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OF THE REPUBLIC OF KAZAKHSTAN
of the Institute of Plant Biology and Biotechnology

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THE GROWTH SIGNALING Akt KINASE

Abstract. Growth factor signaling regulates cell proliferation, survival, and differentiation by activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling. Deregulation of this signaling pathway is common in human diseases including cancer and metabolic disorders. Growth factors by binding to their specific receptor tyrosine kinases located on the plasma membrane recruit and activate the signaling factors including the key component identified as the PI3K lipid kinase. A crucial downstream effector of PI3K is the Ser/Thr protein kinase Akt or also known as PKB. Akt transduces the myriad of cellular signals by phosphorylating a wide spectrum of substrates and its activity is strictly controlled by PI3K. The translocation step of Akt to the plasma membrane is a primary step in its activation leading to phosphorylation of Akt on the kinase domain and the regulatory hydrophobic motif. The phosphorylation of both these sites are required to fully activate Akt. In this chapter we describe the mechanisms how the growth factor dependent PI3K signaling regulates Akt by its translocation and phosphorylation.
Keywords: Growth factor signaling, Akt, phosphorylation, kinase domain.

1. Introduction. Deregulation of growth factor signaling pathway is common in human cancers. The recent sequencing studies of multiple human tumor samplesstrengthen this relationship by indicating that genes encoding the components of growth factor signaling are mutated in high frequency(Ding et al., 2008; Parsons et al., 2008).Growth factors initially have been identified as the peptide ligands secreted by cells as autocrine factors required to maintain proliferation of cells in culture. Following many years of studyinggrowth factor signaling pathways, it has been defined that this signaling pathway plays a crucial role in regulation of cell proliferation, survival, and differentiation(Cantley, 2002; Engelman et al., 2006; Fruman et al., 1998). Binding of growth factors to their specific receptor tyrosine kinases (RTKs) initiates thereceptor dimerization and activation of the receptor tyrosine kinase activity. It results in autophosphorylation of the receptor cytoplasmic domains and tyrosine phosphorylation of the regulatory docking proteins. These tyrosine phosphorylated sites function as a recruitment sites of a wide spectrum of regulatory proteins. The specific phosphorylation dependent protein-protein interactions are mediated by the tyrosine phosphorylation binding Src Homology 2 (SH2) domains, whereas the SH3 domain accommodates recruitment of proteins by binding to the proline rich sequences.The growth factor dependent protein-protein interactions nucleate two major signaling pathways carried by activation of the Ras GTPase and PI3K (phosphoinositide 3-kinase).The adaptor protein Grb2 mediates recruitment of a specific guanine nucleotide exchange factor (GEF) of Ras known as SOS (Son of Sevenless). Grb2 binds to a specific phosphotyrosine site on the receptor by its SH2 domain and its SH3 domains recruit SOS to the close proximity to plasma membrane required to the functional activity of SOS as a rate limiting step

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in activation of Ras GTPase. In parallel, the heterodimer of PI3K containing the regulatory subunit p85 and catalytic subunit p110 is activated by its recruitment to plasma membrane. The SH2 domain of its p85 regulatory subunit binds to a specific phosphotyrosine site on activated RTK(Shaw and Cantley, 2006). This translocation event to the close proximity within plasma membrane to the PI3K substrate is a critical step in activation of this important lipid kinase.

Ras proteins act as molecular switches of signaling pathways involved in regulating of cell proliferation, differentiation, survival, and motility. They comprise a subfamily of highly related G-proteins identified as H-ras, N-ras, and K-ras (Giehl, 2005). Ras proteins function as the membrane-associated monomeric GTPases that cycle between a GTP-bound active and a GDP-bound inactive state. The GTP/GDP cycle of ras proteins is tightly regulated by a wide range of cell surface receptors including RTKs. This regulation is mediated by two classes of regulators, the guanine nucleotide exchange factors (GEFs) and the GTPase-activating proteins (GAPs), which modify accordingly the kinetics of GDP dissociation and GTP hydrolysis (Cherfils and Chardin, 1999; Donovan et al., 2002). The active GTP-bound ras interacts with various effectors to produce pleiotropic cellular effects. The most characterized ras effector is raf kinase where ras binds to the well-defined ras binding domain on raf. This interaction activates raf and leads to activation of the raf/MEK/ERK cascade also known as the mitogen-activated protein kinase (MAPK) pathway. Another well-known effector of ras is PI3K: ras binds to the ras binding domain on the p110 kinase subunit of PI3K and causes the up-regulation of its kinase activity (Giehl, 2005). Constitutive activation of ras signaling is linked to cancer development and the ras genes are defined as the most frequently mutated genes in human cancers. The mutated variants of ras proteins are found in 30% of all human cancers in which the vast majority of mutations are traced to the k-ras gene (Friday and Adjei, 2005). Mutations in ras genes are not common in breast cancer but the highly active ras proteins have been identified in approximately 50% of the studied breast tumors (von Lintig et al., 2000).

Members of the PI3K family are the conserved intracellular lipid kinases that phosphorylate the inositol ring of PI(4,5)P2 at the D-3 position to form PI(3,4,5)P3. This phosphorylation event initiates multiple signaling pathways involved in regulating of diverse physiological processes including cell proliferation, survival, metabolism, morphology, and vesicle trafficking. The PI3Ks are classified into three groups according to their substrate preference and structural similarity (Engelman et al., 2006). Class I PI3Ks are coupled to membrane receptors and divided into two subfamilies. Class IA PI3Ks are activated by growth factor receptor tyrosine kinases (RTKs) and they function as heterodimers that contsist of a p85 regulatory subunit and a p110 catalytic subunit. Three genes PI3KR1, PI3KR2, and PI3KR3 encode the p85α, p85β and p55γ isoforms of the p85 regulatory subunit, respectively. All p85 regulatory isoforms contain a p110 binding domain that is flanked by two SH2 containing domains. The p85 regulatory subunit mediates activation of Class IA PI3K by RTKs (Fruman et al., 1998). The SH2 domains of the p85 subunit bind to specific phosphotyrosine sites (pYxxM) on the growth factor activated RTKs and also on adaptor proteins such as IRS1 (Songyang et al., 1993). The binding of p85 via its SH2 domains precludes its inhibitory effect on p110 catalytic activity and at the same time recruits an active PI3K to the proximity of its lipid substrate on plasma membrane (Yu et al., 1998). Like its regulatory counterparts, the p110 catalytic subunit consists of 3 isoforms, p110α, p110β, and p110δ which are encoded by 3 individual genes, PI3CA, PI3CB, and PI3CD, respectively. The p110 isoforms possess an N-terminal p85 regulatory subunit binding domain, a Ras binding domain (RBD), a C2 domain, a phosphatidylinositol kinase (PIK) homology domain, and a C-terminal catalytic domain (Fruman et al., 1998). Class IB PI3Ks are activated by G-protein-coupled receptors and this subfamily also functions as heterodimers represented by a p101 regulatory subunit and a p110γ catalytic subunit. Two additional regulatory subunits, p84 and p87PIKAP, have recently been identified (Suire et al., 2005; Voigt et al., 2006). Class II PI3Ks members consist of only one p110-like catalytic subunit with three isoforms encoded by different genes. Class II PI3K members bind clathrin and localize in coated pits, indicating that they play a role in regulating membrane trafficking and receptor internalization (Gaidarov et al., 2001). Finally, the Class III PI3K is represented by the highly conserved member, Vps34 (vacuolar protein-sorting defective 34), which consists of a single catalytic subunit that was originally identified in budding yeast as a gene required for trafficking vesicles from the Golgi apparatus to the vacuoles (Engelman et al., 2006; Odorizzi et al., 2000).

Up-regulation of the Class IA PI3Ks is associated with Akt activation. Activation of both RTKs and Ras leads to deregulation of this family of PI3Ks and is known as a hallmark in human cancers accounting for up to 30% of all human cancers (Fresno Vara et al., 2004; Luo et al., 2003). Diverse genetic abnormalities cause deregulation of the PI3K signaling in human cancers. Amplification of the genes encoding the p110α PI3K catalytic subunit and Akt2 has been reported in ovarian, breast, and pancreatic cancer (Luo et al., 2003). Mutations of the gene encoding the PI3K regulatory subunit p85a have been linked to some primary colon and ovarian tumors (Bader et al., 2006). Strong evidence has been collected from a large-scale effort to sequence exons of PI3K genes in human tumors. One particular study revealed clustered regions of point mutations in the p110α catalytic subunit in 20%-30% of the breast, colon, brain, and gastric tumors examined (Samuels et al., 2004). An important finding is that the follow-up study of these common mutations identified in tumors has linked them to functional up-regulation of the PI3K activity and cell transformation (Samuels et al., 2005). Although high rates of activating mutations in p110α are associated with tumorigenesis, the multiple studies have pointed out that a loss of PTEN is the most common mechanism of PI3K activation in human cancers. PTEN lipid phosphatase acts as an enzyme to reverse the kinase reaction catalized by PI3K. PTEN catalizes removal of the D3 phosphate from PI(3,4,5)P3 and therefore counterbalances the PI3K signaling (Maehama and Dixon, 1998). A large number of sporadic mutations of PTEN are identified in a high level in many tumor types, including breast, ovarian, and colon cancers and glioblastoma, defining PTEN as the second most commonly mutated tumor suppressor gene after p53 (Shaw and Cantley, 2006).

Nucleation of growth factor signalingdownstream of RTKs takes place onthe plasma membrane.A specific binding of growth factor to its RTK initiates growth factor signaling by recruiting regulatory proteins to the plasma membrane leading to activation of the Ras and PI3K pathways. One of the crucial-downstream effector of PI3K identified as the Akt kinase, also known as PKB (protein kinase B) and it is activated by its translocation tothe plasma membrane and phosphorylation(Shaw and Cantley, 2006). How growth factor signaling regulates the Akt kinase is described in this chapter.

2. Regulation of Akt.

2.1. Akt as a member of the AGC kinase familyand its functional domains. Akt belongs to a large AGC (protein kinase A, G, and C) kinase family. The name of this kinase does not refer to its function and “Ak” is referring to a mouse bred and “t” stands for thymoma that was added when a transforming retrovirus was isolated from the Ak strain. Within 518 known human protein kinases, the AGC kinase family is represented by 60 members of the highly conserved and essential kinases. These kinases are defined and classified by their sequence homology to the kinase domains of cAMP-dependent protein kinase (PKA), cGMP-dependent protein kinase (PKG), and protein kinase C (PKC). Among the members of this kinase family, Akt is the evolutionarily conserved serine/threonine kinase (Figure 1A) and an essential downstream effector of the PI3K pathway in growth factor signalingthat act on a wide spectrum of substrates (Bellacosa et al., 2005). Two Akt genes are found in nematode*Caenorhabditis elegans*, whereas in mammals Akt is represented by subfamily of kinases containing three isoforms expressed by the distinct genes, Akt1, Akt2, and Akt3. It indicates that in evolution the rising complexity of growth factor signaling impelled duplication of the Akt gene. All Akt isoforms are highly related structurally and represented by three well-defined domains (Figure 1).

The full length of human Akt1 encoded by the polypeptide of 480 amino acids. Itcontains the N-terminal pleckstrin homology (PH) domain located within the amino acids 6 to 107 that plays a critical role in the functional translocation of Akt to the plasma membrane and its activation. The catalytic kinase domain resides within the amino acids 154 to 477 and its functional activity is regulated by the activation segment located within the kinase domain positioned from residue 219 to 314 also known as activation loop. Phosphorylation of the activated loop on the Thr-308 site required for the Akt kinase activity. The turn motif phosphorylation site resides on the Thr-450 site. Another stretch of amino acids within residue 469 to 474 is identified as the hydrophobic motif (HM) found in a non-catalytic region following kinase domain also involved in regulation of the kinase activity linked to phosphorylation of the hydrophobic Ser-473 site (Figure 1B).

Within the AGC kinase members Akt represents one of the highly regulated members of this family. The detailed functional and structural studies of Akt led to a basic understanding how its known domains and motifs determine the PI3K-dependent regulation of the kinase activity of Akt.

Protein Acc.	Gene	Organism	Homology compared to Homo sapiens (%)
NP_001014431.1	AKT1	Homo sapiens	–
XP_001143158.1	AKT1	Pan troglodytes	99.2
XP_548000.2	AKT1	Canis lupus familiaris	97.0
NP_776411.1	AKT1	Bos taurus	96.2
NP_033782.1	Akt1	Mus musculus	98.3
NP_150233.1	Akt1	Rattus norvegicus	98.1
NP_990386.1	AKT1	Gallus gallus	96.0
XP_001921993.1	LOC792354	Danio rerio	87.6
NP_001023645.1	akt-1	Caenorhabditis elegans	59.6
NP_510357.3	akt-2	Caenorhabditis elegans	56.2

Figure 1 **(A) Sequence homology of the AKT1 gene**. The pair-wise alignment scores were obtained from NCBI databases. Human AKT1 gene product exhibits higher than 95% protein identity with mammals, but only 60% homology with *C. elegans*.

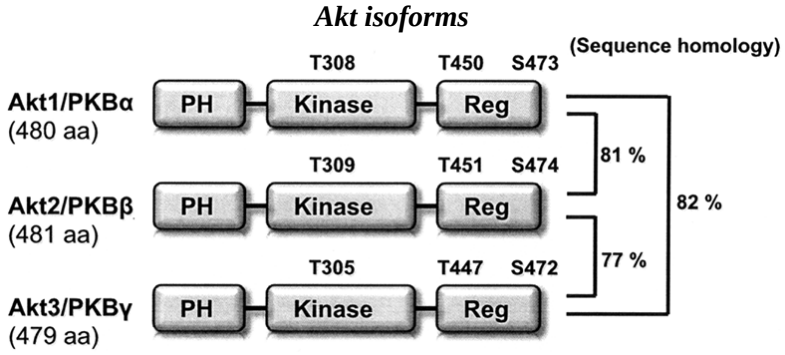

Figure 1 **(B) Akt isoforms.** Akt comprises three mammalian isoforms (Akt1/PKBα, Akt2/PKBβ, Akt3/PKBγ) that are derived from distinct genes and share a conserved structure, which includes three functional domains: an N-terminal pleckstrin homology (PH) domain, a central kinase domain, and a C-terminal regulatory domain containing the hydrophobic motif (HM) phosphorylation site. The amino acid numbers, phosphorylation sites on kinase and regulatory domains of three Akt isoforms were indicated, respectively. Akt1/PKBα shares 81% sequence homology with Akt2/PKBβ and 82% sequence homology with Akt3/PKBγ. Besides, Akt2/PKBβ exhibits 77% sequence homology with Akt3/PKBγ.

2.2. The PI3K-dependent translocation of Akt/PKB to the plasma membrane. Akt is the multi-functional kinase and essential effector of PI3K in growth factor signaling. Akt is mostly resides in cellular cytoplasm and it is cycled to the plasma membrane following stimulation of cells by growth factors where the specific modifications of Akt take place necessary for activation of its enzymatic kinase activity.Activation of PI3K results in accumulation of PI(3,4,5)P3 and a specific binding of the Akt PH domain to PI(3,4,5)P3 recruits Akt to plasma membrane(Cantley, 2002; Engelman et al., 2006). Recently, the ubiquitination of Akt has been identified as a priming step in facilitating the translocation of Akt from cellular cytoplasm to plasma membrane.

2.2.1. Ubiquitination of Akt as a priming step in its translocation to the plasma membrane. Ubiquitination as a modification of cellular proteins by covalently attaching ubiquitin is a common process that plays a critical role in regulation of a wide range of biological processes including cell cycle, cell growth, apoptosis, DNA damage repair, and immune system(Li et al., 2008). Ubiquitin, the ubiquitous and abundant peptide comprising of 76 amino acids, is covalently attached to lysine residues on proteins. This process of ubiquitination is highly regulated and very specific that triggered by the enzymatic cascade of three distinct classes of enzymes termed E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin ligase). The initial cycle of the cascade reactions forms an isopeptide bond between a lysine of the target protein and the C-terminal glycine of ubiquitin. Multiple cycles of ubiquitination lead to formation of polyubiquitination chains by conjugating ubiquitins through two major lysine sites on position 48 (K48) or 63 (K63). The K48-linked protein ubiquitinationis recognized by the 26S proteosome and targets proteins for degradation, whereasthe K63-linked protien ubiquitination does not carry proteolytic functions and mostly involved in regulatory processes.

Recently, a role of ubiquitination in regulation of Akt has been identified(Yang et al., 2009). It has been shown initially that TRAF6 functions as a specific E3 ligase of Akt.In particular, TRAF6 catalyzes the K63-linked ubiquitination of Akt on its highly conserved lysine residues within the PH domain (K8 and K14). This specific modification of Akt might be recognized by a shuttling complex orreceptor localized on plasma membrane that initiates the translocation process. Based on the current model, the Akt ubiquitination is a transient process and following the initial step in facilitating Akt translocation, the deubiquitination takes place. Following this step, the PH domain of Akt in a close proximity to plasma membrane binds PIP3 (Figure 2A and B). This model explains how Akt is efficiently translocated to plasma membrane in cells stimulated by growth factors. The detailed mechanism of this process including how growth factor signaling activates TRAF6 remains to be characterized (Yang et al.). Later, the other E3 ligases Skp2 and TRAF4 have been also identified as the factors carrying a similar regulation of Akt by mediating its K63-linked ubiquitination (Chan C-H, 2012; Li et al., 2013). It has been further shown that a recently developed specific Skp2 E3-ligase inhibitor was effective in suppression of survival and Akt-mediated glycolysis in cancer cells (Chan et al., 2013). The ubiqutination of Akt is a transient modification associated with its activation that occurs by facilitating its translocation to the plasma membrane.Deubiquitination of Akt takes place following its translocation by a specific deubiquitinating (DUB) enzyme CYLD (Lim et al., 2012; Yang et al., 2013)and it explains a transient nature of this modification that remainedelusive until recent studies.

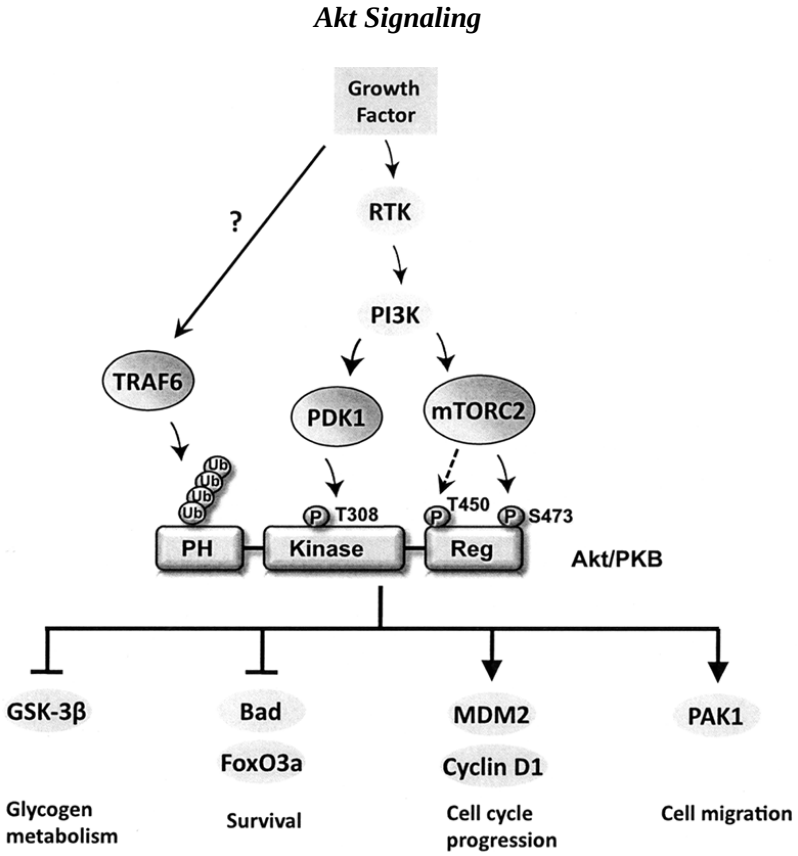

Figure 2 **(A) The simplified scheme of Akt signaling.** Upon growth factor stimulation, the receptor tyrosine kinases (RTKs) activate phosphoinositide 3-kinase (PI3K), which further triggers Akt Thr-308 and Ser-473 phosphorylation by PDK1 and mTORC2, respectively. Both phosphorylation events are required for Akt activation. The ubiquitination of the Akt PH domain by TRAF6 is required for recruitment of Akt to plasma membrane and its activation. Moreover, growth factor-independent Thr-450 phosphorylation of Akt also depends on mTORC2 activity and is required for Akt protein stability. Activated Akt controls numerous biological functions by phosphorylating distinct protein substrates. For example, Akt coordinates glucose metabolism by regulating GSK3β activity. Akt promotes cell survival by phosphorylating and inactivating proapoptotic proteins, such as Bad and Foxo3a. Akt regulates cell cycle progression by phosphorylating and activating oncogenic proteins, such as Mdm2 and cyclin D1. Moreover, Akt controls cell migration by inducing the phosphorylation-dependent PAK1 activation.

Regulation of Akt

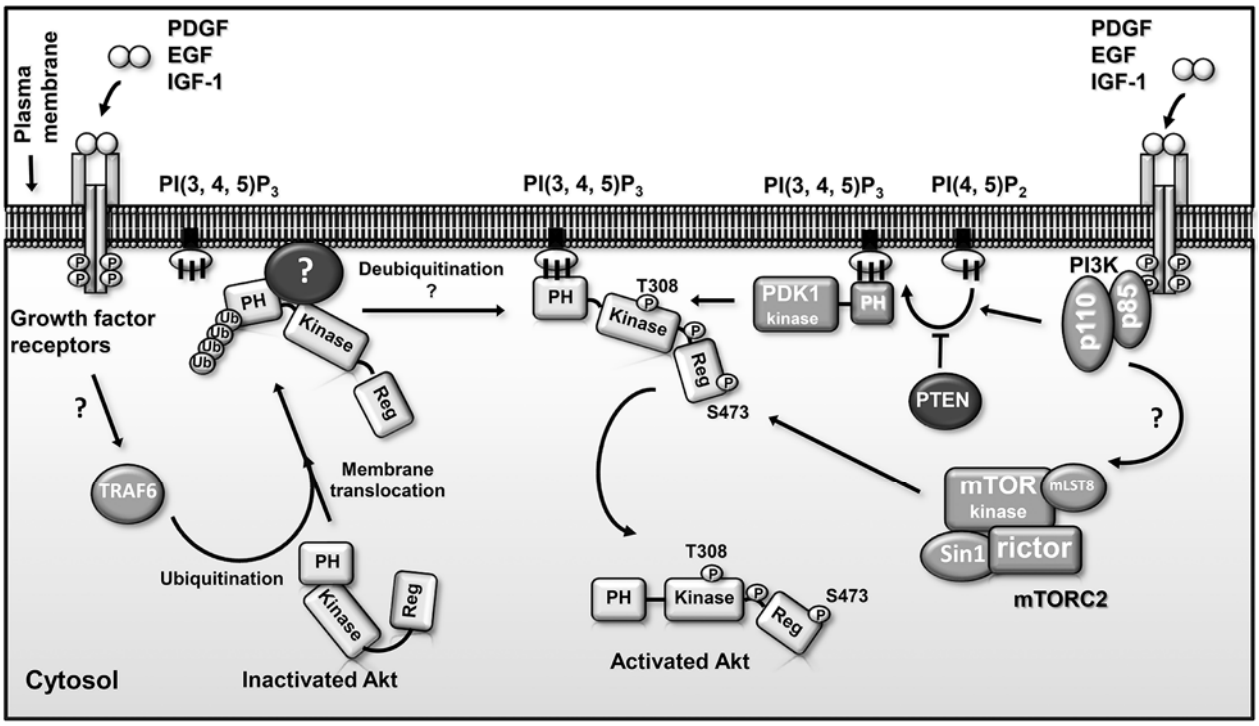

Figure 2 **(B) The diagram describing regulation of Akt.** Binding of the growth factors (such as PDGF, EGF, and IGF-1) to their specific receptors initiates the dimerization and activation of the receptor tyrosine kinases (RTKs) activity. The resulting tyrosine phosphorylated sites of the receptor cytoplasmic domains provide a recruitment site for phosphoinositide 3-kinase (PI3K). The translocation event of PI3K to plasma membrane activates its activity and renders PI3K accessible to its substrate, PI(4,5)P2. PI3K is the conserved intracellular lipid kinase that phosphorylates the inositol ring of the PI(4,5)P2 at the D-3 position to form PI(3,4,5)P3. Importantly, PI(3,4,5)P3 triggers following signal transduction events by recruiting the PH domain-containing proteins, such as Akt and PDK1. The membrane localization of Akt is regulated by Akt ubiquitination by TRAF6 E3 ligase. TRAF6 is activated by growth factors through an unknown mechanism, and then interacts with Akt and triggers K63-linked ubiquitination of Akt on PH domain. It is possible that the ubiquitinated Akt may recruit the essential adaptors (?) to facilitate Akt membrane localization. Upon translocation of Akt to plasma membrane, deubiquitination takes place and then Akt binds PI(3,4,5)P3 through PH domain. In the meantime, the membrane-recruited PDK1 phosphorylates Thr-308 residue on Akt kinase domain, and mTORC2 phosphorylates Ser-473 residue on Akt regulatory domain, leading to the full activation of Akt. The activation of mTORC2 by growth factor signaling remains to be addressed.

Hyperactivation of Akt linked to deregulation of growth factor signaling is common in human cancers. The ubiquitination of Akt might be also relevant to deregulation of Akt in human cancers. The initial study determined that there are only two TRAF6 ubiquitination sites on Akt (K8 and K14). The specific mutation of Akt (E17K) is associated with a subset of human breast and colon cancers(Carpten et al., 2007). In comparison to the wild type Akt, this particular mutant exhibits a higher PIP3 binding, membrane localization, and activity. Interestingly, this mutation by providing the additional lysine ubiquitination site on Akt enhanced its membrane localization and activation that was associated with the hyperubiquitination of Akt(Yang et al., 2009). It has been proposed that deregulation of Akt by this mutation is carried on by hyperubiquitination and also hyper-PIP3 binding. Recently, the similar type of mutation of Akt (E49K) has been described in bladder cancers(Askham et al.). This mutation also caused hyperactivation of Akt that might be dependent on its enhanced ubiquitination.

How a specific ubiquitination facilitates the translocation of Akt to plasma membrane is yet to be characterized(Yang et al.; Yang et al.). This K63-linked ubiquitination plays a role in protein/protein interactions and it might function as a binding motif to recruit the regulatory factor initiating its specific translocation. It is possible that this regulatory factor is also mediating the deubiquitination of Akt at the plasma membrane location. The mediator in this translocation step of Akt from cytoplasm to plasma membranehas been proposed for many years(Bellacosa et al., 1998)and this regulatory mechanism might determine the orderly activation as a rate-limiting step in this process.

2.2.2. Translocation of Akt to the plasma membrane is mediated by its PH domain. The plasma membrane accumulation of PI(3,4,5)P3 is generated by the growth factor dependent PI3K activity. The PH domain of Akt by binding to the phosphorylated head group of PI(3,4,5)P3 positions Akt on the plasmamembrane (Figures 3B and 3C). This binding determines the localization of Akt at its activation site and also primes Akt for activation as discussed in the next section.

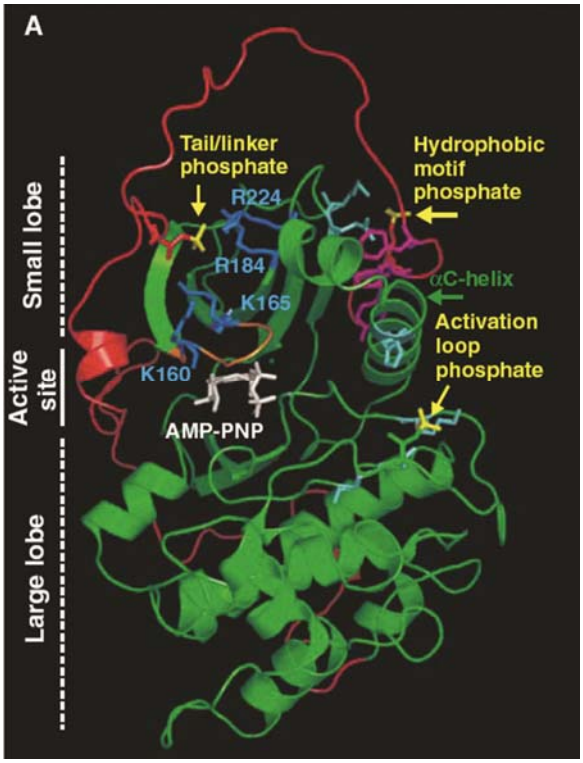

Figure 3 **(A) The molecular modeling of the Akt structure.** The kinase domain shown in green and the C-terminal tail including the turn and hydrophobic motifs are shown in red. The phosphorylated sites are shown in yellow: the activation segment (indicated as "loop" in the model) Thr-308 site, the turn motif (indicated as "tail/linker phosphate" in the model) Thr-450 site, and the hydrophobic motif Ser-473 site. The basic residues predicted to bind the turn motif Thr-450 site are shown in blue. Reproduced from (Hauge et al., 2007) with permission from Nature Publishing Group.

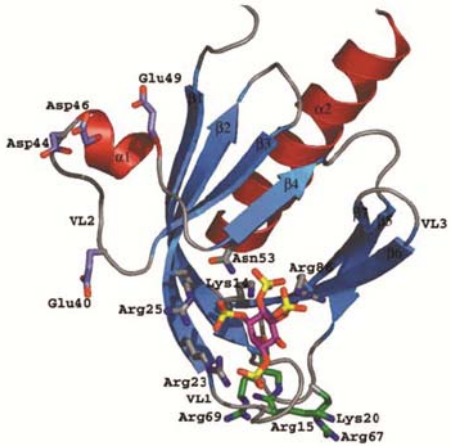

Figure 3 **(B) Structure of PKB_PH Complexed to Ins(1,3,4,5)P4.** A ribbon drawing of the Akt_PH-Ins(1,3,4,5)P4 complex, with the seven βstrands (labeled β1–7) shown in blue and the two αhelices (labeledα1–2) shown in red. Ins(1,3,4,5)P4 is shown as purple carbons. The side chains of residues interacting with this molecule are shown as graycarbons. The basic residues thought to interact with the membrane have their side chains shown as sticks with green carbons. The negativelycharged residues on VL2 that are hypothesized to interact with the kinase domain are shown as gray-blue carbons.Reproduced from (Thomas et al., 2002) with permission form Elsevier.

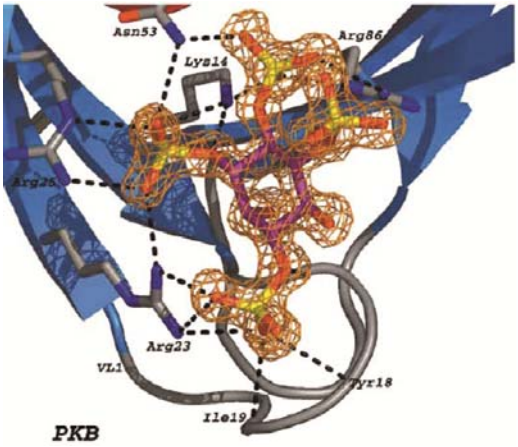

Figure 3 **(C) Ribbon diagrams of the Ins(1,3,4,5)P4 binding sites of Akt.** The Ins(1,3,4,5)P4 is shown as purple carbons. Forthe Akt-Ins(1,3,4,5)P4 structure, the experimental electron density map from SOLVE after density modification is shown in orange (contouredat 2.25δ). Residues that are hydrogen bonding the ligand are shown as sticks with gray carbons. Hydrogen bonds are shown as black dottedlines. Reproduced from (Thomas et al., 2002) with permission form Elsevier.

The PH domain is found in numerous proteins involved in cellular signaling and comprised of approximately 100-120 residues that functions as thephospholipid binding domain and therefore mediates association of proteins with cellular membranes. Among of the known PH domain containing proteins (about 100 proteins) the sequence is not highly conserved but all the studied PH domains show a remarkable similarity in their three-dimensional structures. The PH domain of Akt reveals a standard domain containing seven β strands forming two orthogonal antiparallel β-sheets, the three loops (VL1, 2, and 3), and this domain is capped by a C-terminal α–helix(Thomas et al., 2002). Importantly, the three VL loops lie at the bottom of this β barrel and form a positively charged binding pocket. The phosphorylated head group of PI(3,4,5)P3 specifically fits to the binding pocket of the PH domain of Akt. Theprotein/lipid interaction is stabilized by formation the specific hydrogen bonds between the phosphate groups (at positions D3 and D4)and the basic residues within the loops located on the bottom of the PH domain binding pocket(Rong et al., 2001; Thomas et al., 2002). The PI head group at position D3 interacts with the three basic residues of Lys14, Arg 23, Arg 25, and also polar group of the residue Asn53, whereas the D4 phosphate interacts with the similar residues of Lys14 and Asn53, and the distinct residue of Arg86. The crystal structure studies of the Akt PH domain bound to the phosphorylated head group of PI(3,4,5)P3 explains that the specificity of binding is determined by phosphorylation of the PI head group at D3 and D4 excluding the binding of PI(3)P or PI(3,5)P2 (Figure 3B and C). It also explains why Akt can interact with the similar high affinity with both PI(3,4)P2 and PI(3,4,5)P3.

The functional studies of the PH domain of Akt strongly indicate that this domain is not only the adaptor domain responsible forthe membrane binding but it is also an important regulatory domain of the Akt kinase activity. The PH domain at the closed “PH-in” conformation locks Akt at its kinase inactive state by preventing its activation(Huang et al., 2003). The binding of the PH domain to membrane switches to the open “PH-out” conformation unlocking the Akt kinase activation(Calleja et al., 2009; Milburn et al., 2003). The recent work identifiedthe inositol pyrophosphate IP7 (5-diphosphoinositol-pentakisphosphate) as the novel physiological regulator of Akt that acts by interfering with its PH domain inhibits activation of Akt. IP7 is formed by a family of three inositol hexakisphosphate kinases (IP6Ks) and their activity is coupled to activation of insulin signaling (Chakraborty et al.). This allosteric mechanism in regulation of Akt opens a new approach in development of the novel class of the specific inhibitors of Akt (Wu et al.).

2.3. Regulation of the Akt kinase by phosphorylation. The phosphorylation-dependent regulation is commonamong the multiple AGC kinase members. In regulation of Akt the phosphorylation of three sites are critical to turn on the Akt kinase to active mode (Figure 3A). The phosphorylation of Akt on Thr-308 and Ser-473 sites is dependent on the growth factor/PI3K signaling, whereas its Thr-450 site is constitutively phosphorylated (Figure 2A and B). Following growth factor stimulation and translocation of Akt to the plasma membrane location, Akt is phosphorylated on the Thr-308 and Ser-473 sites, the key phosphorylation sites, required to fully activate Akt (Bellacosa et al., 2005). The activation loop of Akt on Thr-308 is phosphorylated by the phosphoinositide-dependent kinase 1 (PDK1) that required for the kinase activity of Akt (Alessi et al., 1997)(Stephens et al., 1998). PDK1 as the Akt kinase was identified in 1997, whereas the regulatory Ser-473 kinase of Akt, named PDK2, was identified following several years only in 2005 as the mTOR Complex 2 (mTORC2) (Sarbassov et al., 2005b).Although several candidates were proposed earlier as PDK2 (Dillon et al., 2007), the mouse genetic studies confirmed the role of mTORC2 as the Ser-473 kinase of Akt (Guertin et al., 2006; Jacinto et al., 2006; Shiota et al., 2006; Yang et al., 2006). Recently, the DNA protein kinase (DNA PK) activated following the DNA damage response has been also shown to phosphorylate AKT on its hydrophobic Ser-473 site (Bozulic et al., 2008). Interestingly, the constitutively phosphorylated site of Akt on Thr-450 known as the turn motif site is also dependent on mTORC2, but in this case it is not dependent on growth factor signaling. It has been shown that phosphorylation of Akt on Thr-450 is coupled with a nascent polypeptide synthesis of Akt(Oh et al., 2010). This finding indicates that mTORC2 mediates a proper folding of Akt by phosphorylation its turn motif Thr-450 sitein association with ribosomes as a co-translational event. A constitutive nature of this phosphorylation has been recently unraveled (Chen et al., 2013) that will be discussed in the following chapter 2.3.3. Importantly, a recent study linked regulation of Akt by phosphorylation to cell cycle. It has been shown that the extreme C-terminus of Akt is phosphorylated on Ser-477 and Thr-479 by cyclin-dependent kinase 2 (Cdk2)/cyclin A or also by mTORC2. This phospho-

rylation event promotes Akt activation through facilitating or functionally compensating for the Ser-473 phosphorylation defined as the hydrophobic motif site (Liu et al., 2014).

2.3.1. Regulation of the Akt kinase activity: the input from its structure. The Akt kinase activity is highly regulated and controlled by the PI3K-dependent phosphorylation of this kinase. The structural studies of Akt show that its stringent regulation by phosphorylation is determined by stabilization of the ATP-binding pocket that controls the catalytic activity of Akt (Figure 3A).The resolved AGC kinase domain structures including Akt show the prototypical bilobal kinase fold containing a small N-terminal lobe (N-lobe) and a large C-terminal lobe (C-lobe) where the ATP binding pocket of the kinase is located between the N and C lobes(Pearce et al., 2010). Regulation of the kinase activity is linked to the activation segment found within the C-lobe that connected to the N-lobe through the distinct αC helix. This segment is adjacent to the ATP-binding site which positions ATP for phosphoryl transfer. The phosphorylation of the activated segment on the Thr-308 site of Aktleads to conformational changes primarily on the αC helix. These changes trigger formation of the appropriate hydrogen bonds between the ATP phosphates and particular amino acid residues of ATP binding pocket required for the catalytic kinase activity of enzyme.The active conformation of the αC helix is stabilized by the hydrophobic motif of Akt located at the C-terminus. This motif by extending from the C-lobe embraces the N-lobe and binds to the hydrophobic pocket formed by the αC helix.The structural studies outline that the activation segment and hydrophobic motif facilitate positioning of the αC helix in an active conformation. Both the activation segment and hydrophobic motif are regulated by the growth factor/PI3K dependent phosphorylation of Akt on Thr-308 and Ser-473.

The AGC kinases also carry the additional distinct regulatory motif defined as the turn motif. The turn motif of Akt is located close to C-terminus by preceding the hydrophobic motif and is constitutively phosphorylated on the Thr-450 site. This motif is important in regulation of the Akt protein stability and a proper arrangement of C-terminal tail around the N-lobe that is critical in facilitating binding of the hydrophobic motif and hydrophobic pocket of Akt(Hauge et al., 2007). Based on the modeling it has been proposed that four basic residues of Akt2 (K160, K165, K184, R224) interact with the phosphorylated turn motif site (Figure 3A). These residues areconserved among the 23 related AGC kinase members containing the C-terminal hydrophobic regulatory site (Hauge et al., 2007).

2.3.2. PDK1 is the active segment kinase of Akt. PDK1 is a conserved member of the AGC kinase family that caries a distinct feature as the constitutively active kinase. It is a polypeptide comprised of 556 amino acids with the kinase domain spanned from the residue 80 to 342 and the PH domain located at the C-terminus. PDK1 is an essential kinase encoded by a single gene that regulates at least 23 AGC kinases by phosphorylation the activation segments required to activation of their kinase domains(Mora et al., 2004; Pearce et al., 2010).In mice missing the PDK1 gene, the embryo development is ceasedat day 9.5 carrying the multiple abnormalities including lack of somites, forebrain, and neural crest derived tissues. Interestingly, the hypomorphic mice expressing low level of PDK1 (about 10%) are viable and fertile but were only half size of normal mice(Bayascas, 2008; Mora et al., 2003; Mora et al., 2004). This PDK1-dependent reduction in animal size was due to the cell size but not cell number effect and this effect on cell size has not been linked to deregulation of the important PDK1 substrates S6K1 and Akt. The mechanism how PDK1 controls regulation of cell growth and cell size remains poorly understood.

A specific phosphorylation of the multiple substrates by PDK1 is coordinated by the priming of these substrates for activation by various extracellular signals(Pearce et al., 2010).In case of Akt, its binding to PI(3,4,5)P3 leads to the conformational change that functions as thepriming step by promoting the phosphorylation of Akt by PDK1 on its Thr-308 site. This model is assumed based on the in vitro kinase studies indicating that the presence of PI(3,4,5)P3 is required for the efficient phosphorylation of Akt by PDK1, but the lipid moiety is not required if the substrate is missing the PH domain. From the kinase point of view, the binding of PDK1 to PI(3,4,5)P3 by its PH domain does not stimulate activation of the kinase activity. Instead, PDK1 is the constitutively activekinase determined by the constant phosphorylation of its activation segment residue on Ser-241. It has been shown that this phosphorylation event is carried out by the PDK1 intrinsic capability to trans-autophosphorylate this important regulatory site (Casamayor et al., 1999).In this setting, the substrate-directed mechanism of regulation determines the coordinated phosphorylation of the multiple substrates by PDK1.

The PH domains carried by PDK1 and its substrate Akt are preferentially bind to PI(3,4,5)P3 and thought to facilitate the growth factor/PI3K-dependent colocalization of both these kinases on the plasma membrane. The colocalization of both kinases might play a role in regulation of Akt because only a weak phosphorylation of Akt has been detected in cells expressing the PDK1 [K465E] or triple mutant with non-functional PH domain(Bayascas et al., 2008; McManus et al., 2004). At the same time, a functional role of the PDK1 PH domain remains questionable because a pool of PDK1 is constitutively associated with the plasma membrane and its level does not change following the stimulation of cells by growth factors. Instead, it is believed that PDK1 is widely distributed in cells by binding to soluble inositol phosphates (Komander et al., 2004).

2.3.3. The mTOR Complex 2 is the regulatory kinase of Akt.

2.3.3.1. The mTOR Complex 2. Originally, mTOR was discovered as a target for the lypophilic macrolide rapamycin. Rapamycin is well known as a potent immunosuppressant, as a potential anti-cancer drug, and also for effectively preventing restenosis after angioplasty. All these anti-proliferative effects of rapamycin are related to its specific targeting and inhibition of mTOR, a central component of the essential and highly conserved signaling pathway (Harris and Lawrence, 2003). mTOR exists in two distinct complexes that play different roles in cells (Sarbassov et al., 2005a). The first complex, mTORC1, is assembled by the mTOR interacting proteins raptor and mLST8, also known as GβL (Hara et al., 2002; Kim et al., 2002; Kim et al., 2003). The mTORC1 complex monitors the level of amino acids available to cells and controls cell growth and cell size. It functions as a nutrient-sensitive kinase complex that phosphorylates its two substrates, S6K1 and 4EBP1, the well-known regulators of protein synthesis. Rapamycin in a complex with its intracellular receptor FKBP12 specifically binds the FKBP12/rapamycin binding (FRB) domain on mTOR and inhibits the mTORC1 function, but the cause of that inhibition is not well understood (Kim et al., 2002). In addition to nutrients, various physiological stimuli, including growth factors and cellular stress conditions signal to mTORC1 by differently regulating the tuberous sclerosis complex (TSC) and the Ras homologue enriched in brain (rheb) signaling module (Hay and Sonenberg, 2004). Growth factor signaling through Ras-ERK and PI3K-Akt activates mTORC1. In contrast, stressful conditions like hypoxia are associated with up-regulation of the AMP level and activation of AMP-activated protein kinase inhibits mTORC1. The mTORC2 substrate Akt positively regulates mTORC1, whereas the mTORC1 substrate S6K1 has a negative effect on the PI3K/mTORC2/Akt signaling by inducing rapid turnover of IRS1, which causes attenuation of the insulin/IGF signaling (Guertin and Sabatini, 2005).

The second mTOR complex, mTORC2, is assembled by mTOR and its interacting proteins rictor, Sin1, and mLST8 (Frias et al., 2006; Jacinto et al., 2006; Jacinto et al., 2004; Sarbassov et al., 2004). The mTORC2 complex identified as the regulatory Ser-473 kinase of Aktexpands the mTOR function to regulation of cellular proliferation, survival, motility, and metabolism (Figure 2). A role of mTORC2 in regulating of PKCα and the cytoskeleton has also been reported (Jacinto et al., 2004; Sarbassov et al., 2004). A central component of this complex is mTOR, it is an essential and highly conserved protein. It contains multiple HEAT repeats at the N-terminal half of the protein that are known to form a scaffolding structure for protein/protein interactions. The FRB domain responsible for binding of the rapamycin/FKBP12 complex is a stretch of 100 amino acids located in the C-terminal half of mTOR. The mTOR kinase domain is located at the C-terminus, structurally resembles a kinase domain of PI3K but functions as a serine/threonine protein kinase and it is essential for the mTOR function (Harris and Lawrence, 2003). In contrast to mTORC1, mTORC2 does not bind the rapamycin/FKBP12 complex, suggesting that the FRB domain on mTOR that is responsible for the binding is not accessible on mTORC2. Nevertheless, prolonged rapamycin treatment causes an indirect effect on mTORC2 by inhibiting the assembly of this complex. In some cell types, mostly lymphoma cells, the prolonged rapamycin treatment causes inhibition of Akt because of a dramatic effect on the abundance of mTORC2 (Sarbassov et al., 2006).

Two mTOR interacting proteins, mLST8 and DEPTOR, are found in both mTOR complexes. The mLST8 protein also known as GbL is a small adaptor protein containing seven WD40 repeats, it binds tightly to the kinase domain and is required for the kinase activity of mTOR (Kim et al., 2003). DEPTOR has been characterized as a negative regulator of mTOR (Peterson et al., 2009). The mTORC2 component rictor forms a low affinity complex with mTOR and it is indispensable for the function of mTORC2. Rictor remains poorly characterized. The full length of the human rictor polypeptide containing

1,708 amino acids reveals no homology with any known functional domain or protein, although it is relatively conserved in all eukaryotes (Jacinto et al., 2004; Sarbassov et al., 2004; Sarbassov et al., 2005b). Initially, rictor's ortholog, *pianissimo,* was identified in *Dictyostelium* as a critical player in chemotaxis and cAMP signal relay (Chen et al., 1997). The recently identified fourth component of mTORC2, Sin1, might provide more insights into the regulation and function of mTORC2. Two Sin1 functional domains have been proposed: the Raf-like Ras binding domain (RBD) and a pleckstrin homology domain (Schroder et al., 2007). The RBD domain points out Ras as a potential up-stream effector of mTORC2, and localization of mTORC2 at the plasma membrane might depend on the plekstrin homology domain of Sin1. Like rictor's, Sin1's ortholog was initially identified as an important regulator of chemotaxis and in addition as a Ras interacting protein 3 in *Dictyostelium* (Lee et al., 2005; Lee et al., 1999).

2.3.3.2. The mTOR Complex 2 is the regulatory Ser-473 kinase of Akt. The functional studies of mTORC2 have been initiated following the biochemical identification of two distinct complexes of mTOR.The second mTOR complex has been proposed to carry a novel rapamycin-insensitive function of mTOR because the rapamycin/FKPB12 complex did not bind to mTORC2. Interestingly, the serendipitous finding drew into theinitial link between mTORC2 (at that time known as the rictor-mTOR complex) and Akt(Ali and Sabatini, 2005). The truncated form of S6K1 carrying its hydrophobic Thr-389 site on its C-terminus had been characterized as the rapamycin-resistant isoform of S6K1. It has been assumed that the peptide sequence of S6K1 between the Thr-389 site and its C-terminal residue at Leu-525 functions as the phosphatase binding motif and it is critical in the rapamycin-dependent dephosphorylaiton of the Thr-389 site. The characterization of this phosphorylation by the knock down of raptor or rictor expression showed that the phosphorylation on Thr-389 of the rapamycin-resistant truncated from of S6K1 is dependent on mTORC2 but not mTORC1(Ali and Sabatini, 2005). This unexpected finding strongly indicated that mTORC2 prefers to phosphorylate a hydrophobic site located at C-terminus, and the truncation of S6K1 is switching the substrate specificity from mTORC1 to mTORC2 that also explains its insensitivity to the rapamycin treatment. Akt as the AGC kinase family carries the well-defined hydrophobic motif on its C-terminuis (Figure 1B) that initiated to study a role of mTORC2 in regulation of Akt.In the present time based on the distinct location of the hydrophobic motif site within the AGC kinase family members, mTORC2 has been defined as a major regulatory kinase of Akt (Sarbassov et al., 2005b)and also other essential member of this family of kinasesknown as SGK (Garcia-Martinez and Alessi, 2008).

Regulation of Akt by its phosphorylation on the hydrophobic Ser-473 site is coupled to activation of the growth factor dependent PI3K signaling. The functional role of mTORC2 as the Ser-473 kinase of Akt defines this kinase complex as the component of growth factor signaling (Figure 2B).How growth factor signaling regulates the mTORC2 kinase activityremains very poorly understood. The distinct growth factor dependent phosphorylation of the mTORC2 components mTOR and rictor has been identified. The phosphorylation of mTOR on its hydrophobic Ser-2481 site is linked to the active state of mTORC2(Copp et al., 2009). This site of mTOR has been previously characterized and defined as its hydrophobic autophosphorylation site(Peterson et al., 2000). Why this autophosphorylation site reflects a high kinase activity specifically of mTORC2, but not mTORC1, is not known. The essential component of mTORC2 rictor is a phospho-protein (Akcakanat et al., 2007; Sarbassov et al., 2004). Several distinct phosphorylation sites have been identified on rictor and its Thr-1135 site has been characterized as the phosphorylation site regulated by growth factor signaling. Interestingly, S6K1 is a kinase of the Thr-1135 site on rictor implying its potential role as alink coordinating mTORC1-dependent regulation of mTORC2. This site has been shown to carry a negative role in regulation of mTORC2 by providing a binding site for the 14-3-3 adaptor proteins (Dibble et al., 2009; Julien et al.; Treins et al.). The functional studies indicated that the rictor Thr-1135 site is not essential in regulation of the mTORC2 kinase activity and this phosphorylation takes place independent of mTORC2 (Boulbes et al., 2010).Conversely, the Ser-1235 site on rictor has been identified as an inhibitory phosphorylation site of the mTORC2 kinase activity that unravels a mechanism how ER (endoplasmic reticulum) stress inhibits Akt signaling (Chen et al., 2011). ER stress activates several stress-responsive kinases including glycogen synthase kinase 3β (GSK3β), a well-known substrate of Akt. Under ER stress, a hyperactivated GSK3 phosphorylates the mTORC2 component rictor on Ser-1235 and this modification has been sufficient to inhibit the kinase activity of

mTORC2 representing a large kinase complex of more than 500 kDa. The functional studies indicated that phosphorylation of rictor on a single Ser-1235 site interferes with the substrate binding of mTORC2 and causes a substantial inhibitory effect on the kinase complex activity under ER stress(Chen et al., 2011). This finding defines how ER stress inhibits activaty of Akt mediated by the well-defined substrate of Akt known as GSK3β. How ER stress activates GSK3 remains poorly characterized and it has to be thoroughly addressed to understand the ER stress responsive mechanisms.

Until now, how growth factor signaling regulates the mTORC2 kinase activity remains poorly understood. A strong lead on the growth factor-dependent regulation of mTORC2 has been revealed by the finding that mTORC2 is activated in association with a ribosome (Zinzalla et al., 2011). It is supported by the study indicating that mTORC2 in association with ribosome carries the cotranslational phosphorylation of Akt on turn motif site (Oh et al., 2010). Both theses studies show a strong relation of mTORC2 with ribosomes that is related to the functional studies indicating ER, a cellular organelle enriched with ribosomes, as a main localization site of mTORC2(Boulbes et al., 2011). It is important to point out that localization of mTORC2 in the ER fraction is not sensitive to growth factor signaling, while its substrate Akt gets translocated from the cytosolic to plasma membrane fraction following stimulation of cells by growth factors(Alessi et al., 1997; Boulbes et al., 2011; Stephens et al., 1998). This observation suggests that mTORC2 is localized on a surface of ER and it is accessible to its cytosolic substrate Akt. This functional topology of mTORC2 is supported by the recent work indicating that the active mTORC2 is localized at mitochondria-associated endoplasmic reticulum membranes (Betz et al., 2013). It will be important to show that the active mTORC2 kinase complex resides on ER surface by the functional studies of purified ER fractions and mTORC2 kinase activity.

2.3.3.3. The mTOR Complex 2 phosphorylates the Thr-450 turn motif site of Akt. The carboxyl-terminal tail of Akt carries two distinct phosphorylation sites known as theregulatory hydrophobic Ser-473 site and its neighboring turn motif Thr-450 site(Hauge et al., 2007). Interestingly, both these sites are dependent on the mTORC2 function but their regulation is highly distinct. Regulation of the hydrophobic Ser-473 site is coupled to the growth factor dependent mTORC2 activation. Although the Thr-450 site is located close to the hydrophobic Ser-473 site, its regulation is very different because this turn motif site on Akt is phosphorylatedconstitutively on this residue(Facchinetti et al., 2008; Ikenoue et al., 2008). This phosphorylation site is critical for proper folding of Akt as a part of the carboxyl-terminal tail known to interact with the N- and C-lobes of the kinase domain. The turn Thr-450 site has been also shown to control the protein stability of Akt.

The detailed study of the Akt phosphorylation on the turn motif Thr-450 site has indicated a novel role of mTORC2 in protein processing coupled to translation. It has been shown that mTORC2 can associate with the actively translating ribosomes and during translation of Akt mTORC2 mediates phosphorylation of a nascent polypeptide on the turn motif site(Oh et al., 2010). This study shows that the turn motif phosphorylation by mTORC2 is taking place early during the translation process that facilitates a proper folding of the Akt nascent polypeptide. Prevention of the phosphorylation on Thr-450 by mTORC2 leads to a high rate of misfolding of Akt as detected by binding of the folding chaperone HSP90. A misfolded Akt protein is targeted by the 48K-linked ubiquitination and degraded by the proteosomal pathway.

A basic activity of mTORC2 independent of growth factor signaling is sufficient to retain the constitutive phosphorylation of Akt on Thr-450(Facchinetti et al., 2008; Ikenoue et al., 2008; Jacinto and Lorberg, 2008). How the multi-protein mTORC2 kinase complex associates with ribosomes and specifically recognizes a nascent translated polypeptide of Akt is to be further characterizedto define the mTORC2 function as a protein complex involved in protein processing. Most likely, the mTORC2-dependent phosphorylations of Thr-450 or Ser-473 site are uncoupled and independent events where the distinct localizations of mTORC2 determine its role as the kinase of the turn or hydrophobic motif site of Akt. Regulation of a constitutive phosphorylation of the Thr-450 site of Akt by mTORC2 has been recently unraveled. The initial study on reconstitution of mTORC2 led to observation that the mTOR kinase activity by phosphorylation of the essential mTORC2 component SIN1 maintains integrity and stability of mTORC2 (Chen and Sarbassov, 2011). The further studies indicated that a basal kinase activity of mTORC2 maintains phosphorylation not only Akt on Thr-450 but also its own component SIN1 on Ser-260. A basal kinase activity of mTORC2 is dependent on glucose but not amino acid

deprivation linking it to dependence on cellular ATP level (Chen et al., 2013). The detailed in vitro kinase studies determined that mTOR, as the protein kinase of mTORC2, requires a physiological level of ATP (in a range at least 1.2 millimolar concentration) for its high activity. This study is coherent with the original finding that defined mTOR as a homeostatic ATP sensor because it has a low affinity to ATP that makes it highly sensitive to depletion of ATP in cells (Dennis et al., 2001). It can be concluded that a basal kinase activity of mTORC2 acts as a stabilizing factor by maintaining a constitutive phosphorylation of Akt on Thr-450 and also its component SIN1 on Ser-260. A high sensitivity of mTORC2 to low cellular ATP level determines its disintegration under cellular stress conditions (Chen et al., 2013).

2.4. The regulation of Akt by phosphatases. A steady balance in regulation by phosphorylaiton is determined by kinases and phosphatases. This balance is particular critical in regulation of the tightly controlled and important Akt signaling. Phosphorylation of the activation segment Thr-308 and the regulatory hydrophobic Ser-473 sites of Akt are required to full activation of its kinase activity. As these distinct sites are phosphorylated by two different kinases PDK1 and mTORC2, and these sites are also dephosphorylated by two different phosphatases.

The PH domain leucine-rich repeat protein phosphatase (PHLPP) has been identified as a phosphatase that specifically dephosphorylates the Ser-473 site of Akt (Gao et al., 2005)and therefore it is opposing the phosphorylation reaction catalyzed by the mTORC2 kinase complex. Initially, this phosphatase was selected as a phosphatase candidate of Akt because it represented the only phosphatase family containing the PH domainassumingits potential localization overlap with the PH domain containing proteins including Akt. The functional studies supported a role of PHLPP in regulation of the Akt phosphorylation specifically of its Ser-473 but not Thr-308 site(Brognard and Newton, 2008; Gao et al., 2005). PHLPP is highly conserved in evolution from yeast to humans and most likely it is essential in regulation of cell signaling.

PHLPP is a distinct sub-family of the protein phosphatase 2C (PP2C) family, its catalytic activity depends on the presence Mg^{2+} or Mn^{2+} and is independent of the common phosphatase inhibitor okadaic acid. The PHLPP phosphatases are represented by two members (PHLPP1 and 2) encoded by two different genes where the first PHLPP1 form exists in two forms α and βthat generated from splice variants of the same gene. Several domains have been identified within the PHLPP sequence including the Ras association, PH, leucine rich repeat region, and PDZ binding motif. The functional roles of these PHLPP domains are not well characterized and the initial study indicated that the PDZ domain is indispensable for the phosphatase function(Brognard and Newton, 2008; Gao et al., 2005). It is proposed that PDZ, as the C-terminus protein interaction domain, might assemble PHLPP into signaling complexes required for its phosphatase activity.

The PDK1-dependnet phosphorylation of Akt on Thr-308 within the activation segment is required for the kinase activity and its regulation is critical in the PI3K/Akt signaling. Based on the RNAi-screen in *C. elegans,* a B56 regulatory subunit of the protein phosphatase 2A (PP2A) holoenzyme has been identified as a negative regulator of the activation segment phosphorylation of AKT1. This regulation is highly conserved in evolution and the mammalian B56βregulatory subunit of PP2A has been shown to inhibit phosphorylation of the Thr-308 site of Akt1 in adipocytes (Padmanabhan et al., 2009). The PP2A holoenzyme substrate recognition study showed that its B subunit interacts with a substrate (Shi, 2009; Xu et al., 2008). It is interesting how the PP2A holoenzyme selectivity against the Thr-308 site of Akt is specifically determined by its regulatory B56βsubunit. Recently, it has been also described that the constitutively phosphorylated turn motif Thr-450 site of Akt is regulated specifically by the PP1 phosphatase. The study shows that activity of both α and β PP1 isoforms associate with the dephosphorylation of the turn motif site and inhibition of Akt (Xiao et al.). In the present time a role of the phosphatases in regulation of the Akt kinase activity remains poorly characterized.

2.5. The functional role of Akt. The Akt signaling is engaged in multiple signaling pathways and involved in regulation of a variety of cellular processes, including cell proliferation, growth, survival, and metabolism. Perturbations of the Akt signaling are associated with human diseases including cancer and the metabolic syndrome. Several Akt substrates are functionally relevant to human cancer. Akt has been implicated in regulating of cell cycle through the phosphorylation of the cell cycle inhibitors p21 and p27 by causing their cytoplasmic retention (Viglietto et al., 2002; Zhou et al., 2001a) and also through the phosphorylation of the human oncogene product MDM2, which degrades the p53 tumor suppressor gene

(Zhou et al., 2001b). Akt regulates cell survival through its inactivation of the pro-apoptotic protein BAD (Datta et al., 1997; del Peso et al., 1997) and inhibition of its highly conserved substrates identified as the FOXO transcription factors that drive the expression of pro-apototic genes (Brunet et al., 1999). Akt also plays a role in metabolism by inactivating glycogen synthase kinase-3 (GSK-3) and by activating glycolysis and glucose transport (Cross et al., 1995; Kohn et al., 1996). The role of the Akt signaling in regulation of cell growth and cell size is linked to its up-regulation of the mammalian Target of Rapamycin (mTOR) pathway by the phosphorylation of TSC2 (Inoki et al., 2002)(Manning et al., 2002) and the recently identified PRAS40 (Sancak et al., 2007; Vander Haar et al., 2007).

Knockout studies of the individual Akt isoforms in mice have revealed the specific functional roles of the Akt kinase members (Stambolic and Woodgett, 2006). The targeted disruption of Akt1 has identified its role in regulating of body size and adipogenesis. Knockout of the Akt2 gene in mice is associated with severe insulin resistance and diabetes. Double knockout of Akt1 and Akt2 causes perinatal lethality due to multiple developmental defects. A 20% decrease in mouse brain size has been linked to loss of the Akt3 gene. It is Interesting that different roles of the Akt members have been identified in their signaling in mammary tumor progression. Activation of Akt1 itself is not sufficient to stimulate tumor growth, but it can cooperate with other oncogenic factors in accelerating tumorigenesis (Dillon et al., 2007). Overexpression of Akt2 has been reported to up-regulate b1-integrin and increase the invasion of human breast and ovarian cancer cells. In addition, the expression of Akt2 but not of the other isoforms mimics the effect of invasiveness driven by the PI3K signaling in breast cancer cells, and the introduction of only kinase-dead Akt2, but not Akt1 or Akt3, prevents invasion induced by either activation of PI3K or overexpression of HER2 (Arboleda et al., 2003). Moreover, the antagonistic roles of Akt1 and Akt2 have been identified in cell motility and invasion of breast cancer cells (Irie et al., 2005; Toker and Yoeli-Lerner, 2006). Taken together, these data outline a role of Akt2 as a mediator of the PI3K-dependent cellular adhesion, motility and invasion. This distinct function of Akt2 might be linked to its specific localization adjacent to the collagen IV matrix during cellular attachment (Arboleda et al., 2003).

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ӨСУ ФАКТОРЫН ЕСКЕРТЕТІН В (Akt) ПРОТЕИНКИНАЗАСЫ

Аннотация. Ескертетін өсу факторы фосфоинозит 3-киназы (PI3K) / белгілі Akt активтендіруі арқылы пролиферацияны, жасушалардың өмір сүруін және сараланuын реттейді. Бұл сигналдық жолдың реттелуі – онкологиялық және метаболикалық бұзылыстарды қоса алғанда, жалпы адами ауруы болып саналады. Плазма мембранасында орналасқан рецепторлардың тирозинкиназаларын байланыстыру арқылы липидті киназ PI3K ретінде анықталған негізгі компонентті қоса алғанда өсу факторлары белсендіріледі. PI3K негізгі қозғалтқыш жүйке шеті Akt серин/тре протеинкиназасы немесе В протеинкиназасы болып табылады. Акт әртүрлі жасушалық белгілерді субстраттардың кең ауқымын фосфорлану арқылы түрлендіреді және оның қызметі қатаң түрде PI3K бақыланады. Akt плазма мембранасына ауыстыру кезеңі оны активтендірудің негізгі кезеңі болып табылады, ол Akt киназлы доменге фосфорлануына алып келеді және гидрофобты мотивтерді реттейді. Бұл учаскелердің екеуінің де фосфорлануы Akt толық белсендіру үшін қажет. Бұл мақалада біз PI3K-ге тәуелді ескертетін өсу факторының транслокациясы мен фосфорлануы арқылы Akt реттейтін механизмдерін сипаттаймыз.

Түйін сөздер: белгі беретін осу факторы, В протеинкиназасы, фосфорлану, киназдық домен.

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ПРОТЕИНКИНАЗА B (Akt), СИГНАЛИЗИРУЮЩАЯ ФАКТОР РОСТА

Аннотация. Сигнальный фактор роста регулирует пролиферацию, выживание и дифференцировку клеток путем активации фосфоинозитида 3-киназы (PI3K)/сигнальной Akt. Дерегулирование этого сигнального пути является распространенным заболеванием человека, включая рак и нарушения обмена веществ. Факторы роста путем связывания с их специфическими рецепторными тирозинкиназами, расположенными на плазматической мембране, набирают и активируют сигнальные факторы, включая ключевой компонент, идентифицированный как липидкиназа PI3K. Ключевым нижележащим эффектором PI3K является серин/тре протеинкиназа Akt или также известная как протеинкиназа B. Akt трансформирует множество клеточных сигналов путем фосфорилирования широкого спектра субстратов, и его активность строго контролируется PI3K. Шаг транслокации Akt к плазматической мембране является первичной стадией ее активации, приводящей к фосфорилированию Akt на киназном домене и регулирующему гидрофобному мотиву. Фосфорилирование обоих этих участков необходимо для полной активации Akt. В этой статье мы описываем механизмы того, как сигнализирующий фактор роста, зависящий от PI3K, регулирует Akt посредством его транслокации и фосфорилирования.

Ключевые слова: сигнальный фактор роста, протеинкиназа B, фосфорилирование, киназный домен.

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