Etk/Bmx Tyrosine Kinase Activates Pak1 and Regulates Tumorigenicity of Breast Cancer Cells*

Received for publication, April 9, 2001, and in revised form, May 23, 2001
Published, JBC Papers in Press, May 29, 2001, DOI 10.1074/jbc.M103129200

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Etk/Bmx, a member of the Tec family of nonreceptor protein-tyrosine kinases, is characterized by an N-terminal pleckstrin homology domain and has been shown to be a downstream effector of phosphatidylinositol 3-kinase. P21-activated kinase 1 (Pak1), another well characterized effector of phosphatidylinositol 3-kinase, has been implicated in the progression of breast cancer cells. In this study, we characterized the role of Etk in mammary development and tumorigenesis and explored the functional interactions between Etk and Pak1. We report that Etk expression is developmentally regulated in the mammary gland. Using transient transfection, coimmunoprecipitation and glutathione S-transferase pull down assays, we showed that Etk directly associates with Pak1 via its N-terminal pleckstrin homology domain and also phosphorylates Pak1 on tyrosine residues. The expression of wild-type Etk in a non-invasive human breast cancer MCF-7 cells significantly increased proliferation and anchorage-independent growth of epithelial cancer cells. Conversely, expression of kinase-inactive mutant Etk-KQ suppressed the proliferation, anchorage-independent growth, and tumorigenicity of human breast cancer MDA-MB435 cells. These results indicate that Pak1 is a target of Etk and that Etk controls the proliferation as well as the anchorage-independent and tumorigenic growth of mammary epithelial cancer cells.

* This study was supported in part by National Institutes of Health Grants CA80066 and CA65746 and by the Breast Research program of The University of Texas M. D. Anderson Cancer Center (to R. K.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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§ The abbreviations used are: Etk, epithelial and endothelial tyrosine kinase; PH, pleckstrin homology; Pak1, p21-activated kinase; wt, wild type; aa, amino acid; PCR, polymerase chain reaction; DMEM, Dulbecco’s modified Eagle’s medium; mAb, monoclonal antibody; MBP, myelin basic protein; N-Ter, N-terminal; C-Ter, C-terminal; RT, reverse transcription; HRG, heregulin.

Epithelial and endothelial tyrosine kinase (Etk, also called Bmx)* belongs to the Tec family of nonreceptor protein-tyrosine kinases that are characterized by an N-terminal Tec homology domain located downstream of a pleckstrin homology (PH) domain (1–3). In addition, Etk contains Src homology-3 (SH3) and -2 (SH2) domains, and a catalytic kinase domain (4). The PH domain protein module is commonly found in signal transduction proteins and is believed to help mediate lipid-protein or protein-protein interactions (5). The PH domains of Etk and Btk (a related Tec family member) have been shown to interact with heterotrimeric G protein and protein kinase C (6, 7), and these interactions are believed to regulate kinase activity. Recent studies suggest that activation of PI3-kinase stimulate Etk, probably because of the direct interaction between the lipid product resulting from PI3-kinase reaction and the PH domain of Etk (8). The PH domain is believed to be important because germline mutation in the PH domain of Btk leads to human X-linked agammaglobulinemia (1, 2, 9). In contrast, overexpression of kinase-active Btk induces cellular transformation and protects cells from apoptotic signals (10). Although most of the Tec family kinases such as Btk, Itk, and Tec are of hematopoietic origin, Etk is found to be expressed in a variety of tissues and cell types, including lung and prostate tissues and salivary epithelial and endothelial cells (3, 4, 11).

Because Etk is a cytoplasmic kinase with several motifs characteristic of signaling molecules, it has been implicated in signal transduction networks. For example, Etk/Bmx was shown to mediate activation of Rho and serum response factor in response to the heterotrimeric G proteins Ga-12 and -13 that can be activated by hormones and neurotransmitters (6). In addition, Etk was shown to be a substrate of Src kinases and to be responsible for Src activation of signal transducer and activator of transcription factor 3 (STAT3) and for cellular transformation (12). Experiments using a kinase inactive mutant Etk-KQ showed that Etk kinase activity was required for interleukin 6-induced neuroendocrine differentiation of prostate cancer cells (4). Furthermore, dominant-negative mutants of PI3-kinase blocked interleukin 6-induced stimulation of Etk in this system, suggesting that Etk is an effector of PI3-kinase (4).

In addition to Etk, the p21-activated kinases (Paks) represent another well characterized family of effectors of PI3-kinase. Pak1 is a direct target of the small GTPases Cdc42 and Rac1, and binding of GTPases to Pak1 stimulates its kinase activity via autophosphorylation (13). Expression of kinase-active Pak1 mutant triggers the formation of lamellipodia, dissolution of stress fibers, and dissolution of focal adhesion complexes in fibroblast cells (14, 15). Expression of another kinase-active Pak1 mutant with a mutation in GTPase binding sites triggers the formation of actin ruffles (15–17). Pak1 kinase activity is essential for the formation of polarized lamellipodia at the leading edge (18) and for actin-myosin-mediated cytoskeletal changes (19). Expression of the kinase-inactive Pak1 mutant blocks the ability of Ras to induce transformation of Rat1 fibroblast (20), suggesting that Pak1 plays a role in this cell transformation. Furthermore, expression of kinase-active Pak1 in breast cancer cells stimulates anchorage-independent growth (21, 22).

Despite the recent reports of the involvement of Etk in signaling cascades in human cancer cells and the fact both Etk
and Pak1 are downstream of PI3-kinase, the relationship between Etk and Pak1 kinase and the role of the Etk pathway in the biology of human mammary epithelial cancer cells remain unknown. We sought to determine the role of Etk pathway in breast cancer cells. We present new evidence that Etk is an upstream effector of Pak1 tyrosine phosphorylation and that it is directly associated with Pak1. Furthermore, we found that Etk activity is discovered to be required for the proliferation, anchorage-independent growth, and tumorigenicity of mammary epithelial cancer cells. These results indicate that Pak1 is a target of Etk and that Etk regulates the anchorage-independent and tumorigenic growth of mammary epithelial cancer cells.

EXPERIMENTAL PROCEDURES

Plasmids and Antibodies—T7-tagged wild-type (Wt) pcDNA3-T7-Etk (T7-Etk), kinase-inactive pcDNA-T7-Etk (Etk-KQ), and N-terminal and C-terminal deletion mutants of Etk were previously described (4, 12). N-Ter ETK contains amino acids 1–240 and C-Ter has amino acid 243–674 (4, 12). Myc-tagged Pak1 Wt and Pak1 K299R mutants were generously provided by Jonathan Chernoff and have been earlier described (16, 18). To construct T7-tagged central inhibitory fragment of Pak, Pak aa 83–149, Ref. 18) Pak1 aa 83–149 domain was amplified by PCR and subcloned into pcDNA3.1 His (Invitrogen). Antibodies directed against T7, phosphotyrosine, Pak1, and c-Myc were purchased from Novagen, Upstate Biotechnology, Santa Cruz Biotechnology, and Neomarkers, respectively. Dr. Hsing-Jien Kung kindly provided monoclonal antibody to Etk.

Cell Culture and Transfection—MCF-7, MDA-MB435 human breast cancer cell lines (18), were maintained in Dulbecco’s modified Eagle’s medium (DMEM)/F12 (1:1) supplemented with 10% fetal bovine serum. Cells were transfected with the desired vector using Fugene-6 reagent (Roche, Nutley). Clonal stable cell lines overexpressing Wt-Etk or Etk-KQ or control pcDNA were selected in the presence of G418 resistance (500 μg/ml).

Immunoprecipitation and Kinase Assay—Cells were lysed in a buffer containing 20 mM Tris-HCl (pH 7.5), 100 mM NaCl, 10% glycerol, 1% Nonidet P-40, 10 mM NaF, 1 mM NaVO4, and a mixture of protease inhibitors. The T7-tagged Etk or Myc-tagged Pak1 were immunoprecipitated from the cell lysates with mAb directed against T7 or Myc, respectively, as described (23). When indicated, the immunocomplex was washed with kinase buffer (20 mM HEPES, pH 7.4, 1 mM dithiothreitol, 10 mM MnCl2, and 10 mM MgCl2). The kinase reaction was carried out in buffer supplemented with 7.5 μg of enolase (Sigma) for the Etk kinase assay and with myelin basic protein (MBP) for the Pak kinase assay.

GST Pull-down Assay—Wt-Etk, N-Ter, and C-terminal Etk cDNA (4, 12) were translated in vitro using the TNT reaction kit (Promega) in the presence of [35S]metathionine. Subsequently, 10 μl of reaction volume was diluted in 400 μl of protein-binding buffer (20 mM Tris, pH 7.5, 50 mM NaCl, 10% glycerol, 10 mM NaF, 1% Nonidet P-40, 1 mM NaVO4, and protease inhibitors) and incubated with 2 μg of Pak1-GST or GST protein beads at 4 °C for 4 h. The beads were washed six times with 1 ml of each binding buffer and eluted with 2× SDS-polyacrylamide gel electrophoresis sample buffer. Eluates were resolved onto a 10% SDS-polyacrylamide gel electrophoresis and visualized using a phosphorimager.

Cell Proliferation and Soft Agar Colony Formation Assays—MCF-7 and MDA-MB435 cells (2 × 104 cells per well in a 24-well plate) and counted daily for six days. Anchorage-independent colony assays were performed as described previously (21, 23). Briefly 1 ml of solution of 0.6% DIFCO Agar in DMEM supplemented with 10% fetal bovine serum was layered onto 60 × 15 mm tissue culture plates. MCF-7 or MDA-MB 435 cells (10,000 cells) were mixed with 1 ml of 0.36% Bactoagar solution in DMEM prepared in a similar manner and layered on top of the 0.6% Bactoagar layer. Plates were incubated at 37 °C in 5% CO2 for two weeks. In dominant negative Pak1 experiment, MCF-7 cells or Wt-Etk cells were transfected with 10 μg of GFP or GFP-K299R Pak1 or GFP-Pak1 inhibitor and tested for anchorage-independent growth.

Tumorigenicity Studies—Exponentially growing cells (3 × 106) were injected into mammary fat pad (two sites/animal) of female athymic mice (Nu/Nu, 4 weeks old). Every fourth day, tumor volumes were measured with calipers along two major axes. Tumor volume was calculated as follows: V = (4/3)πr12r2, where R1 is radius 1 and R2 is radius 2 and R1 < R2 (n = 10 per group) (24).

RESULTS

Etk Expression during Embryogenesis and Mammary Gland Development—To explore the role of Etk during cell proliferation and differentiation, we first explored the expression profile of Etk during mouse embryonic development using in situ hybridization. As shown in Fig. 1, Etk mRNA was expressed in high levels in the nervous and epithelial tissue, i.e. the dorsal root ganglia (Drg), the mucosa of the intestine (Int), the pancreas (Pan), and the lung (Lu).

Apoptosis—Tunnel method was used to detect DNA fragmentation as previously described by Gabriel et al. (25). Briefly, paraffin-embedded sections pretreated with protease were nicked and labeled with biotinylated poly(dU), introduced by terminal deoxy-transferase, and then stained using avidin-conjugated peroxidase.

Reverse Transcription (RT)-PCR and Southern Hybridization—Total cytoplasmic RNA was isolated from different stages of mice tissue using the Trizol Reagent (Life Technologies, Inc.) and 500 μg of RNA analyzed by RT-PCR. The forward primer for mEtk was 5′-CACCCACCTCACAAGATTTCATGG-3′ and the reverse primer was 5′-CATACTGGCCTTCCACTTGCC-3′. RT-PCR products were run onto 1% agarose gel, transferred to a blot, and probed with a 520-bp cDNA of mEtk.

In Situ Hybridization—For in situ hybridization, mouse mammary glands or 12-day-old embryos were dissected out and fixed with 4% paraformaldehyde. The tissues were processed into 10 μm of frozen sections, and in situ hybridization was performed as described (24). To make the probe, the Etk cDNA fragment was cloned to TOPO II vector, and RNA probe was labeled with digoxigenin and was synthesized by in vitro transcription. Sense-probe hybridization was used as background control.
epithelial cells, but the expression level is generally low. Despite the low level, accumulating evidence suggests that it play an important role in the growth, differentiation, and apoptosis of epithelial cell (26). To understand the potential function of Etk in mammary gland, we investigated Etk expression during various stages of the mammary gland development by RT-PCR followed by Southern hybridization with a fragment of human Etk cDNA. Results indicated that Etk expression appears to undergo a cyclic change as the expression levels of Etk were down-regulated during pregnancy, early lactation, and again during the late stages of lactation (Fig. 2, B and C). Etk expression was lowest during pregnancy, a stage of high proliferation for mammary glands (Fig. 2, B and C), and highest in non-proliferative weaning and virgin mammary glands, suggesting that Etk may have an important role in the biology of mammary epithelial cells.

Expression and Activation of Etk in Breast Cancer Cells—Because the potential role of Etk in mammary epithelial cancer cells is not known, we next examined the expression of Etk in a panel of breast cancer cell lines by Southern hybridization. Among the breast cancer cell lines used, highly tumorigenic and metastatic MDA-MB435 cells exhibited the highest Etk content, whereas the Etk content of MCF-7 and SKBR-3 was lower (Fig. 2D). Because MCF-7 and SKBR-3 cells do not form tumors and metastasis in vivo, it appears that Etk expression may correlate with the degree of transformation of breast cancer cell lines used here.

To assess the physiological significance of Etk expression in breast cancer cells, we sought to determine whether Etk kinase activity can be stimulated by physiologically relevant molecules in mammary gland, as heregulin-β 1 (HRG), a polypeptide growth factor with a role in the development and tumorigenesi

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cer Cells—Because both Etk and Pak1 are downstream of PI3-kinase, we sought to determine whether Etk could activate Pak1. Co-transfection of MCF-7 cells with T7-tagged Etk and Myc-tagged Pak1 constructs significantly increased Pak1 kinase activity as determined by an immune-complex kinase assay using MBP as a substrate (Fig. 3B, upper panel). Because Etk is a tyrosine kinase, we hypothesized that Etk phosphorylates Pak1 on tyrosine residues. Indeed, we discovered that co-transfection of Etk and Pak1 was accompanied by a substantial stimulation of tyrosine phosphorylation of Pak1 (Fig. 3B, lower panel). To verify that Pak1 is downstream of Etk, we next demonstrated that coexpression of a kinase-defective K299R Pak1 mutant protein (designated dominant-negative (DN)-Pak1) suppressed the ability of Etk to activate Pak1 kinase activity (Fig. 3C). In the targeted Pak1 K299R sequence, the lysine 299 ATP binding site was replaced by arginine, rendering Pak1 catalytically defective as shown by us and others in cell lines (16, 18). To rule out that the observed inhibitory effect of Pak1 K299R mutant was not due to ineffective transduction of Cdc42/Rac signals, we next generated stable MCF-7 clones expressing the central inhibitory fragment of Pak1 aa 83–149 (Fig. 3D, upper panel), which does not interfere with cdc42/Rac1 binding. These stable cell lines expressing control vector or the central Pak inhibitor were transfected with T7-tagged Etk, and the effect Etk on Pak1 kinase activity was measured by subjecting the immunoprecipitated T7-Etk to in vitro kinase assay using MBP as a substrate. The Etk was able to activate Pak1 activity in vector-transfected cells but not in the cells that express Pak inhibitor aa 83–149 (Fig. 3D). Together, these results confirm that Etk regulates Pak kinase activity. While at present, we do not know whether tyrosine phosphorylation of Pak1 induced by Etk contributes to its elevated activity. To our knowledge, this is the first report that shows that Pak1 is tyrosine-phosphorylated and serves as a downstream substrate of Tec family of kinase. While interesting and reproducible, at present we do not know the significance of the tyrosine phosphorylation, and experiments are planned to explore the significance of this finding.

Interaction of Etk with Pak1 in Vivo—To determine whether the observed activation of Pak1 by Etk is due to interactions between the two proteins, we examined the association between T7-tagged Etk and Myc-tagged Pak1 in vivo by reciprocal co-immunoprecipitation and Western blot assays. Results of a representative experiment are shown in Fig. 3E. Transient expression of T7-tagged Etk, but not of control T7 vector, in MCF-7 cells was accompanied by the association of T7-tagged Etk with Myc-tagged Pak1 in both immunoprecipitation experiments. These results suggest that Etk associates with Pak1 and stimulates tyrosine phosphorylation and kinase activity of Pak1 (Fig. 3E).

To determine whether the observed association between Etk and Pak1 was direct or mediated via other proteins, we examined the ability of in vitro translated Wt-Etk or Etk-KQ protein to bind GST-Pak1 in GST pull-down assays. As shown in Fig. 3F, Etk and its N-terminal domain (aa 1–240) strongly interact with GST-Pak1; very little interaction was seen between Etk C-terminal domain (aa 243–674) and GST-Pak1, and GST alone provided a proper negative control.

Etk in Proliferation and Anchorage-independent Growth of Breast Cancer Cells—To further delineate the contribution of Etk in the biology of breast cancer cells, we established stable MCF-7 clones expressing T7-tagged Wt-Etk or kinase-inactive Etk-KQ or control vector. The results shown in Fig. 4A demonstrate the expression of tagged Etk in several representative clones. The functionality of Etk was assessed by performing in vitro kinase assays using enolase as an exogenous substrate (Fig. 4B). To determine how Etk affects the Pak1 pathway, MCF-7/Etk cells were transfected with Myc-Pak1. Overexpression of Etk in MCF-7 cells was associated with significant increases in the phosphorylation of Pak1 on tyrosine (Fig. 4C). MCF-7 cells expressing Wt-Etk were transfected with or without Myc-tagged Pak1, and tagged Pak1 was immunoprecipitated by an anti-Myc mAb and subjected to in vitro kinase assay. The upper and lower bands in Fig. 4D represent the autophosphorylated T7-Etk (73 kDa) and Myc-Pak1 (64 kDa), respectively. These protein bands were identified due to their differential electrophoretic mobilities in the gel.

To examine the influence of Etk expression on the growth characteristics of breast epithelial cancer cells, we measured the proliferation rate and the ability of cells to grow in an anchorage-independent manner. Compared with vector-transfected control cells, cells in which Wt-Etk was overexpressed demonstrated greater ability to form larger colonies in soft agar, and expression of Etk-KQ mutant led to a reduction in the anchorage-independent growth (Fig. 5A and B). In addition, as shown in Fig. 5C, the growth rate of cells expressing Wt-Etk and Etk-KQ was affected 35–40% more than that of the control vector-transfected clone. Because Pak1 has been shown to promote the anchorage-independent growth (21, 22), we next determined whether dominant-negative Pak1 could modulate the ability of Wt-Etk cells to form colonies in soft agar. Wt-Etk cells were transfected with GFP-dominant-negative Pak1 and GFP-Pak1 inhibitor and used for soft agar assay. As shown in Fig. 6, A and B, Wt-Etk cells transfected with dominant-negative Pak1 or Pak1 inhibitor form small colonies compared with Wt-Etk control cells. Together, these findings suggested that Pak1 is a downstream effector of Etk pathway and may contribute to the observed phenotypic changes by Etk.
Effect of Overexpression of Kinase-inactive Etk of Breast Cancer Cells—We next sought to determine whether Etk activity is required for the maintenance of the transformed phenotypes in breast cancer cell lines. Highly tumorigenic and invasive MDA-MB435 cells were stably transfected with T7-tagged kinase-inactive Etk mutant (Etk-KQ) or with control pcDNA vector (Fig. 7A, upper panel). As expected from the results shown in Fig. 4, overexpression of Etk-KQ led to a significant reduction in Etk and Pak1 kinase activities (Fig. 7B). The expression of Etk-KQ was accompanied by a significant inhibition of the growth rate of MDA-MB435 cells (Fig. 7C). In addition, overexpression of kinase-inactive Etk-KQ reduced the ability of cells to grow in soft agar as compared with vector-transfected control cells (Fig. 7D and E).

To investigate the significance of Etk expression in vivo, we next examined the ability of MDA-MB435 clones expressing kinase-inactive Etk-KQ or vector control in a xenograft model. In these experiments, cells were implanted into the mammary fat pad of athymic mice. Inactivation of Etk in MDA-MB435 cells severely affected the ability of cells to form tumors (i.e., by 55–70% compared with vector-transfected cells) (Fig. 8A). Histological examinations of tumors with hematoxylin and eosin staining revealed the presence of necrotic areas in tumors from Etk-KQ clones (data not shown). Reevaluation of these tumors with TUNEL staining confirmed that apoptosis was widespread in Etk-KQ tumors (Fig. 8B). Together, these findings suggest that Etk expression may be required for the maintenance of transformed phenotypes in breast cancer cells.
**DISCUSSION**

Etk is a member of the Tec family of the nonreceptor tyrosine kinases that are characterized by N-terminal PH domains. The PH domain is important in protein-protein interactions and is involved often in cytoplasmic signaling cascades. Etk is one of the few Tec family members, which are expressed in epithelial cells (10). Here we sought to determine the role of Etk in regulating breast cancer growth regulation. We report that: 1) Etk expression is developmentally regulated during mammary gland development; 2) Etk is expressed in the highly tumorigenic MDA-MB435 cell lines; 3) Etk is tyrosine-phosphorylated and is activated by physiologically relevant growth factor in breast cancer cells; 4) Etk phosphorylates Pak1 on tyrosine residues, and kinase-inactive Pak1 mutant blocked Etk activation of Pak1; 5) Etk directly interacts with Pak1 via the N-terminal PH domain-containing region; 6) overexpression of wt-Etk in noninvasive breast cancer line enhanced the ability of the cells to grow in an anchorage-independent manner; and 7) expression of kinase-inactive Etk inhibits tumorigenic phenotypes in a highly tumorigenic breast cancer cell line. Taken together, these observations suggest that Etk play an important role in the regulation of mammary epithelial cancer cells.

The finding that Pak1 kinase activity is stimulated following Etk kinase activation is important, as it implies that Etk kinase constitutes an initial signal for Pak1 activation. This hypothesis is supported by several additional observations: 1) inhibition of Etk kinase by a kinase-defective mutant was accompanied by concurrent inhibition of Pak1 activity; 2) expression of dominant-negative Pak1 mutant blocked the ability of Etk to activate the Pak1 kinase and did not affect the Etk kinase; 3) Etk directly interacted with Pak1 via its N-terminal PH domain; and 4) Etk-mediated stimulation of anchorage-independent growth was blocked by dominant-negative Pak1. These results suggest that Pak1 may be downstream of Etk kinase in breast cancer cells. These findings are inconsistent with those in a recent report (6) that showed activation of Rho rather than of Cdc42 or Rac1 (upstream regulators of Pak1) by TEC family members in mouse 3T3 fibroblast cells. To reconcile these findings, we suggest that the TEC family may utilize distinct members of the small GTPase family members in epithelial cancer and fibroblast cells in humans and/or mice.

Another notable finding in this study was that Etk induced tyrosine phosphorylation of Pak1 and that Etk activity is required for the proliferation, anchorage-independent growth and tumorigenicity of breast cancer cells. This finding strongly suggests that Etk utilises Pak1 tyrosine phosphorylation to influence transformed phenotypes that are generally believed to be driven by tyrosine phosphorylation. This hypothesis is further supported by recent findings by us and by others that overexpression of kinase-active Pak1 mutant (T423E, predominantly serine phosphorylation) in breast cancer cells selectively enhanced the anchorage-independent growth of breast cancer cells (21, 22). Currently, we do not know the precise mechanism by which Etk exerts its profound stimulatory effects in the transformation functions of cancer cells. It is possible that in addition to Pak1, there are other unidentified downstream effectors for Etk pathway that contribute the observed phenotypic changes. Studies are in progress to investigate these and other possibilities.

Our findings clearly established, for the first time, that Etk kinase directly associates with Pak1 and stimulates Pak1 tyrosine phosphorylation and that Etk controls the anchorage-independent growth rate and tumorigenic behavior of human mammary epithelial cancer cells. These observations open a new avenue of investigation closely linking the Tec and Pak families with breast cancer cell activity.

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doi: 10.1074/jbc.M103129200 originally published online May 29, 2001

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