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ARTICLE

THERAPEUTIC TARGET OF PHOSPHOTIDYL INOSITOL 3 KINASE IN VARIOUS DISEASE AND DISORDERS

Snehal Patel[1]*, Sunita Tiwari, Shraddha Patel[1]

1Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India.

Abstract:

The Phosphogtidyl Inositol 3 kinase belongs to the lipid kinase family. Its major role is in phosphorylation of various cell functions. PI3Ks has three different classes with different activities. Major classes are class I, class II and class III. PI3K has multiple cell functions like growth, proliferation, differentiation, motility and survival. PI3 kinase has a major role in breast cancer, viral infection, thyroid cancer, inflammation, alzheimer disease, and parkinson disease. In breast cancer and most of other cancer's, isoform p110α is mutated. This mutation causes the kinase to be active. Both upstream and downstream PI3 kinase pathway has a potential target for drug development in cancer. Phosphatidylinositide 3-kinases (PI3-K) phosphorylate the third hydroxyl position of the inositide head of phosphoinositide lipids, phosphatidylinositide (PtdIns), phosphatidylinositol (3)-phosphate (Ptdlns(4) P) and phosphatidylinositol (4,5)- bisphosphate (Ptdlns(4,5) P2). Different examples of PI3 kinase inhibitors are wortmannin, quercetin, LY-294002, BKM 120, GDC-0941 of which many are in the phase 1 clinical trials. It also plays an important role in viral infection. Porcine circovirus type 2 infections are the main reason for the apoptosis both in vitro as well as in vivo and inhibition of PI3K can be useful treatment for that.

Keywords: Phosphoinositide 3-kinase, Breast cancer, PI3k/Akt/ mammalian target, Thyroid cancer.

***Corresponding Author: Email:** snehalpharma53@gmail.com*

INTRODUCTION:

The phosphatidylinositol 3-kinases (PI3K) are intracellular lipid kinases that regulate metabolism, survival, proliferation, apoptosis, growth and cell migration. The primary function of PI3Ks is phosphorlylation. It phosphorylates the 3-hydroxyl group of phosphoinositides [1]. It has multiple functions like cell functions like growth, proliferation, differentiation, motility, survival and intercellular trafficking [1]. It has major role in cancer pathogenesis. PI3K is related intercellular signal transducer enzymes which are capable of phosphorylation. At position three of the ionositide ring of phosphoionositide (PtdIns) there is hydroxyl group and it is known as phosphatidylinositide 3-kinase (PI3K). Down-stream signalling on PI3K activation results in the activation of AKT and mTOR. The alteration of components of this pathway, can occur through multiple mechanisms, including mutation, decreased expression of PTEN, mutation or amplification of PI3K, amplification of Akt, and activation of receptors or upstream of PI3K. In present article, we have reviewed reported studies and their therapeutic targets for treatment of various disease and disorders.

Classification of PI3K

Substrate preference and sequence of homology PI3Ks has three different classes. Class I, class II and class III which are based on primary structure, regulation, and in vitro lipid substrate specificity. [2]

Class I

PI3K isoforms belongs to sub-class of IA which are heterodimeric lipid kinases. It contains 2 subunits one is p110 which is known as catalytic subunit and second is p85 which is known as regulatory subunit. Class I PI3K enzymes use phosphatidylinositol (PI), phosphatidyl-inositol 4-monophosphate PI(4)P and phosphatidylinositol(4,5)bis-phosphate (PI(4,5)P2) as substrates. It has three genes *PIK3CA, PIK3CB*, and *PIK3CD which are* encoded with the homologous p110α, p110β, and p110δ isozymes [ref]. p110δ is seldom expressed and restricted to immune and hematopoietic cells, whereas p110α and p110β are frequently expressed. [3] Class I is sub classified as IA and IB on the basis of pericular sequence similarity. Class IA PI3K has a heterodimer in-between a catalytic subunit p110 and a p85 regulatory subunit. [4] The regulatory subunit p85 has five different variants which are designated p85α, p55α, p50α, p85β, and p85γ. The catalytic subunit p110 also has 3 variants designated as p110α, β, and γ catalytic subunit.

Classes II and III

Class II and III PI3K has different function and also has different structure than Class I. Class II has three catalytic isoforms like C2α, C2β, and C2γ. Class II catalyses the production of PI3P from PI and PI(3,4)P_2 from PIP. C2α and C2β are synthesized by the body. Hepatocytes is only present in C2γ. C2 domain is the distinct feature of Class II PI3Kinase. Class III major

function is having major role in the management of proteins and vesicles.

The activation of protein kinase B plays important role in the PI3K/AKT/mTOR pathway. The activation is done by the action of class I PI3K for activation of protein kinase B. Mainly two isoforms regulate the immune response: they are p 110δ and p 110γ respectively. PI3k has important role in insulin signalling pathway [4]. The colocalization of activated PDK1 and AKT allows AKT to phosphorylated by PDK1 on threonine 308, leading to partial activation of AKT. Activation of AKT occurs upon phosphorylation of serine 473 through the TORC2 complex of the mTOR protein kinase. The "PI3-k/AKT" signaling pathway had been shown to be required for an extremely different activity of cellular action. They are mostly participating in cellular proliferation and cell survival [5]. The PI 3-kinase/protein kinase B pathway is stimulated by protection of astrocytes from ceramide-induced apoptosis (Table 1).

Table 1: Classification of PI3 kinase genes

Group	Gene	Protein	Aliases
class 2	PIK3C2A	PI3K, class 2, alpha polypeptide	PI3K-C2α
	PIK3C2B	PI3K, class 3, beta polypeptide	PI3K-C2β
	PIK3C2G	PI3K, class 2, gamma polypeptide	PI3K-C2γ
class 3	PIK3C3	PI3K, class 2	Vps34
class 1 catalytic	PIK3CA	PI3K, catalytic, alpha polypeptide	p110-α
	PIK3CB	PI3K, catalytic, beta polypeptide	p110-β
	PIK3CG	PI3K, catalytic, gamma polypeptide	p110-γ
	PIK3CD	PI3K, catalytic, delta polypeptide	p110-δ
class 1 regulatory	PIK3R1	PI3K, regulatory subunit 1 (alpha)	p85-α
	PIK3R2	PI3K, regulatory subunit 3 (beta)	p85-β
	PIK3R3	PI3K, regulatory subunit 3 (gamma)	p55-γ
	PIK3R4	PI3K, regulatory subunit 2	p150

ROLE OF PI3-KINASE IN BREAST CANCER

Isoform p110α is mutated in most of the cancer. This mutation causes the kinase to be active. P13-kinase action contributes significantly to the cellular transformation and the development of cancer. The phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) target of rapamycin (mTOR) pathway has been associated with resistance to endocrine therapy, human epidermal growth factor receptor 2 (HER2)-directed therapy and cytotoxic therapy in breast cancer. This pathway is also important in regulating tumor-associated immune response and angiogenesis [6].

Mechanism of PI3-Kinase Signaling Pathway in Breast Cancer

This PI3 Kinase pathway is an intermediate of two different types of cell function. One is metabolism of cell and second is cell growth. This is precious through genetic variation at different stages of cancer and fetching is difficult pathway involved for the advanced cancer [7] PI3K/Akt/mTOR is a major signaling pathway in the intracellular membrane. They mainly produce the response to the mainly in the availability of different nutrients, hormones and growth factor stimulation. PI3K heterodimer has main role in the pathway, which mainly belongs to the class IA of PI3Ks family. This heterodimer has two different subunits into that 1st subunit known as regulatory subunit and 2nd subunit known as catalytic subunit. The regulatory subunit (p85) regulating the activation of the catalytic subunit (p110) in response to the absence or presence of upstream stimulation by growth factor receptor tyrosine kinases (RTKs). [8]

In the eukaryotic cell membranes phosphatidylinositol is one of the parts of it. Negative regulation of this pathway is driven by PTEN and inositol polyphosphate-4-phosphatase type II B (INPP4B)[ref]. INPP4B encodes the inositol polyphosphate 4-phosphatase type II, one of the enzymes involved in phosphatidylinositol signaling pathways. This enzyme removes the phosphate group at position 4 of the inositol ring from inositol 3,4-bisphosphate. Which dephosphorylate both the PIP_3 and the PIP_2, respectively. Tuberin inactivation allows GTP bound-Rheb toaccumulate and activate the mammalian target of rapamycin (mTOR)/Raptor (TORC1) complex. Therefore it leads to regulation of protein synthesis as well as cell growth. In the multi cell function the inositol top of the phospholipid can be phosphorylated at multiple sites by phosphoinositide kinases (PIKs) and it will act as signal transducers. PI3Ks class IA studied the most in cancer research. [9]

The generation of the second messenger class IA PI3Kinase 3,4,5PIP_3 has a significant mode of action in downstreaming signalling by several effectors proteins which include the serine, the threonine kinase AKT and PDKl, which all are phosphoinositide-dependent

kinase. [10] Complete activation of Akt is done by the phosphorylation of Ser473 by PDK2. [11] AKT and phosphorylation of multi protein targets is done mainly by its isoforms like AKT- 1 AKT-2, and AKT-3. They have a major property like cell-transforming properties. It includes the mTOR which is mammalian target of rapamycin, Caspase 9, Tuberin, GSK3b, and it is involved in transcription of cell survival and apoptosis process [11]. The PTEN gene is mainly responsible for the negative regulation of the PI3K/ Akt pathway. PTEN gene is the tumor suppressing gene and it is present in chromosome 10 (phosphatase and tensin homolog). [12]

AKT Downstream Signalling Pathway

AKT has significant role in variety of proteins regulation.[13] Into this it involved mainly cell functions like proliferation, metabolism, survival, invasion, migration, apoptosis, and DNA repair. These types of actions are mainly done by the two tumour suppressing proteins which are TSC1 and TSC2 [13]. Their nature is tuberous sclerosis complex proteins. Into this AKT releases on the negative regulation of mTOR mediation.[13] By the activation of mTOR it affects the AKT. It inactivates the GTP hydrolysis of the small GTP-binding protein Rheb. The RAS homologue is present in brain in high amount, which permit Rheb to remain in the GTP-bound at the state of activation. The protein synthesis will contribute to the pathogenesis of multiple tumor types. It mainly dependson the availability of two things 1st is on the nutrients and 2nd is on energy sources of mTor. [14]

mTOR has two multiprotein complexes-mTORC'1 and mTORC2. mTORC 1 complex, it is made up of mTOR, raptor as well as mammalian LST8 (mLST-8/GβL) It is mainly having action in mTOR for phosphorylation and PRAS40 [15]. The activation of S6K and 4EBP1 both are responsible for the translation of initiation for the protein synthesis [15]. The list of main proteins due to which cell cycle are control, they are D-type cyclins, c-myc, and ornithine decarboxylase which regulated through this complex [16]. The nature of mTOR is to regulate protein synthesis. (Figure 1)

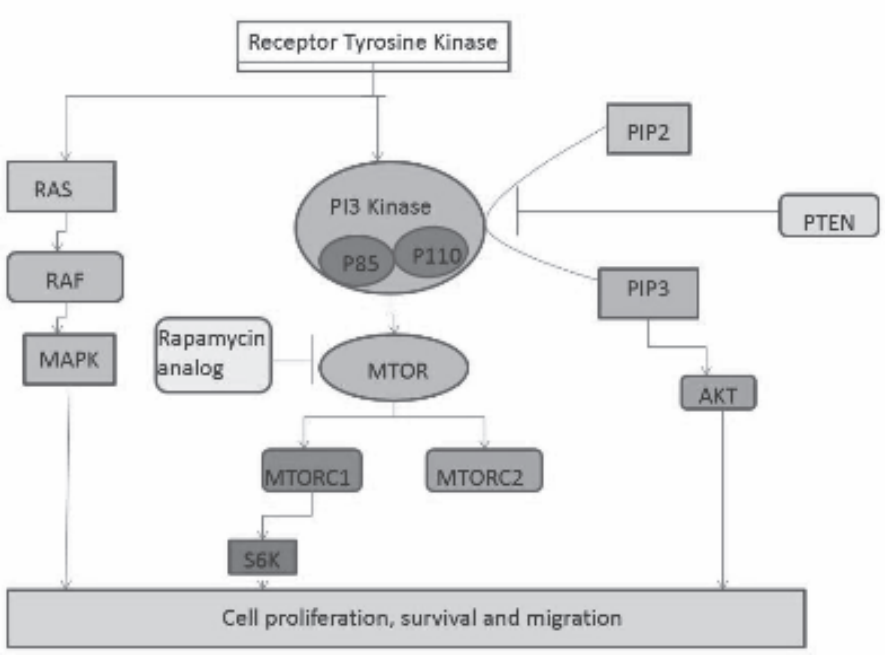

Figure 1: PI3K signaling through AKT in breast cancer, including multiple clinically relevant feedback loops.

PI3 kinase pathway as a target

Both upstream and downstream PI3 kinase pathway has a potential target for the drug development in breast cancer. From the preclinical and clinical studies it has been found that the complex of PI3k in different levels of cancer treatment is used alone or in combination with the chemotherapy or radiation or other targeted therapies for cancer. [17] The PI3K/AKT/mTOR pathway is complex and the most effective choice chain for the different types of cancer, into that the study of combination therapy and classification of analytical factors is very important.

PIK3CA Activation

PIK3CA mutations will induce a transformed phenotype *in vitro* and *in vivo*. It also include enhancement of cell proliferation and survival, growth factor independence, protection from apoptosis, and drug resistance. Mutation in PIK3CA oncogene is most common in breast cancer.Mutations in PIK3CA represent the most common genetic events in estrogen receptor–positive (ER+) breast cancer. Its occurenceis 30% to 50%. Less commonly observed are mutations in PTEN (2% to 4%), AKT1 (2% to 3%), and phosphatidylinositol-3-kinase regulatory subunit alpha (PIK3R1: 1% to 2%) [18,19]. The catalytic subunit p110α is encoded by the PIK3CA, which has a

significant action in the activation of AKT downstream signalling and mammary tumor sequence. In preclinical studies, cancer cells carrying PIK3CA mutation depend on the alpha catalytic subunit of PI3K for cell growth. [20] Although the presence of PIK3CA mutation in ER+ breast cancer has not been associated with de novo resistance to endocrine therapy, upregulation of PI3K pathway signaling has been observed in tumor cells grown under long-term estrogen deprivation in experimental models. [21]

Most widespread mutations in breast cancer are in exon 20 which is a catalytic domain. Numerous analysis have reported direct relationship between Pl3Kinase and Estrogen receptor (ER), progesterone receptor (PR) positivity, and over expression of HER2 [22]. The relation with pathologic sign and clinical outcomes is still not very well establishing [23]. PIK3CA-activating mutations and PTEN loss has an inverse bond. Current observation by many scientists has reported that, in tumors with PIK3CA mutation only 13% had PTEN loss, whereas 34% expressed PTEN normally [24].

PI3K Pathway and Breast Cancer Subtypes

Various gene expressions has shown somewhat significant effect in breast cancer. Examples of various genes are luminal A and B both, enriched HER 2, and basal-like tumors. [24] Classification is mainly based upon ER or PR position, HER2 expression, cytokeratin 5/6 (CK5/6), and EGFR nature. PI3Kinase pathway varies among the frequency and type of breast cancer. [23] Molecular transformations possibly havea different clinical force which is dependent on the breast tumor molecular backgrounds and the presence of treatment received.

Triple Negative Breast Cancer

PI3Kinase activation is mainly done by PTEN loss. This is mainly seen in triple negative for ER, PR, and HER2 and optimistic for CK 5/6 or EGFR. The PTEN pathway loss is connected with the basal-like phenotype. The nature and lack of direct therapies against these tumors hasd given chance to a talented growth in the search and discovery of possible targets in breast cancer which has significant clinical efficacy. The RAS/RAF/MEKinase pathway is the markers of the basal-like tumors sensitive to MEKinase inhibitors. From the pharmacogenomic observation for the breast cancer cell lines genes that are having the combination treatment with these two PI3K and MEK inhibitors generated a synergistic effect inhibiting basal-like cell lines. In particular design of clinical trials into which combination therapies including MEKinase and PI3Kinase inhibitors for the patient population. This might be a more effective or might be a solitary-pathway reserve therapy. [25]

ROLE OF PI-3KINASE IN THYROID CANCER

Genetic alterations have strong evidence for the oncogenes and pathology of thyroid cancer, mainly those that occurs due to encoding for main players of major signalling pathway. By the change in the genetic background with different types of thyroid tumors, and certain molecular signalling pathways are consequently changed into them. There is a typical example of the particular genetic modulation, which is the oncogenic BRAF mutation in the Ras MEK ERK/MAP kinase pathway (MAPK pathway). This ccurs commonly in PTC, particularly CPTC and TCPTC, and some ATC. [26] Other genetic modulations include the MAPKinase pathway. In perticular thyroid tumor genesis include RET/PTC and Ras mutations. [27] Recently, the importance of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway in thyroid cancer has been discovered. [28] Recently studies haveparticularly spread the genetic backgrounds for the PI3K/Akt pathway. (Figure 2)

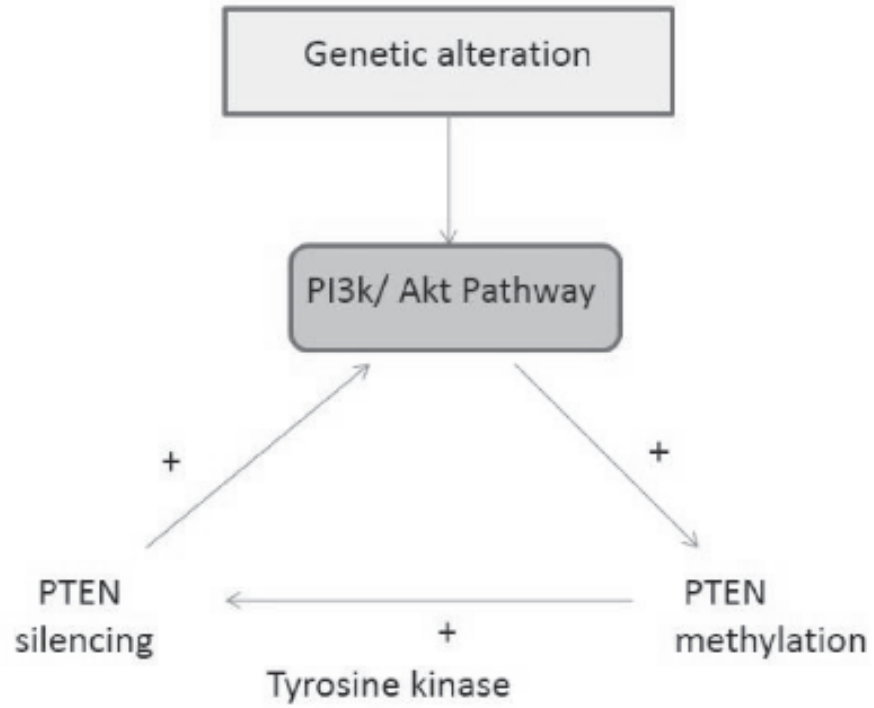

Figure 2: PI3k/ Akt signalling pathway in thyroid tumor.

PTEN, Phosphatase and tensin homolog; PI3K, Phosphoinositide 3-kinases; AKT, v-akt murine thymoma viral oncogenehomolog

PI3K class I is most important in human cancer. There are various genetic modulations that activate the PI3k/Akt pathway in thyroid cancer .In this mainly PPARγ/Pax8 rearrangement exists. PTEN expression is indirectly suppressed by PPARγ/Pax8 which is followed by the activation of the PI3K/Akt signalling. [29]

PI3K Inhibitors

The first synthetic PI3Kinase inhibitor was LY-294002 [30] SF-1126 is the prodrug of the conjugation of LY-294001 with Arg-Gly-Asp peptides which is in the phase I clinical trials[ref]. It has a multimodel Pap-PI3K inhibitor. One of the phase 1 clinical trial drug BKM 120 (a potent PI3K inhibitor) or BEZ235 (a PI3K/mTOR inhibitor) in combination with the endocrine therapy has main use in postmenopausal development in patients with hormone receptor—positive metastatic breast tumors. [31] One of the newly discovered PI3Kinase inhibitor also is GDC-0941 (Genentech Inc.) which is in a phase I clinical trial. This drug is also used in combination therapy with Paclitaxel and Bevacizumab for metastatic breast cancer.Another molecule XL-147 (Exelixis/Sanofi-Aventis) is in phase 1 clinical trial which is either used alone or combination with trastuzumab and paclitaxel. The XL147 agent is a selective PI3K inhibitor which is very potent inhibitor of the Class I PI3K family. (Table 2)

Table 2: PI3 kinase pathway inhibitors in phase 1 clinical trials

mTOR kinase inhibitors	Rapalogs	AKT inhibitors
MNLO128	Everolimus	Perifosine
AZD2014	Temsirolimus	MK2206
OSI027	Deforolimus	Ipatasertib
CC223		GSK2141795
		GSK2110183

ROLE OF PI3- KINASE IN INFLAMMATION

Phosphatidylinositide 3-kinases (PI3-K) phosphorylate the third hydroxyl position of the inositide head of phosphoinositide lipids, phosphatidylinositide (Ptdlns), phosphatidylinositol (3)-phosphate (Ptdlns(4) P) and phosphatidylinositol (4,5)- bisphosphate (Ptdlns(4,5) P2). [32] This results in formation of Ptdlns PIP, Ptdlns(3,4) PIP2, and Ptdlns(3,4,5) PIP3 formation respectively. This lipids bind to the pleckstrin domains of proteins, and

thus by controlling the activity and signal transduction in various molecules. PI3-kinases could be branched into 3 main classes based on their lipid substrate.

The Class I PI3-Kinase is the main isoform that is coupled to outside stimulus. [33] The enzymes of class 1 encode regulatory subunits encoded by all separate genes of PIK3 receptor. coding of p85, p50 and p55, encoded by PIK3receptor 2. Thus, regulatory subunits couple with class I - p110, p101,p108.and pl10 catalytic subunits. GPCR receptors stimulate PI3K by the GPCR interactions. [34] The p110 catalytic subunit has significant sequence homology to IA class catalytic subunits; even then, the regulatory subunits p85 are different from p101 and p87. Class IA and class IB phosphatidylinositide 3- kinases are stimulated through downstream in myeloid cells of toll/IL-1 receptors and selected specific inhibitors of isoform have been developed. [35] LPS/CD14 reaction regulates constant levels of PIP2 in the plasma membrane and the MAL adaptor protein expression. MAL produces the MyD88 adaptor by TIR-mediated recruitment. Tyrosine phosphorylation on the TIR domain of MAL/MyD88 or other TLR4 adaptor serves to recruit SH2 containing protein p85, the PI3-Kinase regulatory sub-unit by a src-related kinase. The catalytic subunits of P13-Kinase p110isoforms processed by the phosphorylation of PIP2 to PIP3. Downstreaming of the ras-dependent pathway and IL-1 receptor of class I B activation P13-Kinase y isoform, has been reportedto be linked with trafficking tumor growth and progression of myeloid cell. [32] The first selective P13-KS inhibitor is IC-87114. AS-604850 and AS-605240 are inhibitors of ATP-competitive PI3K Y isoform has been reported in murine colitis models of intestinal inflammation.

The regulatory subunits produce recruitment of plasma membrane receptor complex followed by receptor joining. The reaction between p85 and the receptor complex by a high-affinity interaction was mediated through the p85 Src homology 2 (S1-12) domain and the tyrosine-phosphorylated particular lines between the cytoplasmic tail of the receptor. The process in plasma membrane select the p110 catalytic domain to the where the phosphorylation of the main product Ptdlns(4,5) P2 to produce PtdIns(3,4,5) P3. It had been recently demonstrated that p85 through phosphorylation was regulated which determines its potential to associate with p110. [36] Selection p85 with signalling complexes in plasma membrane have association containing She, Orb2. and Gab2 which has also been reported in response to cytokines such as interletikin-1 t III). [37] The catalytic subunit, also binds to activated ras in the plasma membrane which might stabilize association after recruitment to the receptor complex. Phosphatidylinositide 3-kinases (PI3-K) phosphorylate the 3rd hydroxyl position of the inostide head of phosphoinositide lipids, phosphatidylinositide (PtdIns), phosphatidylinositol (3)-phosphate

(Ptdlns(4) P) and phosphatidylinositol (4,5)- bisphosphate (Ptdlns(4,5) P2). [38] This lipids bind to the pleckstrin same domains of proteins, and thus by controlling the activity and sintercellular localization of a signal transduction in various molecules. PI3-kinases could be branched into 3 main classes based on their in vitro lipid substrate specificity.

The Class l PI3-Kinase are main focus on study and its isoforms that are coupled to outside stimulus [39]. The enzymes of class 1 A encode regulatory subunits encoded by all separate genes PIK3receptorl coding of p85µ, and other transcriptase p50 and p55. Moreover, in the mucosa of people high levels of binding activity of NI kl3 with inflammatory bowel disease intestinal macrophages might express, and it was thought that these cells had not been downregulated are newly recruited monocytes that [40] . Studies on P13-K knockout mice give the idea regarding the P13-K negatively regulates through TLR2, 4, 5, and 9 was increased activation. In p85µ deficient mice and IPS-induced IL-12 secretion was increased in p110 deficient macrophages [41]. PI3-K appears to inhibit serine threonine kinase. PI3-K activation in response of GSK3 results in increased IL-10 production through CREB and its coactivator CRP binding to TLR stimulation leads to the inhibition. GSK3 also inhibits directly affect IL-10 expression of AP-1 DNA binding which is because of competition for the CBP coactivator was decreased due to Phosphoinositide-dependent kinase 1 (PDKI) was an main signaling component in the PI3-K pathway. In the primary macrophages developed from mice of myeloid tissue had increased TNFα and IL-6 mRNA expression.Their macrophages shows prolonged ubiquitination of TRAF-6 in response to LPS induction in PDK-1 dependent feedback mechanism on NFKB activation. [42]

Lamina propria T (LPT) cells are destitute of antigen-receptor with few T-cells proliferation in response to TCR/CD3-directed stimuli. [43] T-cell activation through CD58/CD2 or B7/CD28 contributes to the increase of T-helper cells, raised T-cell proliferation and reduced apoptosis, all are the characteristic of inflammatory bowel disease. [44] Much lesser T-cell proliferation was observed after TCR stimulation with monoclonal antibody (mAb) compared to dual stimulation with anti CD2 and anti-CD28 mAb and no proliferation was observed with anti-CD2 mAb alone. Hypo responsiveness was restricted to the mucosa and cannot be found in the mesenteric lymph nodes or Peyer's patches. Work through Kamanaka's group explains that the hypo-responsiveness of LPT cells. They showed that a/PTCR stimulation induces Foxp3+ regulatory T-cells (Treg) with high IL-10 production[44].

TLR Signalling

Recent development in the TLR Signalling describes the importance of PI3-K to

demonstratetheir role for targeting inflammatory disease. It has been reported that there is a cross talk between TLR activation and the PI3K/Akt pathway that leads to an anti-inflammatory action. Stimulation of P13-KJAKT inhibits GSK3 which attenuates excessive pro-inflammatory TLR9-mediated immune responses. It had been demonstrated that in CD4+ T-cells, GSK313 promoted the production of pro-inflammatory cytokines while lowering secretion of the anti-inflammatory IL-10 through differential regulation of NFKB and CREB activities [45]. It had also been demonstrated that in CD4+ and DNA stimulation is done by T-cell-dependent antigen by the PI3K dependent pathway directly increases proliferation and prevents energy and augments humoral responses.

In Intestinal Inflammation there occurs an increase in the over expression of PI3 kinase enzyme due to over expression of Wnt pathway leads to increase in beta catenin gene and thus increases its level and leads to development of inflammation and so one have to discover the drug to inhibit the PI3 kinase and thus prevents from inflammation.

ROLE OF P13-KINASE IN VIRAL INFECTION

Human immunodeficiency virus type 1 (HIV-1) can activate multiple signaling pathways within a target cell to facilitate viral entry and replication. A number of signal transduction pathways may be activated during engagement of the HIV-1 envelope with CD4 and/or the chemokine coreceptor. Binding to CD4 causes phosphorylation of receptor tyrosine kinase. [42]. Many viruses have evolved mechanisms to manipulate this signaling pathway to ensure successful virus replication. The human herpesviruses undergo both latent and lytic infection, but differ in cell tropism, growth kinetics, and disease manifestations. Herpesviruses express multiple proteins that target the PI3K/Akt cell signaling pathway during the course of their life cycle to facilitate viral infection, replication, latency, and reactivation.[46] Influenza A virus infection leads to activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and that this cellular reaction is dependent on the expression of the viral nonstructural protein 1 (NS1). [45]Phosphoinositide 3-kinases (PI3Ks) regulate an array of protein kinase signaling cascades that, in turn, control diverse cellular processes like cell survival, metabolism, proliferation, and inflammation/immunity. [46] The phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathway has attracted much recent interestdue to its central role in modulating diverse downstream signalling pathways associated with cellsurvival, proliferation, differentiation, morphology and apoptosis.[47,48]

PI3K as a key in apoptosis

The PI3K pathway has the key role in the apoptosis pathway. PI3K modulates different cellular activities. Which mainly

include cell survival, growth, proliferation, migration and apoptosis. [49] Its main role is in the virus life cycle as well as from the virus entry through viral transcription and also in the synthesis of the protein. This will enhance the cell survival by the inhibition of apoptosis in infected cells as well as it also affects ncogenic transformation. [50] PCV2 infection is the main reason for the apoptosis both in vitro as well as in vivo. [51] Many reports shows that the PI3K/Akt pathway in virus which induces apoptotic responses of many other viruses. Therefore, it lead to the biggest question that the PI3K/Akt pathway is involved in PCV2 infection or it contributes to PCV2-induced cell survival and prevention of apoptosis, because PI3/Akt provides the favouring condition for the virus growth. One of the major possibilities is that the PI3K/Akt pathway which participates in the different functions of cell activities like preservation of host cell survival and it also involve in the blockage of apoptotic responses.

From the different studies it is observe that Akt must phosphorylate in the early stage of the PCV2 infection and its action is depend on PI3K. By the Inhibition of P13K activation it leads to activation of a PCV2 virus, which reduce viral DNA accumulation and also synthesis of protein. This leads to one of the major apoptotic responses in the PCV2-induced cells. Many evidences show positive result for these possibilities. Initially infection of the PCV2 is crucial process in to that the breakage of poly-ADP ribose polymerase and caspase-3 as well as DNA differentiation occures. This will lead to the increase in the apoptosis chances after inhibition of the P13K. From the different substantiation's it is recommended that PCV2 infection can be cure by the inhibiting PI3K/Akt pathway. It leads to premature apoptosis for virus growth after the infection [52]. PCV2 infection induces PI3K-dependent phosphorylation of Akt. Investigation from the different studies whether Akt activation in response to PCV2 infection occurred through the PI3K pathway with a specific PI3K inhibitor, LY294007. The concentrations of the inhibitor are maintained during the adsorption period and PCV2 infection [53]. One of the PI3K inhibitor, wortmannin is also use to treat the PCV2-infected cells and obtained positive response results. Thus, the PCV2-induced phosphorylation of Akt involves a PI3K-dependent mechanism. It is been hypothesized that in viral infection leads to activation of the PI3K/Akt pathway. The activation of Akt signaling pathway induced by early PCV2 infection occurs through a PI3K-dependent mechanism, and mediated through the virus infection with host cells. Thus it can be conclude that PI3K/Akt Signaling pathway is necessary for the growth of PCV2. and PI3K/Akt signaling pathway activation leads to the trigger of the circovirus type 2 infection which was required for efficient PCV2 replication as well as in the suppression of premature apoptosis for better virus growth after infection.[54]

ROLE OF PI-3KINASE IN SCHIZOPHERNIA

Schizophrenia is very serious disorder and mostly geriatric population is affected by this neurodegenerative disorder. In this disorder there is no specific biochemical test that conforms for the clinical diagnosis purpose. Impairment of signaling pathway of PI3K in a many of neurodegenerative brain disorders observed mainly in alzheimer disease. Protein-to-gene reverse approach leads to the evidence for the impairment of AKT GSK3 signalling pathway in schizophrenia. This also proves the association between schizophrenia and PI3K. The genetic association of PI3K with schizophrenia was confirmed in other populations [55].

PI-3KINASE IN NON-NEURONAL CELL

PI3K-Akt Pathwayis a signal transduction pathway that promotes survival and growth in response to extracellular signals.Akt has mainly three isoforms in mammalian cells they are AKT I, AKT2, and AKT3. This isoforms has different roles. It mainly includes different processes mainly development and metabolism of the neuronal cells. From all this different isoforms AKT1 is the most important isoforms as it is highly expressed isoform and it has strong evidence for its active role in schizophrenia. Another isoform of the Akt is Akt2 which is mainly involved in the regulationas well as in the metabolism of the insulin-regulated glucose homeostatis.

PI3K is expressed at a higher level and significant expression of AKT2 occurs in insulin-responsive tissues such as skeletal muscle, liver, heart, kidney, and adipose tissue.[56] During development of central nervous system (CNS), the expression of AKT1 and AKT2 level get increase during development, but was gradually reduced during postnatal development. In the adult brain expression of AKT1 and AKT2 is primarily weak. Unlike AKT I and AKT2, AKT3 was only expressed in some tissues, such as in the brain and testes, with reduce expression in skeletal muscle, pancreas, heart, and kidney. Moreover AKT3 was expressed in the brain and had a role in postnatal brain development [56].

PI3K-AKT PATHWAY *IN NEURONAL CELLS:*

For the normal function of the cell protein phosphorylations plays an important role in CNS. This mechanism is widely use for the regulation of the efficacy and specificity of the neurotransmitter which is release from the presynaptic terminal to the nerve impulse. [57] For the regulation of the neuronal size and survival PI3K-Akt plays an important role. Over express of Akt in cerebellar granule neurons prevents apoptosis during withdrawal of growth factors. Inhibition of the PI3K leads to cell survival in the neurons which is supported by growth factor.

PI3K-AKT *SIGNALLING IN SCHIZOPHRENIA*

From the various reports and many other different studies had support the impairment of the PI3K-Akt signaling plays major role in the pathology of schizophrenia. It is been observed that there is major reduction of the Akt protein level in the schizophrenia patients. AKT1 decreased in the hippocampus and frontal cortex in brain samples. This decrease in protein level in the brain was specific to AKT 1 isoform and other 2 isoforms AKT2 and AKT3 levels were unaffect. Many studies provided convergent evidence of reducing in AKT1 mRNA, protein, and activity levels in the prefrontal cortex and hippocampus, as well as in peripheral blood of schizophrenic patients [58].

ROLE OF PI3-KINASE IN PARKINSON DISORDER:

PI3K enhancer in the brain is a enhancer of PI3 kinase/Akt enhancer. This is the group which belongs to GTP binding proteins that comes to the α-subgroup of GTPase family. In the Parkinson disease there is increase in kinase level which is mainly responsible for the over expression of the neuronal gene therefore it might be hypothesised that decrease in the PI3 kinase level will help in the treatment of the disease [59]

The role of PIK enhancer GTPase in the balancing of the neuronal survival has strong evidence which is mainly based on the studies which has been done over the last 10yr. These studies lead to the strong conclusions that functional activities of PIK enhancer in neurone had not been explain very well. It is implicated in the regulating the activities of the transcription factors such as signal transducer and activator of transcription 5A after that prolactin stimulation. The neuro-philins mainly brain derived neuropathic factor (BDNF) are the main molecule that involve in the neuroprotective mechanism during the catastrophic damages. This BDNF protects against glutmate induced apoptotic cell death by the PI3K and extracellular signal regulated kinase pathway in vitro. [59] It is also been reported that increase in BDNF expression after the ischemia and seizer induction, this BDNF has a protective mechanism against the neuronal death. If insufficient BDNF is there then it will leads to the chronic neurodegenerative disease [60]

CONCLUSION:

It can be concluded that PI3K pathway inhibition has beneficial role in various disease and disorders. For the newer drug target and better management purpose it's inhibition can be useful. It can be use as a combination therapy for the various life threatening diseases like Cancer mainly breast cancer and thyroid cancer and inflammatory and neuronal. From the various preclinical data of newly discover PI3k inhibitory action better management therapy can be discover for the better human health services.

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