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RAKing in AKT: A Tumor Suppressor Function for the Intracellular Tyrosine Kinase FRK

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Abstract

The Fyn related kinase FRK, originally called RAK, is a member of a small family of intracellular Src-related tyrosine kinases that includes PTK6 and Srms. These kinases share a conserved gene structure that is distinct from that of the Src family. Expression of FRK and PTK6 was originally identified in melanoma, breast cancer cells and normal intestinal epithelium, and both FRK and PTK6 have been implicated in the regulation of epithelial cell differentiation and apoptosis. Recently FRK was reported to phosphorylate the tumor suppressor PTEN (phosphatase and tensin homolog deleted from chromosome 10), a negative regulator of phosphatidylinositol 3 kinase (PI3K) signaling and AKT activation. FRK-mediated tyrosine phosphorylation of PTEN suppressed its association with NEDD4–1, an E3 ubiquitin ligase that may target it for polyubiquitination and proteosomal degradation. As a positive regulator of PTEN, FRK suppresses AKT signaling and inhibits breast cancer cell tumorgenicity in xenograft models. Both FRK and the related tyrosine kinase PTK6 appear to have multiple context-dependent functions, including the ability to regulate AKT. Although PTK6 negatively regulates AKT signaling in normal tissues in vivo, it may enhance AKT signaling in breast cancer cells. In contrast, FRK, which is expressed in the normal mammary gland but lost in some breast tumors, has tumor suppressor functions in mammary gland cells.

Keywords

RAK; FRK; PTK6; BRK; PTEN; AKT; Tyrosine Kinase; Tumor Suppressor

INTRODUCTION

Tyrosine kinases play important roles orchestrating cellular functions including cell migration, differentiation, cell-cell adhesion, exocrine signaling, proliferation, and death [1]. Unique extracellular domains and a variety of domains that facilitate intra and inter protein-protein interactions mediate their versatility [2]. Tyrosine kinases are regulated by external and internal signals, and play an integral part in signaling within multicellular organisms. Aberrant tyrosine kinase signaling leads to an array of problems and contributes to diseases such as cancer. Src, the first tyrosine kinase and oncogene to be identified, was discovered thirty years ago. Src family members are composed of several distinct functional domains referred to as Src-homology (SH) domains. These include the SH1 tyrosine kinase domain, the phosphotyrosine-binding SH2 and polyproline-binding SH3 domains, which regulate enzymatic activity and confer substrate specificity, and the SH4 domain that promotes membrane targeting.

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The FRK/PTK6 family of tyrosine kinases is distantly related to the Src-family, but members of this family share an exon-intron structure distinct from Src-family members [3]. A recent study postulated that an ancestral FRK/PTK6 kinase in metazoans duplicated and diverged to give rise to the FRK/PTK6 and Src tyrosine kinase families [4]. Members of the vertebrate FRK/PTK6 family include Fyn-related kinase (FRK; also called RAK and in rodents Bsk, Gtk, Iyk), Protein tyrosine kinase 6 (PTK6; also called BRK and in mice Sik), and SRMS (also called SRM). Herein we use the approved HUGO gene symbols FRK and PTK6. Like Src family members, FRK/PTK6 family kinases are composed of a catalytic tyrosine kinase domain, SH2 and SH3 domains, and a regulatory carboxy-terminal tyrosine. However, most FRK/PTK6 family members lack N-terminal myristoylation/palmitoyaltion signals, and are therefore not targeted to the membrane, thus having flexibility in intracellular localization. The exception is rodent FRK that contains a partial myristoylation signal and is composed of 512 amino acids compared with 505 amino acids for the human homolog [5]. The FRK SH2 domain contains a bipartite nuclear localization signal, which can direct FRK localization to the nucleus.[6] Both FRK and PTK6 appear to have nuclear functions [6–10].

FRK Expression and Function

FRK was first identified in primary human breast cancer and the 600PEI breast cancer cell line [11], in human melanocytes [12], and the human hepatoma cell line Hep3B [13]. In human tissues, FRK expression was shown in the epithelium of the kidney and liver, as well as in breast and colon cancer cell lines [7, 11]. The rodent homolog of FRK was identified in rat small intestine [14, 15], insulin producing beta-cells [16], and the mouse mammary gland [5]. In a survey of FRK expression in rodent tissues, expression was highest in the small intestine [5].

In the rat, FRK has been shown to localize to the brush border membrane of the columnar gut epithelium and it can be activated by MET [15, 17]. In normal human breast tissue, FRK is localized to the cytoplasm and nucleus during the follicular phase of the menstrual cycle, and it becomes more cytoplasmic during the luteal phase, suggesting that cytoplasmic FRK localization correlates with cell proliferation [18]. Phosphorylation of the C-terminal tyrosine Tyr497 (rodent Tyr504) of FRK regulates activity and localization, and activating mutations of Tyr497 to phenylalanine decrease cell proliferation [19], suggesting that nuclear FRK may have a tumor suppressor function.

FRK can regulate production of endocrine cells during pancreatic development. At embryonic day 15.5, reduced numbers of insulin producing beta-cells and increased numbers of glucagon producing alpha-cells were observed, although no differences were detected in adult mice [20]. Expression of FRK in the PC12 pheochromocytoma cell line resulted in neurite outgrowth, supporting a role in differentiation, and increased SHB phosphorylation and association with FAK1 were observed [21, 22]. Transgenic mice overexpressing kinase active FRK under the insulin promoter showed increased beta-cells mass [23, 24]. Partial pancreatectomy of transgenic mice also showed increased cell growth [24], albeit increased sensitivity to cytokine-induced cell death was also observed [23, 25]. Cells isolated from Frk−/− mice showed resistance to cell death [26].

Overexpression of human [6, 27] and murine FRK [19, 28] induces growth arrest. Association of FRK with the tumor suppressor protein pRB during G1 and S phase was observed [6]. FRK protein levels are lowest during mitosis and highest during G1 arrest, and over-expression of FRK was shown to cause G1 arrest and decrease growth and colony formation [6, 27]. Although FRK was shown to bind the A/B binding pocket of RB [6], G1 arrest occurred independent of pRB [27]. Interestingly, FRK kinase activity, but not the SH2 or SH3 domains, was required for cell cycle arrest [27].

FRK positively regulates the tumor suppressor PTEN

PTEN (phosphatase and tensin homolog deleted from chromosome ten) is a tumor suppressor that is often mutated or deleted in cancers [29, 30]. PTEN antagonizes phosphatidylinositol 3 kinase (PI3K) by dephosphorylating PIP3 to PI(4,5)P2, thereby preventing PIP3-mediated activation of AKT. Through its regulation of AKT, PTEN can negatively regulate proliferation, survival, and cell motility (reviewed in [31]). PTEN also plays a role in the nucleus, maintaining chromosome integrity by binding to Cenp-c in the centromere [32]. A role of PTEN in promoting DNA repair has also been established because it can coordinate with E2F to upregulate expression of the repair protein Rad51, as well as block AKT-dependent inactivation of the checkpoint protein Chk1 (reviewed in [33, 34]).

Recently FRK was identified as a PTEN associated protein, and a direct correlation between FRK levels and PTEN levels was observed in breast cancer tissue samples [35]. PTEN is degraded via the proteosomal degradation pathway, and NEDD4–1 is an E3 ubiquitin ligase that is involved in the ubiquitination of PTEN [36]. To determine if ubiquitination of PTEN was influenced by FRK, Yim and colleges determined that PTEN ubiquitination was increased when FRK was knocked down. Furthermore, knock down of FRK resulted in increased association of PTEN with NEDD4–1. FRK was found to phosphorylate PTEN at tyrosine residue 336, and mutation of this residue negated stabilization of PTEN protein by FRK, and resulted in increased PTEN association with NEDD4–1. Phosphorylation of PTEN tyrosine residue 336 by FRK appeared to be sufficient and necessary to protect PTEN from NEDD4–1 mediated degradation [35].

Ectopic expression of FRK in the MCF7 breast cancer cell line increased PTEN protein levels, and knockdown of FRK in the nontransformed immortalized MCF10A cell line reduced PTEN protein expression [35]. Alteration of FRK in either cell line did not affect PTEN mRNA levels, supporting a role for FRK in post-transcriptional regulation of PTEN. In fact, knockdown of FRK reduced the half-life of PTEN, while FRK over-expression increased PTEN stability. Increased PTEN activity in the presence of FRK was verified by lipid phosphatase assays, detection of reduced levels of activated phospho-AKT, a shift of nuclear to cytoplasmic β-catenin, and reduced β-catenin/Tcf4 signaling. Knockdown of FRK was sufficient to transform the MCF10A cell line, showing increased cell growth, colony formation and tumor growth in xenografts. Overexpression of FRK in MCF7 breast cancer cells, on the other hand, suppressed tumor growth [35].

DISCUSSION

Yim and colleagues have provided evidence that FRK is a tumor suppressor that associates with and phosphorylates PTEN, leading to its subsequent stabilization by preventing its ubiquitination by NEDD4–1 in breast cancer cells [35]. While NEDD4–1 appears critical for targeting PTEN for degradation in breast cancer cells, Fouladkou et al. showed that disruption of NEDD4–1 expression had no impact on PTEN stability and localization in MEFs and hearts from two strains of knockout mice [37]. However, it is possible that another mechanism compensates for NEDD4–1 loss in mice, or that tissue specific factors play an important role in determining how PTEN is regulated by NEDD4–1. In addition, it has been proposed that NEDD4–1 may target PTEN only in response to specific signals [38].

Previous studies of FRK function using *Frk* −/− mice did not yield evidence for a tumor suppressive role in vivo [20, 39]. Only a mild phenotype in circulating T3 hormone levels was observed in adult mice [39], and FRK seems to be involved in determining glucagon versus insulin producing cell differentiation in the pancreas of day 15 embryos and newborns, but not in adults [20]. *Frk* −/− mice may be able to compensate for loss of FRK through a redundant mechanism, such as overlapping functions with another FRK or SRC family

member, such as PTK6 (Table 1). It is possible that a conditional loss of FRK in the adult mouse is less likely to be compensated, and the effects would be more apparent.

Like FRK, PTK6 was first identified in melanocytes [12], breast cancer cells [40] and the normal intestine [41, 42]. PTK6 positively regulates enterocyte [43] and keratinocyte differentiation [44, 45]. Both FRK and PTK6 promote cell death; FRK promotes pancreatic islet cell death in response to cytotoxic cytokines [26], while PTK6 sensitizes nontransformed cells to apoptotic stimuli in culture [46], and promotes DNA damage induced apoptosis in the intestine [47]. Both kinases can negatively regulate AKT; PTK6 has been shown to associate with and phosphorylate AKT directly [48]. In addition, increased AKT activation has been reported in the intestines of *Ptk6* null mice [43, 47] (see Figure 1). It will be important to examine the phenotypes of FRK/PTK6 double null mice to determine if they are more prone to developing tumors, particularly in tissues where they are coexpressed, such as in the intestine. Untreated *Ptk6* $-/-$ mice have a mild growth and differentiation phenotype [43].

Context specific functions of FRK and PTK6 may be dictated by the intracellular localization of these kinases. It was first proposed that intracellular localization of PTK6 may play a significant role in regulating signaling outcomes [10]. Indeed, targeting PTK6 to the membrane or nucleus influences whether PTK6 has oncogenic or growth suppressive functions [49], (Palka-Hamblin and Tyner, unpublished). FRK contains a bipartite nuclear localization signal, and it will be interesting to determine if it plays a distinct role in regulating nuclear localization and/or nuclear functions of PTEN [34, 50]. NEDD4–1 has been shown to regulate both monoubiquination and polyubiquitination of PTEN, leading to its nuclear translocation or proteosomal degradation respectively [32, 36].

While FRK and PTK6 signaling have many parallels, each kinase appears to have its own tissue specific functions. Human FRK and PTK6 share only 44% amino acid identity. Unlike FRK, PTK6 is not expressed in the normal mammary gland [10, 51, 52], but it is expressed in a high proportion of breast tumors [51, 53]. The *PTK6* gene maps to human chromosome 20q13.3 [54], a region often amplified in breast cancer, and *PTK6* is coamplified with HER2 in some human breast tumors [55, 56]. Several studies suggest that PTK6, referred to as the breast tumor kinase BRK, promotes breast cancer cell proliferation and migration (for examples see [48, 53, 56–60]).

In contrast to *PTK6*, *FRK* maps to human chromosome 6q21-q22.3, a region lost in some breast cancers [61], and loss of FRK expression has been reported in human mammary gland tumors [18]. However, a few reports have also suggested that FRK may have oncogenic potential. FRK appears to be overexpressed in some primary human colon tumors [7] and a third of mammary tumors examined [7, 62]. In a patient with acute myelogenous leukemia, the *Frk* gene was found fused with the ETS transcription factor ETV6 and the ETV6/FRK protein had oncogenic properties [63]. It will be important to determine if promoting expression/activity of FRK during mammary gland tumorigenesis in vivo leads to repression of tumor growth through stabilization of PTEN, and if this is sufficient to counteract tumor promoting functions of the related kinase PTK6.

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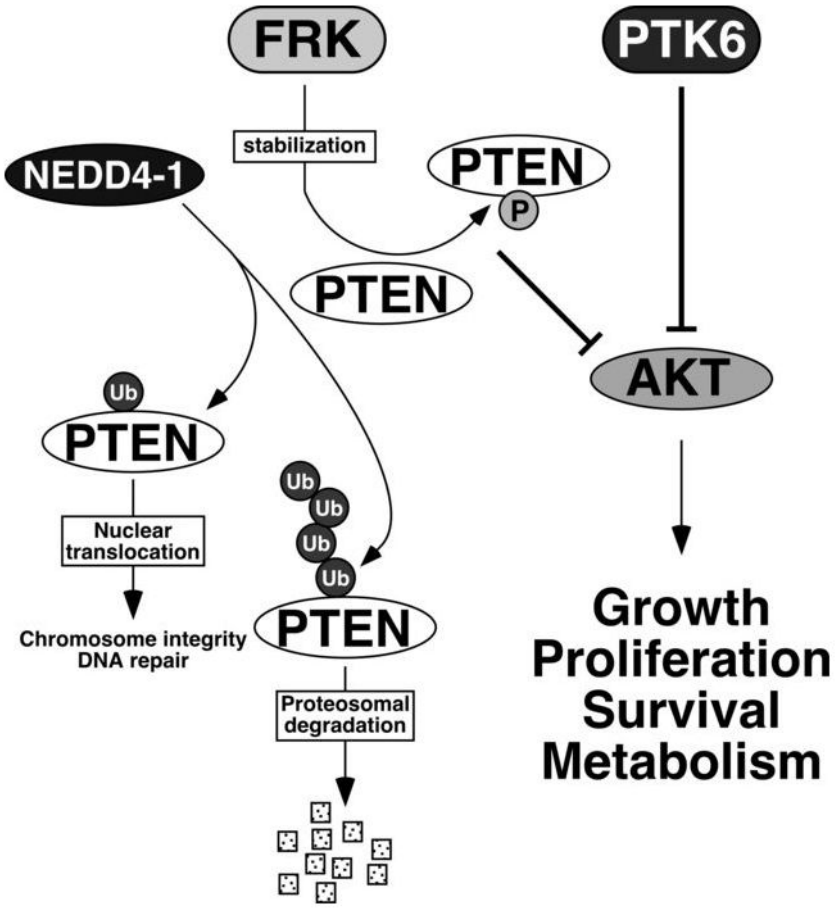

Figure 1.

FRK and PTK6 negatively regulate AKT activity. The ubiquitin ligase NEDD4–1 can monoubiquinate or polyubiquitinate PTEN, leading to its nuclear translocation or proteosomal degradation respectively [32, 36]. FRK directly phosphorylates PTEN and prevents its association with NEDD4–1, leading to stabilization and accumulation of PTEN [35]. PTEN antagonizes the phosphoinositol-3-kinase/Akt pathway. PTK6 may directly associate with and phosphorylate AKT, and has been shown to inhibit AKT in unstimulated cells [48]. Increased AKT activation has been detected in the intestines of *Ptk6* null mice [43, 47].

Table 1

Similar functions for the FRK and PTK6 tyrosine kinases.

FUNCTION		OBSERVATION	REFERENCE
Differentiation	FRK	Neurite outgrowth; generation of insulin producing cells	20, 21
	PTK6	Differentiation of keratinocytes and enterocytes	42, 43, 45
AKT Regulation	FRK	Decreased PI3K signaling; Upregulation of PTEN	35, 64
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Apoptosis	FRK	Sensitization of islet cells to cytokine-induced death	23, 25, 26
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