AKT1S1 (AKT1 substrate 1 (proline-rich))
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Abstract
Review on AKT1S1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Keywords
AKT1S1, cancer, type 2 diabetes

Identity
Other names
Lobe
PRAS40
HGNC (Hugo)
AKT1S1
Location
19q13.33

Akt1 substrate 1 (AKT1S1), also known as proline-rich Akt substrate of 40-kDa (PRAS40) is a component of the Akt and mammalian target of rapamycin complex 1 (mTORC1) signaling cascades (Nascimento and Ouwens, 2009; Wang et al., 2012; Wiza et al., 2012). AKT1S1 can act as a negative regulator of the mTORC1 complex, and binds YWHAZ (14-3-3) when phosphorylated (Nascimento and Ouwens, 2009; Wang et al., 2012; Wiza et al., 2012). Several tumors and tumor cell lines display increased levels of phosphorylated AKT1S1 (Andersen et al., 2010; Huang and Porter, 2005), but it is incompletely understood to what extent AKT1S1 participates in tumorigenesis. Finally, AKT1S1 function is critical for the regulation of insulin sensitivity in skeletal muscle (Wiza et al., 2014; Wiza et al., 2013a).

Figure 1. Genomic location of the AKT1S1 gene at chromosome 19.
AKT1S1 (AKT1 substrate 1 (proline-rich))

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Figure 2. AKT1S1 transcript variants and isoforms.

DNA/RNA

Description
The gene for AKT1S1 spans a genomic region of 9324 bases, and is composed of seven exons.

Transcription
The gene encodes five transcript variants, which result in two protein isoforms. The longest one, transcript variant one, differs from the other variants in the 5' untranslated region and results in the 276 amino acid protein isoform A. Transcript variants 2-5 all result in the 256 amino acid protein isoform B. The gene for PRAS40 is ubiquitously expressed, but there is no information on changes in the expression of the various transcript variants among tissues and organs.

Protein

Note
The protein encoded by the AKT1S1 gene has been identified as YWHAZ (also known as 14-3-3) binding protein in lysates from PC12 cells treated with epidermal growth factor or nerve growth factor, and was termed p39 (Harthill et al., 2002). This protein is identical to the YWHAZ-binding protein 'proline-rich Akt-substrate of 40-kDa' purified from insulin-treated hepatoma cells (Kovacina et al., 2003), and the nuclear phosphoprotein AKT1S1 purified from HeLa cells (Beausoleil et al., 2004). Furthermore, AKT1S1 is a component of the cytosolic mammalian target of rapamycin complex 1 (mTORC1) (Fonseca et al., 2007; Oshiro et al., 2007; Sancak et al., 2007; Vander Haar et al., 2007; Wang et al., 2007), and a nuclear complex containing the ribosomal protein L11 (RPL11) (Havel et al., 2014).

Description
The AKT1S1 proteins occur as two single polypeptide chain proteins of 276 (isoform A) and 256 (isoform B) amino acids, respectively. Isoform A differs from isoform B by a 20 amino acid extension at the amino terminus. Both isoforms share multiple conserved regions. At the amino terminus there are two proline-rich stretches with an undefined function. These are followed by two short sequences, the TOS- and RAIP-motif that mediate the interaction with mTORC1 (Fonseca et al., 2007; Oshiro et al., 2007; Vander Haar et al., 2007; Wang et al., 2007). The FVMDE-stretch (amino acids 149-153 of isoform A and amino acids 129-133 of isoform B) represents the TOS motif, while the KSLP-stretch (amino acids 202-205 of isoform A and 182-185 of isoform B) resembles the RAIP-motif. Furthermore, the proteins contain a leucine-enriched nuclear export sequence (amino acids 238-247 of isoform A and amino acids 218-227 of isoform B) (Havel et al., 2014; Wiza et al., 2013b). Finally, AKT1S1 is phosphorylated on multiple sites (Wiza et al., 2012) (Figure 3). While Akt, Pim-1 and AGC-kinase have been linked to the phosphorylation of Thr266/Thr246 (isoform A and B, respectively), all other phosphorylations on AKT1S1 have been ascribed to mTORC1 (Figure 3).

Expression
The protein shows a ubiquitous expression, but there is no information available regarding the protein abundance of the two isoforms in various tissues and organs.

Localisation
The protein is found both in the cytosol and in the nucleus. The transport from the nucleus to the cytosol is mediated by the leucine-enriched nuclear export sequence at the carboxy terminus of the protein (Havel et al., 2014; Wiza et al., 2013b).

Function
Regulation of mTORC1 activity
AKT1S1 acts as an inhibitor of mTORC1 activity (Wiza et al., 2012). Phosphorylation of AKT1S1 results in the dissociation of the AKT1S1 from raptor within the mTORC1 complex thereby promoting the activity of mTORC1 (Oshiro et al., 2007; Sancak et al., 2007; Vander Haar et al., 2007). However, knock-down of AKT1S1 impairs the phosphorylation of mTORC1-substrates in certain cell types, suggesting that AKT1S1 is also important for mTORC1 signaling via mechanisms which are still incompletely understood (Fonseca et al., 2007; Hong-Brown et al., 2010; Wiza et al., 2013a).
Nucleolar stress response
Nuclear AKT1S1 binds to the ribosomal protein L11 (RPL11) (Havel et al., 2014). This interaction is dependent on the phosphorylation of Ser221 and Thr246 within AKT1S1 (Havel et al., 2014). RPL11 has been linked to the inhibition of the E3 ubiquitin ligase HDM2. This results in increased p53 protein stability and activation of the nucleolar stress response pathway, which is defined as the activation of a specific transcriptional program resulting in cell cycle arrest, apoptosis or senescence. The activation of this pathway is prevented when RPL11 is bound to AKT1S1 (Havel et al., 2014).

Cell survival
Akt1S1 protects neurons against cell death following spinal cord injury (Saito et al., 2004). Overexpression of AKT1S1 in rats reduces infarct size following cerebral ischemia (Saito et al., 2006; Yu et al., 2008).

Proteasome activity and insulin sensitivity
The silencing of AKT1S1 promotes the degradation of insulin receptor substrate 1 (IRS1) in skeletal muscle through activation of the proteasome (Wiza et al., 2013a). As a consequence, the insulin-mediated activation of IRS1/Akt signaling pathway regulating glucose uptake is impaired (Wiza et al., 2013a). Conversely, overexpression of AKT1S1 inhibits proteasome activation and increases IRS1 stability (Wiza et al., 2014). This results in increased insulin sensitivity even under conditions of insulin resistance. Overexpression of AKT1S1 improves insulin signaling via the IRS1/Akt-axis in the heart and liver of a high-fat diet mouse model for insulin resistance (Völlkers et al., 2014).

Homology
AKT1S1 homologs in higher species are almost identical to human AKT1S1 with conservation of the regulatory domains and phosphorylation sites. In lower species, like amphibians, fish, and insects, proteins almost identical to the carboxy terminus of human AKT1S1 have been reported (Wiza et al., 2012). These proteins show conservation of the TOS- and RAIP-motif as well as of the key phosphorylation sites equivalent to Ser183 and Thr246 of human AKT1S1. Importantly, in D. melanogaster, dPRAS40 is also a component of the dTORC1-complex, indicating that it is appropriate to consider the variants found in these lower species as homologs for human AKT1S1 (Pallares-Cartes et al., 2012; Sançak et al., 2007; Vander Haar et al., 2007).

Mutations
No specific mutations in AKT1S1 have been associated with pathological conditions.

Implicated in
Various cancers
Multiple cancers and cancer cell lines display elevated levels of (phosphorylated) AKT1S1 (Huang and Porter, 2005; Jiang et al., 2014). The elevated levels of phosphorylated AKT1S1 are mostly found in associated with increased activity of kinases regulating the phosphorylation of AKT1S1, such as Akt, Pim-1 and mTORC1. Nevertheless, some of the cellular functions of AKT1S1, such as the regulation of the nucleolar stress response, proteasome activity and cell survival, suggest that AKT1S1 may participate in tumor progression. Finally, pharmacological studies have identified phosphorylated AKT1S1-Thr246 as suitable biomarker to predict the sensitivity to Akt-inhibitors in multiple cancers (Andersen et al., 2010; Madhunapantula et al., 2011).

Meningioma
Immunohistochemical examination of 25 WHO grade I and 25 WHO grade II meningiomas showed that 56% and 36% of the tumors were positive for AKT1S1-Thr246 (Johnson et al., 2009).

Melanoma
Phosphorylation of AKT1S1 was increased during melanoma tumor progression and closely related to elevated Akt3 activity (Madhunapantula et al., 2007). Knock-down of AKT1S1 decreased anchorage-independent growth and increased apoptosis in melanoma cell lines (Madhunapantula et al., 2007).

Non-small-cell lung cancer
In radiation-resistant non-small cell lung cancer cells, phosphorylation of AKT1S1 promotes the formation of a complex with YWHAZ and FOXO3, and the translocation of this trimeric complex from the nucleus to the cytosol (Kim et al., 2011). This translocation prevents the induction of pro-apoptotic genes by FOXO3, such as Bim and FasL. Treatment
with PIM-1 kinase inhibitors reduces the levels of phosphorylated AKT1S1 thereby increasing the amount of nuclear FOXO3 and the radiation sensitivity of the non-small cell lung cancer cells (Kim et al., 2013; Kim et al., 2011).

**Gastric cancer**

Immunohistochemical examination of 114 gastric cancer tumors showed that 45% of the tumors were positive for phosphorylated AKT1S1-Thr246. Furthermore, phosphorylated AKT1S1-Thr246 associated with malignant progression and poor prognosis of the patients (Lu et al., 2014).

**Type 2 diabetes**

The insulin-mediated phosphorylation of AKT1S1 on Ser183 and Thr246 in skeletal muscle is increased after weight loss in obese patients with type 2 diabetes, indicating impaired phosphorylation of AKT1S1 in patients with type 2 diabetes (Jazet et al., 2008; Nascimento et al., 2010).

**Diabetic nephropathy**

Glucose-induced phosphorylation of AKT1S1 on Thr246 associates with mesangial cell hypertrophy in a streptozotocin-induced rat model for type 1 diabetes, and lipid droplet accumulation in human kidney cells (Dey et al., 2010; Hao et al., 2014).

**Diabetic cardiomyopathy**

Overexpression of AKT1S1 protects against the development of diabetic cardiomyopathy in mice hearts by inhibition of hypertrophy and improved insulin signaling (Völkers et al., 2014).

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