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SH3PXD2A (SH3 and PX domains 2A)

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Abstract

The TKS5 protein, encoded by the gene SH3PXD2A, is a scaffolding protein essential for the formation of podosomes and invadopodia in untransformed cells and cancer cells, respectively. Podosomes and invadopodia (which collectively are termed invadosomes) are actin-rich cellular protrusions capable of secreting proteolytic enzymes that can degrade the extracellular matrix. These structures are thought to regulate cellular migration and invasion, as well as adhesion and the release of growth factors. In the context of cancer, TKS5-dependent invadopodia activity has been shown to play important roles in tumor growth and metastasis in various cancer types. Multiple isoforms of TKS5 exist due to alternative mRNA splicing and promoter usage.

Keywords
SH3PXD2A; TKS5; podosomes; invadopodia; metastasis.

Identity

Other names: TKS5, FISH, SH3MD1, KIAA0418
HGNC (Hugo): SH3PXD2A
Location: 10q24.33

DNA/RNA

Description
The SH3PXD2A gene is located on chromosome 10 (10q24.33). It contains 15 exons.

Transcription
The full-length SH3PXD2A transcript is 11264 nt in length. Multiple TKS5 isoforms arise as a result of alternative mRNA splicing involving exons 7 and 10, and alternative use of transcription start sites.

Protein

Description
The full-length SH3PXD2A transcript (TKS5-LONG or TKS5-ALPHA) is transcribed from a promoter upstream of exon 1 and is translated into a 150 kDa protein that contains a Phox-homology (PX) domain in the N-terminus and five Src homology 3 (SH3) domains in the C-terminus. The shorter isoforms that arise from downstream transcription start sites lack the PX domain but retain the five SH3 domains. Because the PX domain is required for binding to the cell membrane, full-length TKS5 is able to localize to invadoposome foci but the short isoforms cannot.

Expression
TKS5 expression is detected in many tissue types, including brain, lung, liver, heart, skeletal muscles, and, kidneys, but was low in spleen and absent in testis (Lock et al., 1998). Tks5 has also been detected in many cell types, including macrophages, myoblasts, neural crest cells, osteoblasts, and neurons (Burger et al., 2011; Thompson et al., 2008; Murphy et al., 2011; Oikawa et al., 2012; Santiago-Medina et al. 2015).
The SH3PX2A locus encodes multiple TKS5 isoforms as a result of alternative splicing at exons 7 and 10 as well as alternative promoter usage. Genomic information was obtained from the UCSC genome browser (http://genome.ucsc.edu/). Short-form Tks5 (Tks5-short and Tks5-beta) have been reported by Li et al. (2013) and Cejudo-Martin et al. (2014).

**Localisation**
Cytoplasmic and at invadosome foci.

**Function**
TKS5 was initially identified as a substrate for SRC (Lock et al., 1998), and was subsequently shown to play a critical role in invadosome formation in multiple cell types (Courtneidge, 2011; Murphy and Courtneidge, 2011; Paz et al., 2013). Full-length TKS5 functions as an adaptor for recruiting other proteins to the cell membrane for invadosome formation. The recruitment of TKS5 to the cell membrane depends on its PX domain and phosphorylation by Src (Abram et al., 2003). It has been proposed that phosphorylation of TKS5 releases its PX domain from intramolecular interaction and allows TKS5 to bind to cell membrane phosphatidylinositol lipids, such as phosphatidylinositol-3,4-bisphosphate (PI(3,4)P2) (Abram et al., 2003; Oikawa et al., 2008). At the cell membrane, TKS5 is thought to interact with multiple components of invadosomes either directly or indirectly, and thereby mediates invadosome formation and maturation (Sharma et al., 2013). These interacting partners includes adaptor proteins and actin regulatory proteins, such as NCK1, NCK2, GRB2, CTTN (Cortactin), WASL (N-WASP), ACTR2/ACTR3 (Arp2/3) complex, and ARHGAP35 (p190RhoGAP) (Crimaldi et al., 2009; Oikawa et al., 2008; Stylli et al., 2009). TKS5 also interacts with NOXA1 and CYBA (p22phox), which are components of the NADPH oxidase complex, and thereby promotes reactive oxygen species (ROS) production by NOX enzymes at invadosomes (Diaz et al., 2009; Gianni et al., 2010; 2009). ROS have been shown to facilitate invadosome formation by maintaining or amplifying the phosphorylation of TKS5. As such, TKS5 is thought to promote invadosome formation via ROS in a positive feedback loop.

The full-length TKS5 mRNA encodes a protein that contains a PX domain and five SH3 domains, as well as proline-rich regions (PxxP) and Src phosphorylation sites (Y). The various short isoforms lack the PX domain.
Finally, TKS5 has also been shown to interact with members of the ADAM family metalloproteases, specifically ADAM12, ADAM15, ADAM19 (Abram et al., 2003). It is believed that Tks5 recruits these proteases to the invadosome foci for processing growth factors and regulating cell motility. For example, ADAM12 has been shown to promote ectodomain shedding of HBEGF (heparin-binding EGF-like growth factor) and enhance invadopodia formation in cancer cells (Diaz et al., 2013).

In the context of cancer, TKS5-dependent formation of invadopodia is thought to promote metastasis by mediating local tumor invasion and intravasation at the primary site, as well as extravasation and colonization at the distant site (Murphy and Courtneidge, 2011; Paz et al., 2014). In the context of normal development, TKS5-dependent podosomes are important for mediating cell migration during embryogenesis. Knockdown of Tks5 in zebrafish led to impaired dorsal-ventral migration of neural crest cells and defective craniofacial structures and pigmentation (Murphy et al., 2011). Similarly, genetic deletion of Tks5 in mice led to complete cleft of the secondary palate and neonatal death (Cejudo-Martin et al., 2014). In addition, study in Xenopus showed that Tks5-dependent podosomes are also required for the migration of neuronal growth cones (Santiago-Medina et al., 2015).

While most studies have focused on full-length TKS5, shorter isoforms of TKS5 that lack the PX domain have been reported (Lock et al., 1998; Li et al., 2013; Cejudo-Martin et al., 2014).

There are few reports on the functions of these short isoforms.

Experiments in mouse lung cancer cell lines showed that overexpression of a short isoform (Tks5-short) suppressed invadopodia function by disrupting the stability of invadopodia (Li et al., 2013). In addition, overexpression of a short-form equivalent protein, ΔPX-Tks5, in Xenopus neural crest cells inhibited invadopodia functions and impaired motoneuron axon extension into the peripheral myotomal tissue in Xenopus embryos (Santiago-Medina et al., 2015). These data suggest that the short forms of TKS5 can function as negative regulators of invadosomes. At the mRNA level, the transcription of full-length Tks5 has been shown to be synergistically inhibited by the developmental regulators NKX2-1, FOXA2, and CDX2 in lung adenocarcinoma (Li et al., 2015). Furthermore, TKS5 has been shown to be a target of the microRNA mir200-c (Sundararajnan et al., 2015). In terms of protein stability and abundance, the full-length isoform of TKS5 is positively regulated by Src, while the short isoform (TKS5-beta) is negatively regulated by Src (Cejudo-Martin et al. 2014).

**Homology**

TKS5 is homologous to SH3PXD2B (TKS4), another adaptor protein that functions as a Src substrate and promotes invadosome function (Buschman et al., 2009). TKS4 contains a PX domain at the N-terminus and four SH3 domains in the C-terminus.

**Implicated in**

**Breast cancer**

TKS5 expression is increased in human primary breast tumors compared to normal tissues, and is further increased in metastases (Stylli et al., 2014). TKS5 is required for invadopodia formation in breast cancer cells (Seals et al., 2005). TKS5-dependent invadopodia have been shown to promote tumor growth in a transplantation setting, cancer cell intravasation and extravasation, and metastasis formation (Eckert et al., 2011; Gligorijevic et al., 2012; Leong et al., 2014; Blouw et al., 2015).

Expression of full-length TKS5 in human breast tumors correlated with poor prognosis (Blouw et al., 2015).

**Lung cancer**

TKS5 expression is increased in human lung tumors compared to normal tissues (Stylli et al., 2014). Full-length Tks5 is required for metastasis in a mouse model of lung cancer (Li et al., 2013). Furthermore, higher expression of full-length TKK5 relative to short-form TKS5 correlated with poor survival of early-stage lung adenocarcinoma patients (Li et al., 2013).

**Melanoma**

TKS5 is required for invadopodia formation in melanoma cells (Seals et al., 2005).

**Prostate cancer**

TKS5 expression is increased in human prostate tumors compared to normal tissues, and is required for invadopodia function in prostate cancer cells (Stylli et al., 2014; Burger et al., 2014).

**Gliomas**

TKS5 expression correlates with poor survival of glioma patients (Stylli et al., 2011).

**Colon Cancer**

TKS5 expression is increased in human colon tumors compared to normal tissues (Stylli et al., 2014).

**Alzheimer disease**

KS5 and ADAM12 have been proposed to mediate the toxicity of amyloid-β peptide (Aβ), which is a potential cause of Alzheimer's disease as it has been
shown to mediate neurodegenerative alterations that are associated with amyloid plaques (Malinin et al., 2005; Harold et al., 2007).

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