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Gene Section

Review

PTK6 (protein tyrosine kinase 6)

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Abstract

Review on PTK6, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: BRK

HGNC (Hugo): PTK6

Location: 20q13.33

Note: Chromosome 2 in Mouse.

DNA/RNA

Description

The PTK6 gene contains 8948 bp comprising 8 coding exons. PTK6 belongs to a small family of intracellular tyrosine kinases with conserved functional domain homology that is related to, but distinct from, the SRC family of kinases (Lee et al., 1998); reviewed in (Serfas and Tyner, 2003; Brauer and Tyner, 2010). Members of the PTK6 family are defined by a highly conserved intron-exon structure that is distinct from other major intracellular tyrosine kinase families; other family members include FRK (FYN-related kinase, also known as Rak) and SRMS (SRC-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristoylation sites). The PTK6 and SRMS genes are tightly linked on human chromosome 20q13.3 (Kohmura et al., 1994; Llor et al., 1999; Serfas and Tyner, 2003).

Transcription

Alternative splicing gives rise to an RNA encoding a small protein containing the amino terminus, the SH3 domain, and a unique carboxyl terminus (isoform 2) (Mitchell et al., 1994; Brauer et al., 2011).

Protein

Description

Isoform 1

Size: 451 amino acids; ~ 52 KDa.

PTK6 contains SH3 and SH2 protein-protein interaction domains, an SH1 kinase domain, and a regulatory carboxy terminus.

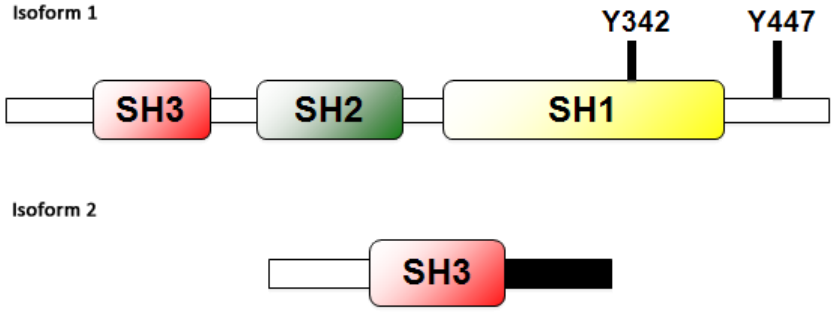
Phosphorylation of residue Y342 is required for full activation of kinase activity and activity is negatively regulated by tyrosine phosphorylation of its carboxy-terminal tyrosine residue, Y-447 (Qiu and Miller, 2002; Qiu and Miller, 2004; Qiu et al., 2005).

Isoform 2 (also known as ALT-PTK6, delta m5)

Size: 134 aa; ~15 KDa.

ALT-PTK6 is the product of an alternatively-spliced RNA that encodes a truncated protein due to a premature stop codon; alternative splicing deletes exon 2 and causes in a frameshift.

The N-terminus and SH3 domain of ALT-PTK6 are identical to the full-length protein, but it has a unique C-terminus lacking the SH2 and SH1 domains and is thus catalytically inactive (Mitchell et al., 1994; Brauer et al., 2011).



Two additional PTK6 sequences, CRA_a (GenBank: EAW75262.1) and CRA_b (GenBank: EAW75263.1) that would encode larger ~59 kDa proteins have been identified by Celera Genomics, but these isoforms have not been characterized and their biological significance is not known.

Expression

Normal Epithelium

PTK6 was first identified in cultured human melanocytes (Lee et al., 1993), breast tumor cells (Mitchell et al., 1994), and mouse small intestine (Siyanova et al., 1994). It is primarily an epithelial kinase that is first detectable in the differentiating granular layer of the skin during late embryogenesis of the mouse at E15.5 (Vasioukhin et al., 1995). In adults, PTK6 is predominantly expressed in the epithelial cells of the gastrointestinal tract (Siyanova et al., 1994; Llor et al., 1999), and skin (Vasioukhin et al., 1995; Wang et al., 2005). In regenerating tissues, such as the small intestine, colon, and skin, PTK6 expression is largely restricted to epithelial cells that are exiting the cell cycle and undergoing terminal differentiation, which are located on the villi in the small intestine, surface epithelium in the colon (Haegebarth et al., 2006), and the suprabasal layer of the skin (Vasioukhin et al., 1995; Wang et al., 2005) as well as in the oral mucosa (Petro et al., 2004). PTK6 is also expressed in the nuclei of normal epithelium of the prostate (Derry et al., 2003), and mammary gland (Peng et al., 2014). Although it is largely restricted to epithelia, PTK6 expression was also reported in activated normal T-cells (Kasprzycka et al., 2006).

Cancer

PTK6 is overexpressed in a large majority of human breast tumors and in most breast cancer cell lines (Barker et al., 1997; Harvey and Crompton, 2003; Ostrander et al., 2007). PTK6 expression is also induced in prostate tumors and cell lines (Zheng et al., 2012); relocalization of PTK6 from the nucleus to cytoplasm was reported in prostate cancer cells (Derry et al., 2003). In breast cancer cells, PTK6 expression has been shown to be mediated by hypoxia via multiple mechanisms; PTK6 protein is stabilized by HSP90 (Kang et al., 2012) and is transcriptionally upregulated by HIF-1α and HIF-2α (Regan Anderson et al., 2013), additionally PTK6 protein can be upregulated in a post-translational manner in response to hypoxia (Pires et al., 2014). PTK6 has been identified as a transcriptional target of CREB, and its expression is upregulated by p90RSK2 phosphorylation of CREB (Jin et al., 2013). PTK6 expression is modestly upregulated in primary colon tumors (Llor et al., 1999), and downregulated in metastatic colon cancer (Chen et al., 1999). In squamous cell carcinoma, PTK6 expression is reduced with increasing malignancy (Petro et al., 2004; Wang et al., 2005).

Function

PTK6 is an intracellular protein tyrosine kinase that has distinct context-dependent functions in different normal and cancerous tissues based on its intracellular localization and kinase activity. Studies in breast and ovarian cancer cell lines find that PTK6 interacts with growth factor receptors EGFR (Kamalati et al., 2000) and ERBB2 (Ostrander et al., 2007; Xiang et al., 2008) to propagate growth factor-mediated signaling. PTK6 binds and phosphorylates IGF-1R (Fan et al., 2013) and promotes anchorage independent growth via interactions with IRS-4 and IGF1R (Qiu et al., 2005; Irie et al., 2010). PTK6 has also been shown to mediate Met receptor signaling, although a direct interaction has not been demonstrated (Locatelli et al., 2012). PTK6 stabilizes EGFR expression by phosphorylating ARAP1 (Arf-GAP, Rho-GAP, ankyrin repeat, and pleckstrin homology domain-containing protein 1) (Kang et al., 2010); interaction with EGFR mediates PTK6 phosphorylation of paxillin (Chen et al., 2004) and p190RhoGAP (Shen et al., 2008) in breast cancer cells as well as AKT in breast (Zhang et al., 2005) and prostate (Zheng et al., 2010) cancer cell lines to promote proliferation, invasion, and migration. PTK6 has also been shown to promote breast cancer cell migration via phosphorylation of KAP3A (Lukong and Richard, 2008) and Dok1 (Miah et al., 2014). Membrane-targeted active PTK6 in prostate cancer cell lines phosphorylates pro-oncogenic substrates BCAR1 (Zheng et al., 2012) and FAK (Zheng et al., 2013a). PTK6

phosphorylates and activates Signal Transducers and Activators of Transcription STAT3 (Liu et al., 2006) and STAT5a (Weaver and Silva, 2007) as well as the related scaffolding protein STAP2 (Mitchell et al., 2000). β-catenin has also been identified as a PTK6 substrate; when targeted to the cell membrane PTK6 can activate β-catenin, while nuclear PTK6 negatively regulates β-catenin transcriptional activity in a kinase-independent manner (Palka-Hamblin et al., 2010). PTK6 phosphorylation of the nuclear RNA-splicing factors SAM68 (Derry et al., 2000) and related SLM1 and SLM2 proteins (Haegebarth et al., 2004), as well as PSF (Lukong et al., 2009) inhibits their RNA-binding activity to promote differentiation and cell cycle arrest. PTK6 is a substrate of the PTP1B phosphatase (Fan et al., 2013).

PTK6 promotes epithelial differentiation of enterocytes in the small intestine (Haegebarth et al., 2006) and keratinocytes in skin (Vasioukhin and Tyner, 1997; Wang et al., 2005). In cultured human keratinocytes, addition of calcium promotes differentiation, which is accompanied by increased PTK6 expression and activation, and elevated levels of the epidermal differentiation markers (Vasioukhin and Tyner, 1997) dependent on PTK6 kinase activity (Wang et al., 2005). Disruption of the Ptk6 gene led to impaired intestinal differentiation and increased intestinal proliferation in mice (Haegebarth et al., 2006). When ectopically expressed, PTK6 sensitized non-transformed Rat1a fibroblasts to apoptosis (Haegebarth et al., 2005). Induction of PTK6 in intestinal crypts following total body γ-irradiation enhanced apoptosis in the murine intestinal epithelium, including in intestinal crypts, where it promotes DNA damage-induced apoptosis (Haegebarth et al., 2009). In human colon cancer cell lines and in murine colon tissue, PTK6 negatively regulates β-catenin transcriptional activity (Palka-Hamblin et al., 2010). PTK6 has a tumor-promoting role in the colon as disruption of the Ptk6 gene impaired carcinogen-induced tumorigenesis in mice (Gierut et al., 2011) and PTK6 promotes survival of colon cancer cell lines following DNA damaging treatments including γ-irradiation and chemotherapeutic drugs via STAT3 activation (Gierut et al., 2012).

Targeting PTK6 to plasma membrane enhanced proliferation, survival, migration and anchorage-independent growth in HEK293 cells, while nuclear targeting inhibited the invasive phenotype (Kim and Lee, 2009). Targeting active PTK6 to the plasma membrane in SYF (deficient for SRC, YES, and FYN) mouse embryonic fibroblasts was sufficient to transform these cells (Zheng et al., 2013a). In prostate cancer cells, targeting PTK6 to the nucleus inhibits proliferation while cytoplasmic PTK6 promotes proliferation (Brauer et al., 2010). Overexpression of membrane-targeted active PTK6 in prostate cancer cells drives epithelial-mesenchymal transition (Zheng et al., 2012) and anchorage-independent survival (Zheng et al., 2013a) as well as in vivo xenograft metastasis (Zheng et al., 2013b). Recently, PTK6 was detected in nuclei of normal mammary gland epithelium (Peng et al., 2014), and overexpression of PTK6 promotes oncogenic signaling and invasive phenotypes in breast cancer cells (Harvey and Crompton, 2003; Xiang et al., 2008; Irie et al., 2010). In human prostate and breast cancers, PTK6 is activated at the plasma membrane (Zheng et al., 2013b; Peng et al., 2014).

Mutations

Somatic

A few PTK6 mutations have been reported in human cancers. A frameshift mutation resulting in the deletion of 58 amino acid residues (W78fsX58) has been identified in a human bladder cancer cell line and NSCLC cell line (Ruhe et al., 2007). Two point mutations have been reported in a small number of melanoma cases; W210X within the tyrosine kinase domain and a -7 intronic C>T mutation within a splice site (Prickett et al., 2009). Additional mutations have been identified by genomic sequencing (cBioPortal).

Implicated in

Breast cancer

PTK6 is overexpressed in most human breast tumors and breast cancer cell lines (Barker et al., 1997; Born et al., 2005; Ostrander et al., 2007; Irie et al., 2010). Irie and colleagues detected increased levels of PTK6 mRNA expression in HER2/ERBB2, luminal A and luminal B subtypes of breast cancer and found that high PTK6 expression correlated with reduced recurrence-free survival (Irie et al., 2010). PTK6 protein expression has prognostic significance in breast cancer (Born et al., 2005; Aubele et al., 2009), and active PTK6 protein was detected in human breast tumors but not normal human mammary gland (Peng et al., 2014). Overexpression of PTK6 promotes mammary gland cancer tumorigenesis in mouse models (Lofgren et al., 2011; Peng et al., 2013). PTK6 sustains EGFR signaling via transactivation as well as by inhibition of EGFR degradation (Kang et al., 2010; Li et al., 2012). The correlation between PTK6 and ERBB2 overexpression in invasive human ductal breast carcinomas (Born et al., 2005; Aubele et al., 2007; Ostrander et al., 2007; Xiang et al., 2008) raises the possibility that targeting PTK6 along with ERBB receptors might offer a therapeutic advantage (Harvey and Crompton, 2004; Ostrander et al., 2010). In response to HGF stimulation, PTK6

mediates Met signaling to promote breast cancer cell migration (Castro and Lange, 2010). PTK6 binds with IGF-1R to mediate IGF-1 signaling promoting anchorage-independent growth (Irie et al., 2010). PTK6 expression is upregulated by hypoxia and promotes hypoxia-mediated breast cancer progression (Aubele et al., 2009; Kang et al., 2012; Pires et al., 2014).

Prostate cancer

Elevated expression and relocalization of PTK6 have been reported in prostate cancer. Analysis of Oncomine microarray data showed that PTK6 mRNAs levels are higher in metastatic prostate tumors, and patients with high PTK6 have reduced survival (Zheng et al., 2013b). Knockdown of PTK6 in the human PC3 prostate tumor cell line inhibited xenograft tumor growth (Zheng et al., 2013). In normal prostate epithelium, PTK6 expression is nuclear and expression relocalizes to the cytoplasm and membrane in poorly-differentiated prostate tumors (Derry et al., 2003). Targeting PTK6 to the nucleus in prostate cancer cells arrests their growth while cytoplasmic PTK6 promotes proliferation (Brauer et al., 2010). In the cytoplasm, PTK6 may phosphorylate AKT on tyrosine residues to promote activation and downstream signaling (Zheng et al., 2010). Targeting active PTK6 to the plasma membrane in prostate cancer cells drives epithelial-mesenchymal transition via activation of BCAR1 (Zheng et al., 2012) and anchorage-independent survival via activation of FAK (Zheng et al., 2013a). RSK-mediated expression of PTK6 may contribute to metastasis of prostate cancer cells (Yu et al., 2014).

Colon cancer

PTK6 expression is mildly up-regulated in primary colon tumors (Llor et al., 1999), and down-regulated in metastatic colon cancer (Chen et al., 1999). Disruption of Ptk6 impairs carcinogen induced tumorigenesis in mice, suggesting a tumor-promoting role for the kinase in the colon as well (Gierut et al., 2011). In human colon cancer cell lines, PTK6 promotes cell survival following DNA damaging treatments including γ-irradiation and chemotherapeutic drugs via STAT3 activation (Gierut et al., 2012).

Other cancers

PTK6 has been implicated in several different types of human cancer, with distinct context-specific functions. As in breast and prostate cancers, PTK6 has pro-oncogenic roles in some other cancers. The Ptk6 gene is amplified and PTK6 protein is overexpressed in and may promote the development and growth of ovarian tumors (Schmandt et al., 2006). PTK6 signaling via IGF1R in ovarian cancer promotes cell growth and is inhibitted by PTP1B (Fan et al., 2013). PTK6 is also overexpressed in head and neck cancer, where it may play a role in HNSCC development and progression (Lin et al., 2004). High PTK6 expression is associated with poor prognosis and metastasis in nasopharyngeal carcinoma (Liu et al., 2013a). PTK6 expression is increased in non-small cell lung carcinoma (Fan et al., 2011) and is associated with poor prognosis (Zhao et al., 2013); PTK6 has been identified as a potential therapeutic target in NSCLC (Yauch et al., 2005; Li et al., 2010). It has also been demonstrated that knockdown of PTK6 reduces migration and invasion of pancreatic cancer cells (Ono et al., 2014). Constitutive expression of PTK6 has been reported in cutaneous T-cell lymphomas as well as in other transformed T- and B-cell populations (Kasprzycka et al., 2006).

In some cases, PTK6 may have tumor suppressor functions. It is down-regulated in human esophageal squamous cell carcinomas (ESCC); knockdown of PTK6 in human ESCC cells enhanced xenograft tumor growth (Ma et al., 2012). Low PTK6 expression correlates with poor prognosis in patients with laryngeal squamous cell carcinoma (Liu et al., 2013b). PTK6 expression is reduced with increasing malignancy in squamous cell carcinomas of the skin (Wang et al., 2005) and oral mucosa (Petro et al., 2004).

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