have shown that certain GSK3 subtypes serve particular purposes in various tissues [65].

In several illnesses, GSK3 is thought to be expressed at the confluence of numerous metabolic pathways [66]. Cancer frequently uses the EGFR/RAS/PI3K/PTEN/Akt/GSK3/mTORC1 pathway, and GSK3 is one of its targets. GSK3 (both GSH3α and GSK3β) is inactivated and destined for proteasomal degradation after Akt-induced phosphorylation of either Ser21 (α) or Ser9 (β) in N-terminal regulatory regions in response to PI3K-mediated signalling [63][67]. An intramolecular pseudosubstrate that blocks the binding pocket and prevents the substrate from entering GSK3 is created by the Akt-mediated phosphorylation of GSK3[68].

Different biochemical procedures are impacted by GSK3 expression in cancer. GSK3 functions in tumour metabolism in addition to tumour growth by phosphorylating and inhibiting metabolic enzymes including its substrate glycogen synthase (GS) [69]. Similar to this, another study claimed that the GSK3 inhibitor IX heightens apoptosis and modifies the lipid membrane architecture [70].

FOXOs

Forkhead box Os (FOXOs) constitute of a subgroup of a forkhead box (FOX)- including transcription factor (TF) superfamily. There are four FOXO TFs that are Akt's immediate downstream targets: FOXO1, FOXO3, FOXO4, and FOXO6. In Mammals, these transcription factors regulate the expression of many target genes and is resembled on specific tissues [71].

While the expression of FOXO3 is more common in the brain, heart, kidney, and spleen, that of FOXO1 and FOXO4 is more prevalent in adipose tissue and skeletal muscle, respectively. FOXO6 on the other hand, exhibits a predominant expression in the adult brain, indicating its significant role in the neurological system [72].

The rigorous regulation of FOXOs' location in the cytoplasm and nucleus is one of their key characteristics [73].

TSC2

An evolutionarily conserved activity that stimulates PI3K and Akt in response to growth factors like IGF1 promotes cell development by activating mTORC1 through Akt, phosphorylating TSC2 (also known as tuberin), and inhibiting it [59]. Tumor suppressor genes that are mutated in tuberous sclerosis encode TSC1 and TSC2 (TSC) [74].

The TSC1 and TSC2 complex inhibits the activity of mTORC1. TSC2 converts Ras-related Rheb-GTP, a powerful mTORC1 activator, to Rheb-GDP,102 inhibiting mTORC1 through its C-terminal domain and GTPase-activating protein domain. Though this process is reversed

by the Akt-mediated phosphorylation of TSC2, which is crucial for the regulation of mTORC1 and may reduce TSC2's capacity to inhibit Rheb and mTORC1[75].

MDM2

There is a theory that higher p53 levels cause cell death while lower p53 levels are thought to stop the cell cycle [76]. Through the activation of MDM2, another tumour promoter, the inhibition of p53 may cause the activation of PI3K/Akt signalling [77].

MDM2 is an oncogene that promotes cancer, and p53 regulates its mRNA level in response to DNA damage and oxidative stress [78]. These findings, along with the discovery that MDM2 and wild-type p53 form a complex, show that MDM2 achieves its oncogenic role by interacting with wild-type p53 and inhibiting the transcription of target genes [79-81].

Conclusion:

Numerous discoveries about the PI3K/Akt signalling pathway over the past few decades have revealed its intricate networks, including its mechanism of activation, upstream and downstream targets, and types of inhibitors, which have improved our comprehension of the occurrence and progression of various types of human cancers.

The various roles that PI3K/Akt signalling plays in cells are connected to upstream factors that are triggered by downstream variables. For example, PI3K is attracted to the cell membrane by external growth factors, and the PI3K p110 subunit subsequently triggers the phosphorylation of PIP2 to PIP3, which encourages the localization of Akt to the plasma membrane. Following activation by PDK1 and mTORC2, Akt controls the expression of targets related to the phenotypic of the cell. There is a dynamic system that consists of numerous substrates, crosstalk between them, and crosstalk with other significant signalling networks. The oncogenicity of cancer is modulated significantly by this mechanism.

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