Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

# Gene Section

## Review

# AKT1 (v-akt murine thymoma viral oncogene homolog 1)

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Published in Atlas Database: May 2009

Online updated version: http://AtlasGeneticsOncology.org/Genes/AKT1ID355ch14q32.html
DOI: 10.4267/2042/44725



## Identity

**Other names:** AKT; C-AKT; EC 2.7.11.1; MGC99656; PKB; PKB-ALPHA; PRKBA; RAC; RAC-ALPHA; RAC-PK-alpha

**HGNC (Hugo):** AKT1

**Location:** 14q32.33

**Note**

Location in the mouse: chromosome 12, 57.0 cM, 113892032 to 113912401 bp, complement strand.

For a comparison of the gene location among Homo sapiens, mouse and rat see: NCBI Map Viewer.

## DNA/RNA

### Description

The human AKT1 gene is composed of 14 exons spanning a genomic region of about 26.4 Kb. The open reading frame of the coding region is 1443 bp.

### Transcription

The human AKT1 coding sequence consists of 1443 bp from the start codon to the stop codon. Multiple alternatively spliced transcript variants have been found for this gene (Entrez Gene).

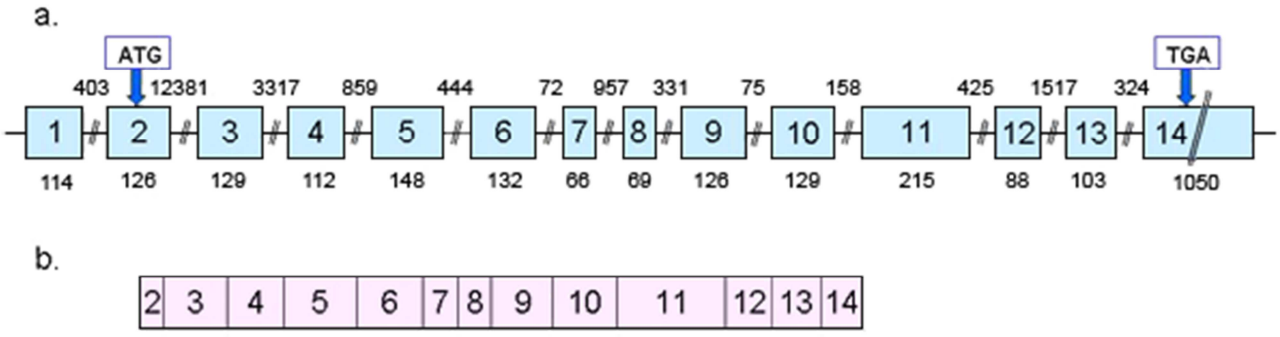
### Pseudogene

No pseudogene of AKT1 known.

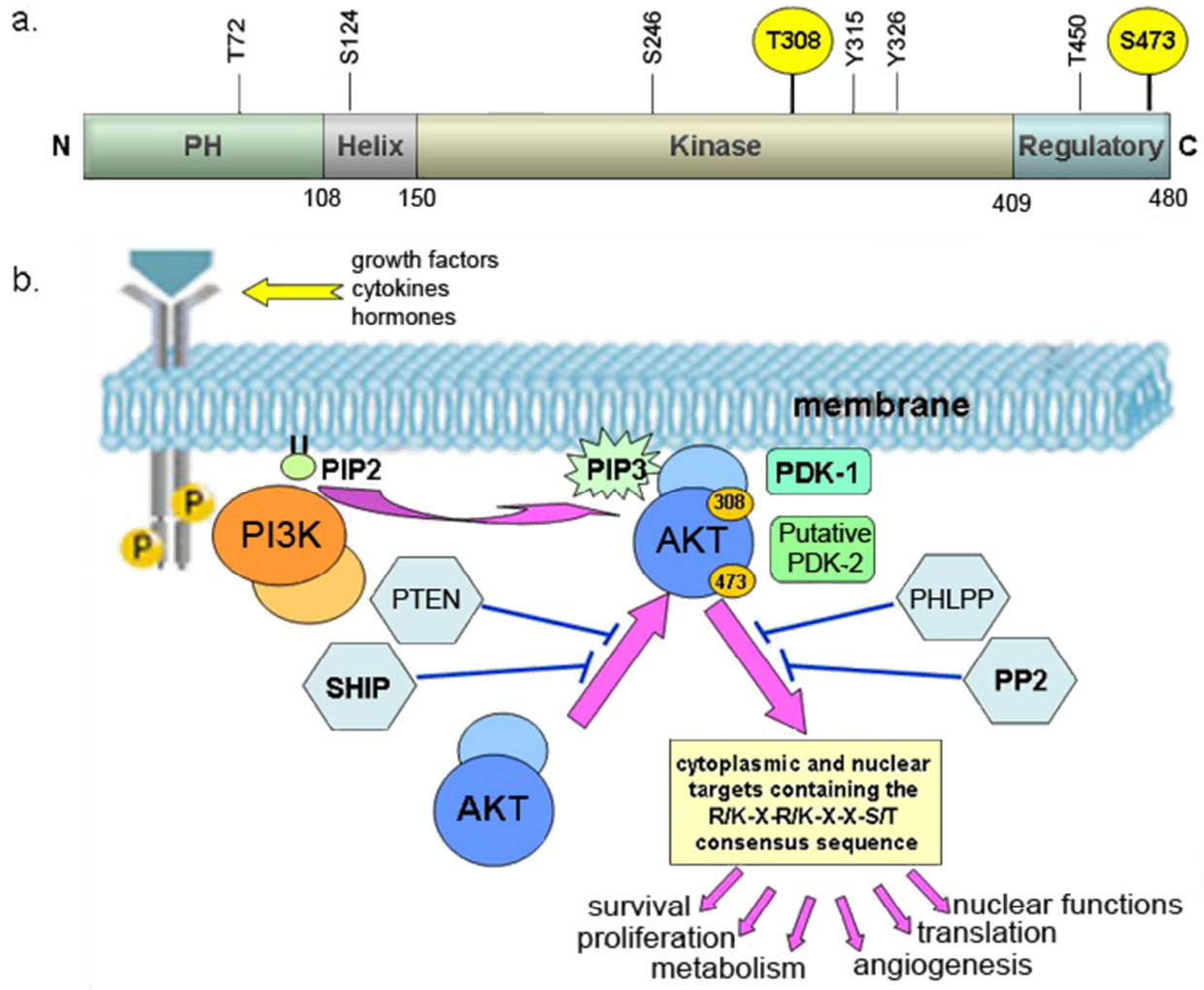
## Protein

**Note**

Although the AKT isoforms are activated in a similar manner and share the same downstream substrates, indicating functional redundancy of the AKT isoforms, their biological function is likely to be different in AKT-knockout mouse models. AKT1 mutant mice display developmental defects, showing decreased size in all organs and impaired placental development (Yang et al., 2004).




a. Genomic organization of human AKT1. The line indicates untranslated regions and boxes indicate coding regions (exon 1-14) of the gene. Exon and intron lengths (in bp) are reported in the upper and lower part of the diagram, respectively. The ATG transcription start site is located in exon 2 and the TGA termination codon is located in exon 14. b. mRNA of human AKT1.




a. Diagram of the human AKT1 protein in scale. The protein domains and their length (indicated by number of limiting residues) are reported. AKT1 contains a pleckstrin homology domain (PH), an helical region (Helix), a kinase domain (Kinase), and a regulatory motif (Regulatory). The two phosphorylation sites essential for complete activation of AKT1 (threonine 308, serine 473) are indicated in the diagram. C: carboxyl-terminal; N: amino-terminal.
b. Schematic representation of the AKT signaling activation and regulation.

AKT1 deficient mice exhibit perinatal morbidity with partial lethality between E13.5 and 3 weeks after birth and growth retardation. Surviving adults are fertile, but show 20% weight reduction accom-panied by reduced sizes of multiple organs, and enhanced apoptosis in some cell types. No effect seen on glucose metabolism. Moreover, AKT1/ AKT2 double-knockout mice display impeded adipogenesis, severe growth deficiency including impaired skin development, severe muscle atrophy, impaired bone development and die shortly after birth (Peng et al., 2003).

## Description

**Structure.** AKT1 protein consists of 480 amino acids, with a molecular weight of 55,686 Da. AKT1 is constituted by a PH domain, a short helical region, a catalytic kinase domain and a regulatory hydrophobic motif.

PH domain is a conserved domain of about 100 residues that occurs in a wide range of proteins involved as cytoskeletal constituents or in intracellular signaling; the structure of the PH domain consists of two perpendicular anti-parallel beta-sheets followed by a C-terminal amphipathic helix; the common fold of PH domains is electrostatically polarized. The PH domain recruits AKT to the plasma membrane by phosphoinositides binding and is required for activation.

The kinase domain has been evolutionarily conserved from Escherichia coli to Homo sapiens; conserved regions are: i) a glycine-rich stretch of residues in close proximity of a lysine amino acid (179, by similarity), involved in ATP binding; ii) an highly conserved activation loop, called T-loop, located between DFG and APE motifs, with a threonine residue important for enzyme activation; iii) a conserved aspartic acid (274, by similarity) as proton acceptor residue, important for the catalytic activity of the enzyme. The kinase domain catalyzes the transfer of the gamma-phosphoryl group from ATP to serine/threonine residues on a consensus

sequence on protein substrates, resulting in a conformational change affecting protein function, cellular location or association with other proteins (Knighton et al., 1991).

The carboxyl-terminal hydrophobic regulatory domain contains several proline-rich regions that potentially serve as protein-protein interaction sites with important roles in regulation of AKT1 activity; this region contains the 473 residue important for the activation process. This domain possesses the F-X-X-F/Y-S/T-Y/F hydrophobic motif, where X is any amino acid, that is characteristic of the AGC kinase family; in mammalian AKT isoforms, this motif is identical (FPQFSY) and is thought to be very important for the enzymatic activity. The conserved SH3-domain binding motif P-X-X-P in the regulatory region is involved in the interaction between AKT1 and its upstream tyrosine kinase Src (Jiang et al., 2003).

The crystallographic structure of AKT1 has been solved (PDB ID 3CQW, 3CQU).

**Activation.** The serine-threonine protein kinase AKT1 is a catalytically inactive cytoplasmic protein. AKT activation occurs by means of stimulation of the growth factor receptor-associated phosphatidylinositol 3-kinase (PI3K) and is a multi-step process that involves both membrane translocation and phosphorylation. When PI3K is activated by either growth factors, cytokines or hormones, PI3K generates 3'-phosphorylated phosphoinositides, i.e. phosphatidylinositol-3,4,5-trisphosphate ($PIP_3$) and phosphatidylinositol-3,4-bisphosphate ($PIP_2$) at the plasma membrane. Both phospholipids bind with high affinity to the PH domain, mediating membrane translocation of AKT. At the membrane, AKT1 is phosphorylated at threonine 308 by PDK1 (Andjelkovic et al., 1997; Walker et al., 1998) and at serine 473 by a second kinase identified with mTOR when bound to Rictor in the so called TORC2 complex (Santos et al., 2001; Sarbassov et al., 2005); however, it is still controversial if this second phosphorylation may occur by DNA-dependent protein kinase (Feng et al., 2004; Hill et al., 2002). Other kinases that have been reported to phosphorylate serine 473 are PKC (Kawakami et al., 2004), integrin-linked kinase (ILK) (Troussard et al., 2003; Lynch et al., 1999; Delcommenne et al., 1998), MAP kinase-activated protein kinase-2 (MK2) (Rane et al., 2001), PDK-1 (Balendran et al., 1999) or Akt itself (Toker et al., 2000). The full activation of AKT1 requires phosphorylation at both sites; threonine 308 phosphorylation increases the enzymatic activity up to 100-fold and serine 473 phosphorylation by a further 10-fold, thus both phosphorylation events enhance AKT1 activity by 1000-fold (Kumar et al., 2005; Alessi et al., 1996). The activation is rapid and specific, and it is abrogated by mutations in the AKT PH domain. Once activated, AKT1 dissociates from the membrane and phosphorylates targets in the cytoplasm and the cell nucleus.

Beside these essential activation sites, threonine 72 and serine 246 residues undergo auto-phosphoryla-tion (Li et al., 2006), serine 124 and threonine 450 residues are constitutively phosphorylated, while tyrosine 315 and 326 in the activation loop can be phosphorylated by Src kinase, maybe regulating AKT1 activity (Chen et al., 2001).

**Regulation.** AKT activation is inversely regulated by phosphatases: PH domain leucine-rich repeat protein phosphatase (PHLPP) dephosphorylates the serine 473 residue of AKT1 (Brognard et al., 2007), and protein phosphatase 2 (PP2) dephosphorylates the threonine 308 residue (Gao et al., 2005). PI(3,4,5)P3 is hydrolyzed by phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and Src homology domain-containing inositol phosphatases SHIP1/SHIP2. PTEN antagonizes PI3K activity by removing the phosphate at the D3 position generating PI(4,5)P2 (Maehama et al., 1998), while SHIP1/2 dephosphorylates the D5 position to produce PI(3,4)P2 (Deleris et al., 2003; Damen et al., 1996).

## Expression

AKT1 is the predominant isoform in the major part of tissues as determined by using quantitative RT-PCR (Yang et al., 2003) and is ubiquitously expressed in most tissues at high levels and in all the human cell types so far analyzed (Hanada et al., 2004; Zinda et al., 2001). A Northern blot analysis of AKT1 in rat tissues indicated lower expression levels in kidney, liver, and spleen (Coffer et al., 1991).

## Localisation

AKT1 protein is predominantly cytoplasmic; it has been found at the plasma membrane for its activation and activated AKT1 is able to translocate into the nucleus. AKT1 translocation into nucleus has been demonstrated in several cell lines in response to stimuli as after IGF-I treatment of NIH3T3 cells (Meier, 1997), NGF stimulation of PC12 cells (Xuan Nguyen et al., 2006; Borgatti et al., 2003), EPO in K562 cells and IGF-I or PDGF mitogen factors in MC3T3 (Neri et al., 2002). Also if AKT1 contains a sequence for nuclear export rich in leucine (Saji et al., 2005) and some proteins may have a role of localization signal for its intranuclear migration, a nuclear localisation sequence on AKT1 inside motif has not yet been identified.

## Function

AKT mediates many of the downstream events of the PI3K signal transduction pathway by its serine-threonine kinase activity. AKT exhibits tight control over cell viability and proliferation, having main role in apoptosis inhibition and promotion of cell cycle progression. AKT is involved also in differentiation; in nervous system development AKT is a critical mediator of growth factor-induced neuronal survival. Further, AKT mediates glucose metabolism, angiogenesis, translation, transcript-tional events, pre-mRNA splicing

and other important nuclear functions such as chromatin condensation and genes transactivation.

AKT exerts its kinase activity toward proteins containing the minimal consensus sequence R/K-X-R/K-X-X-S/T, where S or T are the phosphorylable residues. More subtle AKT preferences were also uncovered for other residues surrounding the phosphorylation site, such as a preference for T at -2 or a bulky hydrophobic residue at +1 (Manning et al., 2007). More than 400 different proteins contain-ing the consensus sequence for AKT phosphoryla-tion have been identified, also if many of them still have to be characterized (Nicholson et al., 2002; Obenauer et al., 2003). The heterogeneity of proteins potentially phosphorylated by AKT supports the key role of this kinase. Over 100 non-redundant AKT substrates are reported in the literature, of which 25% do not contain the minimal requirements for an AKT site. Around 40 substrates which mediate the pleiotropic AKT functions have been characterized (see table below).

**Apoptosis inhibition.** Survival factors can suppress apoptosis and enhance survival of cells by activating AKT, which inactivates components of the apoptotic machinery. AKT directly regulates apoptosis by phosphorylating and inactivating pro-apoptotic proteins such as bad, which controls release of cytochrome c from mitochondria, caspase-9, which after AKT dependent phospho-rylation promotes cell survival (Donepudi et al., 2002; Downward et al., 1999; Franke et al., 2003) and apoptosis signal-regulating kinase-1 (ASK1), a mitogen-activated protein kinase involved in stress- and cytokine-induced cell death that, once phosphorylated on serine 83, reduces apoptosis (Autret et al., 2008; Datta et al., 1997; Del Peso et al., 1997; Zha et al., 1996). The pro-survival proline-rich AKT substrate of 40kDa (PRAS40) can be phosphorylated on threonine 246, attenuating its ability to inhibit mTORC1 kinase activity (Van der Haar, 2007). PRAS40 appears to protect neuronal cells from apoptosis after stroke (Kovacina et al., 2003) and has been proposed to promote cell survival in cancer cells (Huang et al., 2005).

**Proliferation.** AKT can stimulate cell cycle progression through the inhibitory phosphorylation of the cyclin-dependent kinase inhibitors p21 and p27 (Viglietto et al., 2002; Liang et al., 2002; Shin et al., 2002; Zhou et al., 2001; Rossig et al., 2001). The AKT dependent inhibition of GSK3 stimulates cell cycle progression by stabilizing cyclin D1 expression (Diehl et al., 1998). AKT activation can promote progression through mitosis, even in the presence of DNA damage (Kandel et al., 2002); a mechanism explaining this observation is that AKT directly phosphorylates the DNA damage checkpoint kinase Chk1 on serine 280 (King et al., 2004), blocking checkpoint function by stimulating Chk1 translocation to the cytosol. With no K protein kinase-1 (WNK1) seems to be a negative regulatory element in the insulin signaling pathway that regulates cell proliferation. AKT phospho-rylates WNK1 on threonine 60 within the AKT consensus sequence (Vitari et al., 2004). The neuro-fibromatosis-2 (NF2) tumour-suppressor gene encodes an intracellular membrane-associated protein, called merlin, with growth-suppressive function. AKT phosphorylates merlin on threonine 230 and serine 315 residues, abolishing binding partners and leading to merlin degradation by ubiquitination (Tang et al., 2007).

**Metabolism.** AKT phosphorylates the GSK3alpha and GSK3beta isoforms, which are involved in metabolism regulation by decreasing glycogen synthesis and increasing glycolytic enzymes transcription (Jope et al., 2004; Kohn et al., 1996), thus relating AKT activation with high glycolysis efficiency in cancer cells (Warburg effect). AKT1 is also involved in tolerance of cells to nutrient depletion, allowing tumor progression under hypovascular conditions (Izuishi et al., 2000). The TBC1 domain family member 1 (TBC1D1), AKT substrate phosphorylated on threonine 590, may be involved in controlling GLUT1 glucose transporter expression through the mTOR/p70S6K pathway (Zhou et al., 2008). The Rab-GAP AS160 (also known as TBC1D4) has emerged as an important direct target of AKT involved in GLUT4 trans-location to the plasma membrane (Sano et al., 2003). In hepatocytes, AKT can also inhibit gluconeogenesis and fatty acid oxidation through direct phosphorylation on serine 570 of PGC-1alpha (Li et al., 2007), which is a gene coactivator with FoxO1 and other transcription factors.

**Angiogenesis.** AKT plays important roles in angiogenesis through effects in both endothelial cells and cells producing angiogenic signals. AKT activates endothelial nitric oxide synthase (eNOS) through direct phosphorylation on the serine 1179 site, resulting in increased production of nitric oxide (NO) in vascular endothelium, which stimulates vasodilatation, vascular remodelling and angiogenesis (Iantorno et al., 2007).

**Translation.** A well known AKT substrate is the serine/threonine kinase mammalian target of rapamycin (mTOR), which controls the translation of several proteins important for cell cycle progression and growth (Starkman et al., 2005; Varma et al., 2007). AKT can directly phospho-rylate and activate mTOR, as well as cause indirect activation of mTOR by phosphorylating two sites on the tuberous sclerosis complex 2 (TSC2) tumour suppressor protein, also called tuberin (Manning et al., 2002). mTOR forms two complexes: TORC1, in which mTOR is bound to Raptor, and TORC2, in which mTOR is bound to Rictor. In the TORC1 complex, mTOR signals to its downstream effectors S6 kinase/ribosomal protein and 4EBP-1/eIF-4E to control protein translation. In the TORC2 complex, mTOR can phosphorylate AKT itself thus providing a positive feedback on the pathway (Sarbassov et al., 2005). The mTOR effector S6 kinase-1 (S6K1) can also regulate the pathway by inhibiting the insulin receptor substrate (IRS), thus preventing

IRS proteins from activating the PI3K/AKT signaling (Harrington et al., 2004; Shah et al., 2004). The Y box-binding protein 1 (YB-1) is a DNA/RNA-binding protein through the Y-box motif in target sequences. AKT phosphorylates YB-1 on serine 102, leading to an enhancement of cap-dependent translation of multidrug resistance 1 (MDR1) gene (Bader et al., 2008).

**Nuclear functions.** Among the AKT substrates identified into cell nucleus, acinus is a nuclear factor required for chromatin condensation which induces resistance to caspases proteolysis and to apoptosis when phosphorylated by AKT on serine 422 and 573 (Hu et al., 2005). Phosphorylation of the murine double minute 2 (MDM2/HDM2 in humans) oncogene by AKT promotes its translocation to the nucleus, where it negatively regulates p53 function with subsequent modification of the cell cycle in relation to DNA repair mechanisms (Vousden et al., 2002; Mayo et al., 2005). Several Akt substrates are nuclear transcription factors: AKT blocks forkhead trans-cription factors (FKHR/FOXO1) and in particular the FoxO subfamily-mediated transcription of genes that promote apoptosis, cell cycle arrest and metabolic processes. When phosphorylated by AKT, FKHR are sequestrated in the cytoplasm thus inhibiting transcription (Nicholson et al., 2002; Datta et al., 1997). AKT can phosphorylate IKK, indirectly increasing the activity of nuclear factor kappa B (NF-kB), which stimulates the trans-cription of pro-survival genes and regulates the immunity response (Ozes et al., 1999; Romashkova et al., 1999; Verdu et al., 1999). The cAMP-response element binding protein (CREB) is a direct target for phosphorylation by AKT, occurring on a site that increases binding of CREB to proteins necessary for induction of genes containing cAMP responsive elements (CREs) in their promoter regions; CREB has been shown to mediate AKT-induced expression of antiapoptotic genes bcl-2 and mcl-1 (Du et al., 1998). AKT can regulate the telomerase activity necessary for DNA replication; recombinant AKT was found to enhance telomerase activity by phosphorylating the human telomerase reverse transcriptase (hTERT) subunit, which contains a consensus motif as AKT substrate. The helix-loop-helix transcription factor tal1, required for blood cell development, is specifically phosphorylated by AKT at threonine 90, causing its nuclear redistribution (Palamarchuk et al., 2005b). Insulin induces GATA2 phosphorylation on serine 401 by AKT. GATA2 transcription factor is an inhibitor of adipogenesis and activator of vascular cells. AHNAK is a protein of exceptionally large size localized into nuclei and able to shuttle between nucleus and cytoplasm; it is downregulated in several tumors (Amagai et al., 2004). It has been reported that in epithelial cells its extranuclear localization is regulated by AKT dependent phosphorylation (Sussman et al., 2001). ALY is a nuclear speckle protein implicated in mRNA export. The PI3K/AKT signaling regulates its subnuclear residency, cell proliferation, and mRNA export activities through nuclear AKT dependent phosphorylation on threonine 219 and phosphoinositide association (Okada et al., 2008). AKT specifically phosphorylates serine 350 of the Nur77 protein within its DNA-binding domain, decreasing its transcriptional activity by 50-85% and connecting the AKT axis with a nuclear receptor pathway (Pekarsky et al., 2001). The breast cancer susceptibility gene BRCA1 encodes a nuclear phosphoprotein that acts as a tumor suppressor; heregulin induces AKT-dependent phosphorylation of BRCA1, which has been implicated in altering its function (Altiok et al., 1999).

**Table. Characterized Akt substrates**

| SUBSTRATE | PHOSPHORYLABLE RESIDUES | REFERENCES |
|---|---|---|
| Bad* | S136 | Downward et al., 1999 |
| caspase 9* | S196 | Donepudi et al., 2002 |
| ASK1* | S83 | Autret et al., 2008 |
| PRAS40* | S246 | Kovacina et al., 2003 |
| Pdcd4 | S67, S457 | Palamarchuk et al., 2005a |
| tau | S214 | Kyoung Pyo et al., 2004 |
| MLK3 | S674 | Barthwal et al., 2003 |
| YAP | S127 | Basu et al., 2003 |
| p21* | T145, S146 | Rossig et al., 2001 |
| p27* | T157 | Shin et al., 2002 |
| GSK3α* | S21 | Jope et al., 2004 |
| GSK3β* | S9 | Jope et al., 2004 |
| Chk1* | S280 | King et al., 2004 |
| WNK1* | T60 | Vitari et al., 2004 |
| merlin | T230, S315 | Tang et al., 2007 |
| c-RAF* | S259 | Zimmermann et al., 1999 |
| B-RAF | S364, S428 | Guan et al., 2000 |
| TBC1D1 | T590 | Zhou et al., 2008 |
| TBC1D4* | S588, T642 | Sano et al., 2003 |
| PGC-1α | S570 | Li et al., 2007 |
| PFK2 | S478 | Hammerman et al., 2004 |
| ACL | T277 | Berwick et al., 2002 |
| eNOS* | S1179 | Iantorno et al., 2007 |
| YB1 | S102 | Bader et al., 2008 |
| mTOR | S2448, S2481 | Varma et al., 2007 |
| TSC2* | S939, T1462 (S1086/1088, T1422) | Manning et al., 2002 Inoki et al., 2002 |
| acinus | S422, S573 | Hu Y et al., 2005 |
| zyxin | S142 | Chan et al., 2007 |
| MDM2/HDM2* | S166, S186 | Mayo et al., 2001 |
| FKHR* | T32, S253, S256, S315 | Nicholson et al., 2002 |
| IKK* | T23 | Ozes et al., 1999 |
| CREB | S133 | Du et al., 1998 |
| hTERT | S227, S824 | Kang et al., 1999 |
| tal1 | T90 | Palamarchuk et al., 2005b |
| GATA-2 | S401 | Menghini et al., 2005 |
| AHNAK | S5535 | Sussman et al., 2001 |
| ALY | T219 | Okada et al., 2008 |
| SEK1 | S78 | Park et al., 2002 |
| AR factors | S210, S790 | Lin et al., 2001 |
| ER factors | S167 | Campbell et al., 2001 |
| Nur77 | S350 | Pekarsky et al., 2001 |
| BRCA1 | T509 | Altiok et al., 1999 |
| SRK | ? | Koh et al., 1999 |

* substrates assessed independently by multiple reports (Manning et al., 2007).

## Homology

**Homologs.** AKT belongs to the AGC protein kinase family, sharing a high similarity in the catalytic domain with more than 80 kinases from the AGC family (PhosphositePlus). Three isoforms, AKT1, AKT2 and AKT3, plus a fourth isoform defined AKTgamma1,

have been identified in humans. They are codified by different genes with 80% sequence homology.

The AKT isoforms share 80% homology in amino acid sequence.

In particular, the identity between each domain of the AKT isoforms ranges from 76% to 84% in the PH domain, from 87% to 90% in the catalytic domain, and from 66% to 76% in the C-terminal domain (Masure et al., 1999; Kumar et al., 2005). The AKT isoforms are identical in the ATP binding region, except for one residue: AKT1 A230 is conserved in AKT2 (A232), but switches in AKT3 (V228).

**Orthologs.** AKT is evolutionarily conserved in eukaryotes ranging from Caenorhabditis elegans to man. The amino acid identity between C. elegans and human AKT1 is around 60%; the mouse AKT1 is 90% homologous to human AKT1 at the nucleic acid level and 98% homologous at the amino acid level (Hanada et al., 2004; Bellacosa et al., 1993).

For details see: HomoloGene.

Also the phosphorylation sites on the AKT sub-strates are conserved amongst the orthologs from all mammals; this evolutionary conservation can be indicative of the relevance of the substrate toward the AKT cellular functions.

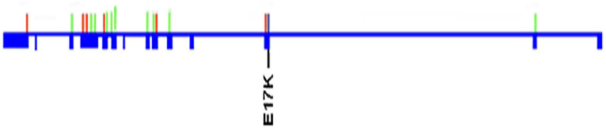
| AKT1 | Identity (%) | |
|---|---|---|
| Species | Protein | DNA |
| Homo sapiens | | |
| vs. Pan troglodytes | 99.2 | 98.8 |
| vs. Canis lupus familiaris | 97.0 | 91.3 |
| vs. Bos taurus | 96.2 | 90.8 |
| vs. Mus musculus | 98.3 | 90.9 |
| vs. Rattus norvegicus | 98.1 | 90.9 |
| vs. Gallus gallus | 96.0 | 76.9 |
| vs. Caenorhabditis elegans | 59.6 | 55.8 |

# Mutations

**Note**

Although mutation of AKT1 is rare, different types of AKT1 alterations are involved in several human diseases, especially in cancer.

No AKT1 mutations have been collected in the COSMIC database.




Schematic representation of SNPs and point mutation in the AKT1 gene. Missense (red), synonymous (green) and frameshift (blue) SNPs are indicated in the upper part; point mutation is reported in the lower part of the figure.
For details see: Single Nucleotide Polymorphism.

## Germinal

No germline mutations of AKT1 have been described.

## Somatic

**Amplification and LOH.** Amplification of AKT1 has been described in human gastric adenocar-cinoma, in lung and other cancers (Staal, 1987; Lockwood et al., 2008).

High level amplification in breast tissues and LOH in several tissues have been reported: CONAN: Copy Number Analysis.

**SNPs.** 17 esonic variations (missense, synonymous and frameshift SNPs) have been described.

Moreover, statistical significance for single markers and multilocus haplotypes has been reported for the association between the AKT1 gene variants in samples of families with schizophrenia using single-nucleotide polymorphisms (Schwab et al., 2005; Emamian et al., 2004).

**Point mutation.** The E17K mutation occurs in the lipid-binding pocket of AKT1 PH domain. Lysine 17 alters the electrostatic interactions of the pocket and forms new hydrogen bonds with a phosphoinositide ligand. This mutation activates AKT1 by means of pathological localization to the plasma membrane, stimulates downstream signaling, transforms cells and induces leukemia in mice. The E17K mutation occurs in a small percentage of human breast, ovarian, and colorectal cancers (Carpten et al., 2007). It has been found also in squamous cell carcinoma of the lung and in prostate cancer (Malanga et al., 2008; Boormans et al., 2008). Some authors suggested that this mutation may not play a crucial role in the development of the most types of human cancers (Kim et al., 2008).

# Implicated in

## Various cancers

**Prognosis**

Immunohistochemical analysis has been used to demonstrate prognostic significance of AKT1 activation. Phosphorylation of AKT1 at serine 473 has been associated with poor prognosis in cancer of the skin (Dai et al., 2005), pancreas (Yamamoto et al., 2004), liver (Nakanishi et al., 2005), prostate (Kreisberg et al., 2004), breast (Perez-Tenorio et al., 2002), endometrium (Terakawa et al., 2003), stomach (Nam et al., 2003), brain (Ermoian et al., 2002) and blood (Min et al., 2004). It has been reported that AKT phosphorylation on both serine 473 and threonine 308 sites is a better predictor of poor prognosis in tumors versus normal tissues than serine 473 alone (Tsurutani et al., 2006; Kornblau et al., 2006).

**Oncogenesis**

The PI3K/AKT pathway is a prototypic survival signaling that is constitutively activated in many types of cancer, due to AKT gene amplification or as a result of mutations in components of the signaling that

activates AKT. Once activated, signaling through AKT can be propagated to a diverse array of substrates. This pathway is an attractive therapeutic target in cancer because it serves as a convergence point for many growth stimuli, and through its downstream substrates,

controls cellular processes that contribute to cancer progression. Moreover, activation of the PI3K/AKT pathway confers resistance to many types of cancer therapy, and is poor prognostic factor for several tumors. Thus, combining conventional therapy with PI3K/AKT pathway inhibitors can overcome this resistance.

Hyper-activation of AKT1 has been found associated to several human cancers:

-Thyroid carcinoma

-Breast carcinoma

-Non-small cell lung carcinoma

-Gastric carcinoma

-Gastro-intestinal stromal tumors

-Pancreatic carcinoma

-Bile duct carcinoma

-Ovarian carcinoma

-Prostate carcinoma

-Renal cell carcinoma

-Acute and chronic leukemia

-Multiple myeloma

-Lymphoma

## Thyroid cancer

**Note**

Genetic alterations in the AKT pathway have been observed in anaplastic and follicular thyroid cancers, in particular AKT has been shown highly phosphorylated in thyroid cancer cell lines and human thyroid cancer specimens (Liu et al., 2008; Mandal et al., 2005). Activated AKT is common to both human and mouse follicular thyroid cancer and is correlated with increased cell motility in vitro and metastasis in vivo (Kim et al., 2005).

## Breast cancer

**Note**

Somatic mutation E17K occurs in the PH domain of AKT1 in 8% of human breast cancers (Carpten et al., 2007). Overexpression of cyclin D1 has been found in breast cancer; elevated cyclin D1 levels result in shortened cell cycle times and thereby contribute to tumor progression. AKT is involved in this mechanism by regulating cyclin D1 expression at transcription, translation and protein stability level (Nicholson et al., 2002). Anti-estrogens such as tamoxifen inhibit the growth of (estrogens receptors) ER-positive breast cancers by reducing the expression of estrogen-regulated genes. AKT, by activating ER, protects breast cancer cells from tamoxifen-induced apoptosis (Campbell et al., 2001). It has been shown that activation of AKT/mTOR promotes angiogenesis via HIF1alpha stabilization in breast cancer cells (Laughner et al., 2001). Recent studies have shown that AKT1 can attenuate breast cancer cell motility, whereas AKT2 enhances this phenotype. AKT1 blocks the migration of breast cancer cells through GSK3beta inactivation and transcription factor NFAT inhibition (Yoeli-Lerner et al., 2009).

## Lung cancer

**Note**

Although AKT1 mutations are apparently rare in

lung cancer (1.9%), the oncogenic properties of E17K-AKT1 may contribute to the development of a fraction of lung carcinoma with squamous histotype (Malanga et al., 2008). Adenocarcinomas of the lung commonly show an increase in the activity of PI3K/AKT signaling pathway. The simultaneous inhibition AKT1 siRNA and Bcl-xL function greatly enhanced the apoptotic response, suggesting that AKT1 and Bcl-xL control cell death in lung adenocarcinoma cells in a synergistic manner (Qian et al., 2009). AKT1 is overexpressed as a direct result of gene amplification in lung cancer, suggesting that amplification of this genome hotspot is a common mechanism of oncogene activation (Lockwood et al., 2008).

## Gastric carcinoma

**Note**

AKT1 gene amplification has been observed in gastric carcinoma. Most gastric adenocarcinomas arise as a longterm complication of Helicobacter pylori infection of the stomach; phosphorylation of AKT and its substrates is inducible by epithelial mitogens such as EGF, which is implicated in the pathogenesis of H. pylori gastritis (Ang et al., 2005). NF-KB activation was frequently observed in early-stage gastric carcinoma and was significantly correlated with better prognosis and Akt activation (Lee et al., 2005). AKT activation and LOH of PTEN play an important role in conferring a broad-spectrum chemoresistance in gastric cancer patients (Oki et al., 2005).

## Colorectal cancer

**Note**

The transforming E17K point mutation in the PH domain of AKT1 in human colorectal cancer (6%) has been identified (Carpten et al., 2007). The Src/PI3K/FAK/AKT pathway has been described as responsible of colon cancer cells metastatic adhesion (Thamilselvan et al., 2007). Cytoplasmic mislocalization of p27, caused by activated AKT1, and functional losses of p27 and p53 have been associated with poor prognosis and are involved in the development of various subtypes of colorectal cancer (Ogino et al., 2007). The inhibitor of the apoptosis protein (IAP) family member XIAP is essential for cell survival in colorectal cancer cells and is activated

through the AKT pathway. The AKT-XIAP up-regulation was shown to be correlated to colorectal cancer progression and may be a potential molecular target for therapy (Takeuchi et al., 2005).

## Glioblastoma and gliosarcoma

**Note**

AKT1 amplification and overexpression have been observed in human glioblastoma and gliosarcoma, a variant of glioblastoma multiforme characterized by two components displaying gliomatous or sarcoma-tous differentiation (Actor et al., 2002; Staal et al., 1987). Glioblastomas frequently carry mutations in PTEN gene, which tumor suppressor properties are closely related to its inhibitory effect on the AKT signaling (Knobbe et al., 2003).

## Pancreatic cancer

**Note**

It was reported that constitutively active AKT1 in mouse pancreas requires S6 kinase 1 for insulinoma formation (Alliouachene et al., 2008). AKT1 serine 473 may undergo both phosphorylation and O-GlcNAc modification, and the balance between these events may regulate murine beta-pancreatic cell apoptosis (Kang et al., 2008). All the AKT isoforms may have protective effects within the cell depending on the type of apoptotic stimuli in human pancreatic MiaPaCa-2 cells (Han et al., 2008). Overexpression of bcl-2 is common in pancreatic cancer, confers resistance to the apoptotic effect of chemo- and radiotherapy and is accompanied to increased activity of AKT as well as its downstream target IKK (Mortenson et al., 2007).

## Hepatocellular carcinoma (HCC)

**Note**

Hyper-activation of the AKT pathway frequently occurs in HCC (Roberts et al., 2005). It was reported that Bortezomib induces apoptosis in HCC cell lines by down-regulating phospho-AKT. Down-regulation of phospho-AKT may thus represent a biomarker for predicting clinical response to HCC treatment (Chen et al., 2008). Moreover, it was observed that a cancer stem cell population in HCC contributes to chemoresistance through preferential activation of AKT and bcl-2 cell survival response (Ma et al., 2008). Knockdown of insulin receptor substrate in primary human HCC HepG2 cell line resulted in reduction of insulin stimulated AKT1 phosphorylation at serine 473 and 50% reduction in the basal level of phosphorylated mTOR (Ser 2448), indicating a pivotal role of the AKT signaling in HCC (Varma et al., 2008). It was also presented that AKT1 was upregulated in HCC cells, and its active phosphorylated form was mainly located in the nucleus (Zhu et al., 2007).

## Ovarian cancer

**Note**

The transforming E17K point mutation in the PH domain of AKT1 in human ovarian cancer (2%) has been identified (Carpten et al., 2007). The AKT pathway plays an important role in cell prolifera-tion, migration, and invasion in ovarian cancer cells; particular importance has the signaling specificity of AKT1, as the inhibition of AKT1 is sufficient to affect these events (Meng et al., 2006; Kim et al., 2008; Gu et al., 2008).

## Prostate cancer

**Note**

Increased AKT1 kinase activity was reported in more than 50% of prostate carcinomas. The androgen receptor (AR) factors phosphorylated by AKT lead to inhibition of their activity and blockade of androgen-induced apoptosis in a prostate cancer cell line (Lin et al., 2001). A study of prostate cancer indicates that AKT is involved more in cancer progression than initiation. The E17K mutation was identified in clinical prostate cancer samples. The mutation was mutually exclusive with respect to PTEN inactivation and PI3K activation; it was suggested that tumors carrying the AKT1 mutation may follow a more favourable clinical course (Boormans et al., 2008).

## Renal cancer

**Note**

Phospho-AKT expression is significantly increased in renal carcinoma cells. A decreased expression of PTEN may be an underlying mechanism for AKT activation and thus an AKT inhibitor may be a therapeutic option for the subset of renal cell carcinoma patients with elevated AKT activity (Hara et al., 2005).

## Melanoma

**Note**

Common mutations and/or deregulated expression of proteins of the AKT signaling, as B-RAF, PTEN, MDM2 and AKT itself, were identified in melanoma (Ch'ng et al., 2009). AKT-dependent phosphorylation of hTERT increases telomerase activity in melanoma cells, indicating that AKT promotes the immortalization of cancer cells by preventing replicative senescence (Kang et al., 1999).

## Acute leukemia

**Note**

The AKT signaling is important for governing cell survival and proliferation in acute myeloid leukemia (AML). The level of AKT phosphorylation on threonine 308 but not on serine 473 is associated with high-risk cytogenetics and predicts poor overall survival in AML (Gallay et al., 2009). AKT activation critically mediates survival during the early phase of drug (i.e. imatinib) resistance development (Burchert et al., 2005). PTEN phosphorylation, associated with increased AKT phosphorylation, is found in 75% of AML (Cheong et al., 2003a). Also SHIP1 alteration is shown to result in AKT activation in AML cells (Luo et

al., 2003). AKT constitutive activation is observed in more than 50% of AML cases and correlates with chemotherapy resistance and poor prognosis (Min et al., 2003; Grandage et al., 2005; Martelli et al., 2007). In acute leukemias, AKT

activation gives rise to the upregulation of several downstream targets as FoxO transcription factors in AML patients with poor prognosis (Tamburini et al., 2007; Cheong et al., 2003b), Bad, p27, GSK3beta, IKK, p70S6K and 4E-BP1 in AML blasts (Zhao et al., 2004; Guzman et al., 2001; Xu et al., 2003).

AKT signaling plays an important role in cell survival mechanisms in acute promyelocytic leukemia (APL) (Billottet et al., 2009); recent advances have defined a novel PML/PTEN/ AKT/mTOR/FoxO signaling network (Ito et al., 2009). The promyelocytic leukemia protein (PML) has established activities as a potent repressor of proliferation and oncogenic transformation, a promoter of apoptosis, an inducer of senescence, and may act as angiogenesis inhibitor. PML tumour suppressor prevents cancer by inactivating phospho-AKT inside the nucleus and suppressing apoptotic rescue (Culjkovic et al., 2008).

In acute lymphoblastic leukemia (ALL) cell lines such as Jurkat T cells, PTEN is deleted thus activating the AKT pathway and promoting survival (Xu et al., 2002; Uddin et al., 2004). In addition, an activating mutation of Notch1 receptor in ALL cells is found to inhibit PTEN expression with subsequent AKT activation (Palomero et al., 2007).

## Chronic leukemia

**Note**

Chronic myelogenous leukemia (CML) is caused by BCR-ABL fusion gene product, that has constitutive tyrosine kinase activity and evokes the PI3K/AKT signaling pathway (Steelman et al., 2004). AKT is constitutively active in primary CML cells of both the chronic phase and blast crisis as well as in CML cell lines (Kawauchi et al., 2003). Introduction of a dominant-negative kinase-deficient AKT mutant (K179M) inhibits leukemo-genesis in murine cells, indicating an important role of AKT in transformation with BCR-ABL through the possible effectors FoxO, MDM2, GSK3beta, S6K and 4EBP-1 (Skorski et al, 1997; Kharas et al., 2005). Furthermore, AKT-dependent phosphoryla-tion of FoxO3A is required for maintaining the leukemic phenotype (Birkenkamp et al., 2007).

## Myeloma

**Note**

In both myeloma cell lines and primary cells IL-6 and IGF-1 activate the PI3K/AKT pathway accompanied by enhanced phosphorylation of downstream targets such as Bad, GSK3beta, and FoxO (Hideshima et al., 2001; Tu et al., 2000; Hsu et al., 2002). The expression of CD45 in myeloma cells negatively regulates the responsiveness to IGF-1 stimulation that leads to AKT activation (Descamps et al., 2004). Furthermore, IL-6 and IGF-1 both upregulate telomerase activity, which is usually coupled with cell division, mediated by AKT signaling (Akiyama et al., 2002). Constitutive phosphorylation of AKT has been reported in primary samples from patients with myeloma (Pene et al., 2002). In addition, inhibition of mTOR induces prevention in tumor proliferation and angiogenesis in myeloma cells associated with high levels of AKT activation (Frost et al., 2004).

## Lymphomas

**Note**

AKT activation has been demonstrated in a variety of B-cell non-Hodgkin's lymphomas (NHL) including Follicular Lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), marginal zone B-cell lymphoma and Mantle Cell Lymphoma (MCL) (Rudelius et al., 2006; Dal Col et al., 2008). Constitutive phosphorylation of AKT on serine 473 has been found also in peripheral leukemia cells of T-cell large granular lymphocytic leukemia (T-LGL) (Schade et al., 2006). Constitutive phosphorylation of AKT, GSK3beta, and mTOR substrates such as S6K and 4E-BP1 was demonstrated in Hodgkin's lymphoma (HL) cell lines, suggesting that the AKT pathway plays a crucial role in survival of HL cells (Dutton et al., 2005). Moreover, proteomic analysis of FL tissues showed overexpression of phospho-AKT on serine 473 (Gulman et al., 2005). In primary DLBCL samples, there is a correlation between poor prognosis and constitutive activation of AKT (Uddin et al., 2006; Ogasawara et al., 2003). In primary samples from anaplastic large cell lymphoma (ALCL) patients, around half of ALCLs exhibit constitutive phosphorylation of AKT on serine 473 and the AKT target p27 is downregulated in ALCL cell lines (Rassidakis et al., 2005). Moreover, mTOR, S6K and 4E-BP1 are constitutively phosphorylated in cell lines and in tissue samples from ALCL patients (Vega et al., 2006), indicating that the AKT pathway may be implicated in cell proliferation and survival of ALCL tumors. AKT and its downstream targets, including GSK3, FoxO3A, p27, MDM2, Bad, p70S6K and 4E-BP1, have been shown to be constitutively phosphorylated in both primary MCL cells and MCL cell lines (Rudelius et al., 2006). AKT is likely to be more active in blastoid MCL variants than in typical MCL, suggesting that the AKT pathway plays a critical role in pathogenesis in aggressive MCL cases. Constitutive AKT activation has been demonstrated in adult T-cell leukemic (ATL) cells as well as in ATL cell lines. HSP90, a chaperone protein for AKT, and the mTOR pathway are required for cell proliferation and survival in primary ATL samples, suggesting a crucial role for the AKT/mTOR axis in ATL expansion (Kawakami et al., 2007). B-cell antigen receptor (BCR)

stimulation has been shown to induce AKT phosphorylation on serine 473 (Poggi et al., 2008; Longo et al., 2007). In addition, CpG-oligodeoxynucleotide (CpG-ODN) stimulates leukemia cell proliferation accompanied by upregulation of AKT phosphorylation on 473 residue in B-CLL patients with poor prognosis (Longo et al., 2008). Therefore, AKT activation seems to be involved in CLL B-cell expansion.

### Various diseases

**Note**

Alteration of AKT activity is associated with several human diseases, including atherosclerosis, cardiovascular disease, Alzheimer disease, schizophrenia and diabetes.

### Atherosclerosis

**Note**

Oxidized low-density lipoproteins LDLs activate the PI3K/AKT network in macrophages/foam cells (Biwa et al., 2000). The amount of phosphorylated AKT and other phosphorylated effector proteins as S6K, S6, GSK3beta and FKHR was found to be reduced in atherosclerotic lesions.

### Cardiovascular disease

**Note**

The first report on a role of the PI3K/AKT pathway in the control of cell and organ size was published more than 10 years ago (Leevers et al., 1996). AKT signaling is relayed via mTOR to control the heart size. The cardiomyocyte-specific inactivation of the lipid phosphatase PTEN and subsequent AKT hyper-activation also triggers heart hypertrophy and culminates in reduced cardiac contractility (Crackower et al., 2002). AKT is involved in the therapy for ischemic limb or heart (Huang et al., 2009; Kruger et al., 2009). Moreover, long-term activation of AKT/mTOR signaling links diet-induced obesity with vascular senescence and cardiovascular disease (Wang et al., 2009).

### Alzheimer disease

**Note**

Microtubule-associated protein tau contains a consensus motif for AKT encompassing the double phospho-epitope (T212/S214). AKT dependent phosphorylation of tau occurs in vitro at both threonine 212 and serine 214 and may play specific roles relevant to Alzheimer disease and other neurodegenerations (Ksiezak-Reding et al., 2003). Modulators of the PI3K pathway might be reduced during aging leading to a sustained activation of GSK3beta, which in turn would increase the risk of tau hyper-phosphorylation (Mercado-Gomez et al., 2008). In primary cultures, AKT selectively phosphorylates tau at serine 214, raising the possibility that 214 residue may participate in AKT-mediated anti-apoptotic signaling (Kyoung Pyo et al., 2004).

### Schizophrenia

**Note**

Association between schizophrenia and an AKT1

haplotype associated with lower AKT1 levels and a greater sensitivity to the sensorimotor gating-disruptive effect of amphetamine, conferred by AKT1 deficiency, has been described. Alterations in AKT1/GSK3beta signaling contribute to schizophrenia pathogenesis and AKT1 gene may confer potential schizophrenia susceptibility. Consistent with this proposal, it has been shown that haloperidol induces a stepwise increase in regulatory phosphorylation of AKT1 in the brains of treated mice, that could compensate for an impaired function of this signaling pathway in schizophrenia (Emamian et al., 2004).

### Diabetes type 2

**Note**

AKT is involved in the pathomechanism of diabetes as it determines beta-cell apoptosis of Langerhans islets and insulin sensitivity of the cells (Cseh et al., 2009; Schulthess et al., 2009). It has been reported that alterations of the AKT/mTOR or the AKT/PRAS40 axis contributes to a diabetic phenotype (Marshall et al., 2006; Nascimento et al., 2006). AKT is required for the metabolic actions of insulin; muscle cells from type 2 diabetic patients displayed defective insulin action and a drastic reduction of insulin-stimulated activity of all AKT isoforms, in particular with altered AKT1 phosphorylation on threonine 308 residue (Cozzone et al., 2008). Insulin resistance can be induced by stimulating the degradation of important molecules in the insulin signaling pathway as AKT1 (Wing et al., 2008).

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*This article should be referenced as such:*

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