Rictor and Integrin-Linked Kinase Interact and Regulate Akt Phosphorylation and Cancer Cell Survival

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Abstract

An unbiased proteomic screen to identify integrin-linked kinase (ILK) interactors revealed rictor as an ILK-binding protein. This finding was interesting because rictor, originally identified as a regulator of cytoskeletal dynamics, is also a component of mammalian target of rapamycin complex 2 (mTORC2), a complex implicated in Akt phosphorylation. These functions overlap with known ILK functions. Coimmunoprecipitation analyses confirmed this interaction, and ILK and rictor colocalized in membrane ruffles and leading edges of cancer cells. Yeast two-hybrid assays showed a direct interaction between the NH2- and COOH-terminal domains of rictor and the ILK kinase domain. Depletion of ILK and rictor in breast and prostate cancer cell lines resulted in inhibition of Akt Ser473 phosphorylation and induction of apoptosis, whereas, in several cell lines, depletion of mTOR increased Akt phosphorylation. Akt and Ser473P-Akt were detected in ILK immunoprecipitates and small interfering RNA–mediated depletion of rictor, but not mTOR, inhibited the amount of Ser473P-Akt in the ILK complex. Expression of the NH2-terminal (1–398 amino acids) rictor domain also resulted in the inhibition of ILK-associated Akt Ser473 phosphorylation. These data show that rictor regulates the ability of ILK to promote Akt phosphorylation and cancer cell survival.

Introduction

Mammalian target of rapamycin complex 2 (mTORC2) and integrin-linked kinase (ILK) are regulators of Akt Ser473 phosphorylation in cancer cells (1, 2). Rictor and mSin1 are essential relevant candidate responsible for this activity. Rictor and mSin1 are essential relevant candidate responsible for this activity. ILK is a β3-integrin cytoplasmic domain–interacting protein that acts as a scaffold protein aiding in the formation of protein complexes connecting integrins to the actin cytoskeleton and signaling pathways, as well as a signaling protein involved in the regulation of cell survival, proliferation, and migration (1). ILK regulates Akt Ser473 phosphorylation in a cell/tissue–dependent manner (1, 7) and studies using in vitro and in-gel kinase assays have shown that ILK can directly phosphorylate Akt on Ser473 (8). Furthermore, ILK is a critical regulator of cancer cell survival through the Akt pathway (7). Inhibition of ILK decreases Akt Ser473 phosphorylation in cancer cells in vitro (9, 10) and in xenografts in vivo (11). These studies point to a complex, cell type–specific role of ILK in regulating Akt phosphorylation and function, and suggest a switch toward dependence on ILK for Akt Ser473 phosphorylation and cell survival during cancer progression.

To better understand the molecular events involved in ILK-mediated signaling, we used a combined immunoprecipitation/mass spectrometry (MS) approach to identify novel ILK-mediated protein-protein interactions. One of the identified interacting proteins was rictor, which we now show to interact directly with ILK to regulate Akt Ser473 phosphorylation. We probed several human cancer cell lines with small interfering RNA (siRNA) to elucidate the relative contributions of mTORC2 and ILK in the promotion of Akt Ser473 phosphorylation. Our results show crucial roles for the ILK/rictor complex in the regulation of Akt Ser473 phosphorylation and cancer cell survival.

Materials and Methods

Reagents. The following antibodies were used at a dilution of 1:1,000 for Western blotting: Akt-phospho-Ser473, mTOR, rictor, p70S6K1, and p70S6K1-phospho-Thr389 (all from Cell Signaling Technology), and Akt and ILK (BD Biosciences). The β-actin antibody (Sigma-Aldrich), horseradish peroxidase–conjugated secondary antibodies (Jackson Immunoresearch Laboratories), and IR fluorescent secondary antibodies (Invitrogen Canada; Rockland Immunocchemicals) were used at 1:10,000. siRNA sequences for ILK, rictor, and mTOR have been published previously (3, 7, 10) and SMARTPOOL siRNA were purchased from Dharmacon.

Cell culture. All cell lines were grown as previously described (7). HEK293 cells were stably transfected with FLAG-tag or FLAG-ILK plasmids.

siRNA transfection. Cells were transfected in six-well plates using the SilentFect reagent (Bio-Rad Laboratories) according to the manufacturer’s instructions. To limit “off-target” effects, the total siRNA concentration was limited to <100 nmol/L, while keeping the total amount of lipid carrier added below cytotoxic concentrations. Cell monolayers were incubated with siRNA overnight, split, replated in 100-mm dishes, and incubated for the indicated times.

Cell harvest and lysis. Cells were harvested and lysed as described previously (7, 10). For immunoprecipitation experiments, cell lysis was carried out using a buffer containing 0.3% CHAPS (5). Protein
concentrations were determined using the BCA microplate assay (Pierce Biotechnology).

**Isolation of cytoskeleton.** Cytoskeletal extracts were prepared as described (12) with modifications. Briefly, cells were rinsed with 10 mL of cytoskeleton-stabilizing buffer. The Triton-soluble protein fraction was extracted with 6 mL CSB, containing 1% Triton X-100 and protease inhibitors for 2 min at 37°C. The cytoskeleton was collected in 1 mL of extraction buffer, sonicated, and dialyzed overnight.

**Immunoprecipitation and coimmunoprecipitation.** Details for the anti-FLAG immunoprecipitates are described elsewhere. For ILK, rictor, and mTOR immunoprecipitates, samples containing 1 to 3 mg total protein at 1 mg/mL were precleared with 40 mL protein G Sepharose (Roche Applied Science) for 30 min. Cleared lysates were incubated with 4 mL antibody for 2 h to overnight at 4°C. Forty microliters of protein G Sepharose were added and incubated for 1 h at 4°C. Captured complexes were washed four times in lysis buffer and analyzed by Western blotting.

**Mass spectrometry.** FLAG-ILK and FLAG-control immunoprecipitates were analyzed by gel-enhanced liquid chromatography/tandem MS (GelLC-MS/MS) using SILAC technology as described in detail elsewhere (13). Centrifuged fragment spectra were extracted with DTA Super Charge (14) and searched against the human IPI library (v3.18, 60,090 sequences) using Mascot v2.1.03.

**Western blotting.** Immunoblotting was carried out as previously described (10). For detection of mTOR and rictor, proteins were separated on 4% to 15% SDS-PAGE gradient gels (Bio-Rad Laboratories). The ILK full-length cDNA (pcDNA3.1/ILKwt) was subcloned into the pGBKT7 vector (Clontech). Yeast two-hybrid assay. DNA constructs composed of the NH2-terminal (amino acids 1–398) and COOH-terminal (amino acids 1,323–1,708) portions of rictor were generated by PCR and used to transform Saccharomyces cerevisiae strain AH109 in cotransformation combinations by a lithium acetate protocol. For analysis of interactions, 103 transformed yeast cells were plated on SC medium lacking tryptophan, leucine, and histidine (Invitrogen Biotechnology). The ILK full-length cDNA (pCDNA3.1/ILKwt) was subcloned into the pGBKKT7 vector (Clontech). The ILK full-length cDNA (pCDNA3.1/ILKwt) was subcloned into the pGBKKT7 vector (Clontech). The vectors were cotransformed into the Saccharomyces cerevisiae strain AH109 in cotransformation combinations by a lithium acetate protocol. For analysis of interactions, 103 transformed yeast cells were plated on SC medium lacking tryptophan, leucine, and histidine and incubated at 25°C for 3 d.

**Plasmid construction and transfection.** DNA constructs composed of the NH2-terminal (amino acids 1–398) and COOH-terminal (amino acids 1,323–1,708) portions of rictor were generated by PCR and individually subcloned into pcDNA3.1 vectors (Clontech). MDA-MB-231 cells grown in 10-cm dishes were transfected overnight with 10 mL DNA using a 1:1 ratio of Lipofectamine 2000 (Invitrogen Canada) according to the manufacturer’s recommendations. Assays were carried out 48 h after transfection.

**Apoptosis assay.** Apoptosis was measured using the Cell Death Detection ELISA (Roche Applied Science) as previously described (7). Samples were transfected as described above and, after splitting, an aliquot was removed, counted, plated in 96-well plates, and incubated for the time indicated. Results are expressed as the mean fold change ± SE of triplicate samples. Statistical analyses were done using Student’s t test.


**Results and Discussion**

**Identification of rictor as a binding partner for ILK.** Cytoskeletal extracts prepared from HEK293 cells stably overexpressing FLAG-tag or FLAG-tagged ILK were immunoprecipitated and analyzed by GelLC-MS/MS. Together with proteins already known to bind ILK (eg. PINCH, parvin; ref. 16), novel interactors were identified, including rictor (Fig. 1A, i). Rictor was identified consistently across several independent trials and the association was found to be highly significant (P = 6.03 × 10-5), suggesting the presence of a bona fide interaction. Furthermore, the average specific binding constant for rictor (3.3) derived from the MS analysis approached that of ILK (4), suggesting that this interaction may be stoichiometric, at least in the cytoskeletal compartment of cells overexpressing ILK. The finding of rictor in FLAG-ILK immunoprecipitates was interesting because rictor, originally identified as a regulator of cytoskeletal dynamics (17), is also a component of mTORC2, a complex implicated in Akt phosphorylation. These functions overlap with known ILK functions. To confirm the MS data, the immunoprecipitates were probed for rictor and ILK. Rictor copurified specifically with FLAG-tagged ILK (Fig. 1A, ii), further indicating that rictor can interact with ILK under conditions where ILK is overexpressed.

We next tested for the presence of the ILK/rictor interaction under endogenous conditions in human cancer cells using several complementary experimental approaches. First, we coimmunoprecipitated rictor and ILK from cytoskeletal extracts prepared from HeLa cells, a cell line used in the original identification and characterization of rictor (3), and MDA-MB-231 breast cancer cells. Rictor, but not mTOR, was clearly copurified when ILK was immunoprecipitated from these cells (Fig. 1B, i). Interestingly, we found that in HeLa cells, mTOR was not associated with the cytoskeleton and remained undetectable even when mTOR immunoprecipitations were done to concentrate potential low levels of mTOR in the cytoskeletal preparations (Fig. 1B, ii). To show the specificity of the interaction between ILK and rictor, we knocked down rictor expression in MDA-MB-231 cells using rictor siRNA and immunoprecipitated ILK. Rictor copurified with ILK from cells treated with nonsilencing siRNA, but not from cells depleted of rictor (Fig. 1B, ii). Reciprocal immunoprecipitation experiments were done using MDA-MB-231 and PC3 cells (Fig. 1B, iii), confirming the presence of ILK in rictor immunoprecipitates. The reason for the reduced amount of ILK immunoprecipitated by rictor compared with the amount of rictor immunoprecipitated by ILK is unknown, but may relate to differential abilities of either the immunoprecipitating antibodies or blotting antibodies to detect the binding partner. ILK also did not copurify with mTOR in whole-cell lysates from either MDA-MB-231 or PC3 cells (Fig. 1B, iii). As a control, we coimmunoprecipitated rictor and mTOR to confirm the presence of mTORC2 in the cell models studied (Fig. 1B, iii).

To interrogate intact cancer cells for the presence of ILK and rictor, we did immunocytochemical analyses of PC3 cells and showed a high degree of spatial concordance between ILK and rictor, particularly at the leading edge of cells and at membrane ruffles (Fig. 1C, arrows). ILK and rictor also colocalized in the MDA-MB-231 and HeLa cell lines. To determine whether the ILK/rictor interaction was direct, we prepared five overlapping fragments of rictor and used them...
as bait for several ILK constructs in a yeast two-hybrid assay. We observed growth of colonies with rictor fragments 1 and 5 (Fig. 1D), showing that NH2-terminal and COOH-terminal portions of rictor interact directly with full-length ILK and the COOH-terminal ILK kinase domain, but not with the ankyrin repeat domain of ILK (Fig. 1D). Due to its large size, demonstration of the interaction of full-length rictor with ILK was not technically feasible.

**Figure 1.** Identification of rictor as a binding partner for ILK. **A,** identification of rictor in HEK293 cells stably expressing FLAG or FLAG-tagged ILK. i, collision-induced dissociation spectra of two rictor peptides identified in GeLC-MS/MS analysis of FLAG-ILK immunoprecipitates. The mass-to-charge ratio of the doubly charged ion of LSDGFVAAEAK was measured to 0.3 ppm and that of the doubly charged ion of LYANLDLDFAK was measured to 0.4 ppm. The peptides were identified by Mascot with scores of 72 and 55, respectively. Intensity values on the ordinate axis are in arbitrary units. Fragment assignments are labeled on each spectrum and sequence insert according to standard Roepstroff-Biemann nomenclature. ii, coimmunoprecipitation of rictor and FLAG-tagged ILK. Five milligrams of cytoskeletal extracts were immunoprecipitated using anti-FLAG antibodies and analyzed by Western blotting. B, coimmunoprecipitation of endogenous rictor and ILK from human cancer cells. i, 3 mg of cytoskeletal extracts were immunoprecipitated with ILK antibodies and probed for rictor. Immunoprecipitation (IP) with an equal amount of rabbit IgG was performed to control for nonspecific binding. mTOR immunoprecipitations were done using 3 mg of cytoskeletal lysate (CS lysate) from HeLa cells. The detection of total Akt served as a control for the specific absence of mTOR. ii, siRNA-mediated depletion of rictor results in its loss from ILK immunoprecipitates. MDA-MB-231 cells were treated with 100 nmol/L rictor or nonsilencing control siRNA, and ILK was immunoprecipitated from 3 mg of CHAPS-based cell lysate. Copurifying proteins were analyzed by Western blotting. The extent of rictor knockdown is shown in the panel labeled “Lysate.” iii, reciprocal coimmunoprecipitation of endogenous ILK and rictor from cancer cells. CHAPS-based cell lysates were immunoprecipitated with rictor or mTOR antibodies and probed for ILK, rictor, and mTOR. Immunoprecipitation with species-specific nonimmune IgG was used to control for nonspecific binding. C, colocalization of ILK and rictor. PC3 cells were fixed and stained for ILK (green) and rictor (red). Arrows, areas of colocalization. Original magnification, ×60. D, analysis of the rictor/ILK interaction using a yeast two-hybrid assay. cDNA fragments encoding human rictor and the cytoplasmic domain (residues 736–798) of integrin α1 subunit (ITGα1) were subcloned into the pGBK7 vector. Full-length ILK, the ILK kinase domain, and the ILK ankyrin repeat domain were subcloned into the pGADT7 vector. These vectors were cotransformed into the yeast strain AH109. The interactions were examined by a growth test on SC-Leu-Trp-His medium. Growth was scored as positive (white disc) or negative (gray disc).
Finally, we examined the ILK/rictor complex for the presence of other mTORC2 components. We did not observe the presence of hSIN-1, mLST8, or Protor/PRR5 in the unbiased proteomic screen that we used to identify ILK interactors and, further, we could not show the presence of hSIN-1 by direct blotting of ILK immuno-precipitates using currently available commercial hSIN-1 antibodies.

The data presented here show, for the first time, an interaction between rictor and proteins outside of the mTORC2 complex, and show the differential capacity of rictor to interact with mTOR and ILK in human cancer cells. The ability of rictor to function as a constituent of both mTORC2 and the ILK multiprotein complex is not unique among the components of mTORC2. For example, the recently identified member, mSIN1, is required for mTORC2 function (4), but also binds to and regulates c-Jun NH2-terminal kinase (18) as well as Ras (19). Importantly, the demonstration of rictor as a common component of mTORC2 and ILK-containing complexes raises the possibility that these two multiprotein systems work in concert under physiologic and pathologic conditions to control various cellular processes, including cytoskeletal organization and regulation of Akt Ser473 phosphorylation.

RNA interference–mediated down-regulation of rictor and ILK inhibits Akt Ser473 phosphorylation. Our findings that rictor and ILK interact and colocalize in human cancer cells, together with published data describing ILK and mTORC2 as Akt Ser473 kinases, led us to investigate the relative role of each component in regulating Akt Ser473 phosphorylation. Using siRNA to down-regulate gene expression, we were able to achieve near-complete inhibition of ILK, rictor, and mTOR protein expression in several cancer cell lines (Fig. 2A–C). In particular, we were able to reduce the amount of mTOR expressed by these cell types to levels similar to those reported by other laboratories (20). We found that Akt Ser473 phosphorylation was suppressed by knockdown of ILK (Fig. 2A, i) or rictor (Fig. 2B) gene expression. Depletion of ILK did not alter Thr308 Akt phosphorylation (Fig. 2A, ii), showing specificity of ILK for the Ser473 phosphorylation site. In contrast, functional inhibition of mTOR, as shown by suppression of mTOR protein expression and down-regulation of S6 kinase 1 (S6K1) Thr389 phosphorylation, resulted in an...
increase in Akt Ser\textsuperscript{473} phosphorylation in some cancer cell lines (Fig. 2C). Similar data were obtained in experiments using ILK, rictor, and mTOR SMARTPOOL siRNAs (Fig. 2D). It should be noted that independent knockdown of each of the examined genes had minimal or no effect on the expression of the other genes under investigation (see Fig. 3B for an illustration). These data show that, whereas both ILK and rictor can regulate Akt Ser\textsuperscript{473} phosphorylation, global knockdown of mTOR gene expression results in enhanced phosphorylation in some cancer cell types.

The increase in Akt Ser\textsuperscript{473} phosphorylation in some cell lines following efficient mTOR knockdown was surprising, given the positive contribution to Akt phosphorylation ascribed to mTORC2 (2). Initial studies reported down-regulation of Akt Ser\textsuperscript{473} phosphorylation in response to mTOR knockdown in both Drosophila and mammalian cells, although the extent of inhibition varied with cell type (3). Subsequent reports have shown mixed effects of depletion of mTOR expression on Akt Ser\textsuperscript{473} phosphorylation, illustrating the complexities of its regulation (6, 20, 21).

Several laboratories have reported increased Akt Ser\textsuperscript{473} phosphorylation with rapamycin treatment in cancer cells (6, 22), an observation attributed to the inhibition of a negative feedback loop involving mTOR, S6K1, and IRS-1, leading to phosphatidylinositol 3-kinase (PI3K) activation (23, 24). Given that the activation of Akt by ILK is PI3K dependent (1) and our current findings show that depletion of mTOR inhibits S6K1 activity, we were interested in establishing the role of ILK in the increased Akt Ser\textsuperscript{473} phosphorylation resulting from inhibition of mTOR. Cells were treated with rapamycin or mTOR siRNA, exposed to PI3K and ILK inhibitors, and analyzed for inhibition of mTOR and changes in Akt Ser\textsuperscript{473} phosphorylation status. The increased phosphorylation induced by mTOR knockdown was PI3K dependent, as treatment of cancer cells with LY294002 completely inhibited Akt Ser\textsuperscript{473} phosphorylation, and treatment with QLT0267, a specific small-molecule inhibitor of ILK (7), significantly reduced the increased phosphorylation mediated by mTOR knockdown (Supplementary Fig. S1A). Inhibition of mTOR with rapamycin produced similar results (Supplementary Fig. S1B). Together, these data suggest that ILK is, in part, responsible for regulating Akt Ser\textsuperscript{473} phosphorylation in mTOR-dysregulated or mTOR-depleted cells and indicate a role for ILK in mediating Akt activation after release of mTOR-mediated feedback inhibition of the PI3K pathway.

ILK and rictor interact in cells depleted of mTOR and regulate Akt Ser\textsuperscript{473} phosphorylation and cell survival. Our findings demonstrating that, in certain cancer cell types, genetic down-regulation of mTOR expression to levels sufficient to inhibit mTORC2 function resulted in increased Akt Ser\textsuperscript{473} phosphorylation led us to investigate the kinase systems potentially responsible for this activity. To determine whether the ILK/rictor interaction remains intact when mTOR is absent, coimmunoprecipitations were performed using cells in which mTOR expression was silenced with siRNA. ILK copurified with rictor in mTOR-depleted MDA-MB-231 breast cancer cells (Fig. 3A), demonstrating the maintenance of the ILK/rictor complex in the absence of mTOR expression.

Next, we knocked down ILK and rictor coordinately with mTOR and assessed the levels of Akt Ser\textsuperscript{473} phosphorylation. Down-regulation of ILK or rictor gene expression, concomitant with knockdown of mTOR gene expression, inhibited Akt Ser\textsuperscript{473} phosphorylation in MDA-MB-231 cells (Fig. 3B). These data indicate that rictor and ILK maintain the ability to regulate Akt Ser\textsuperscript{473} phosphorylation although mTOR activity within mTORC2 is functionally compromised.

Because increased Akt Ser\textsuperscript{473} phosphorylation is a key event in the activation of cellular survival pathways, we investigated the downstream consequences of inhibiting ILK, rictor, and mTOR. Cellular apoptosis was determined as described in Materials and Methods. mTOR knockdown alone had a modest but significant effect (P = 0.002 compared with control siRNA) on cell death (Fig. 3C). However, when cells depleted of mTOR were used as the baseline comparator, a combination of ILK and rictor knockdown significantly enhanced the apoptotic response (P = 0.001 compared with control siRNA).
with mTOR siRNA alone; Fig. 3C). The combination of ILK, rictor, and mTOR siRNA also resulted in a significant increase in cell death compared with pairwise knockdown of mTOR and rictor as this combination did not boost levels of apoptosis beyond that of mTOR alone. Similar experiments were carried out using pharmacologic inhibitors of mTOR and ILK. Cells treated with a combination of rapamycin and QLT0267 exhibited a robust apoptotic response that was significantly greater than with either inhibitor alone (Supplementary Fig. S1C). These data suggest that ILK and rictor can regulate Akt Ser473 phosphorylation and cell survival in the absence of mTOR gene expression. Indeed, levels of immunoprecipitated ILK and rictor are similar to that present in cells treated with control siRNA (compare lanes 1 and 3 in Fig. 4A), suggesting that mTOR depletion does not affect levels of the complex.

Akt and phosphorylated Ser473 Akt are associated with the ILK/rictor complex. To begin to dissect the mechanism of the ILK/rictor complex in regulating Akt Ser473 phosphorylation, we investigated whether Akt associates with the ILK/rictor complex. Akt and Ser473P-Akt were found in ILK immunoprecipitates in addition to rictor (Fig. 4A). Akt Ser473 phosphorylation was inhibited in ILK immunoprecipitates from cells in which rictor was depleted, whereas total Akt levels were not altered (Fig. 4A). These results suggest that rictor facilitates ILK-mediated Ser473 Akt phosphorylation. Moreover, in cells in which mTOR expression had been depleted, ILK immunoprecipitates contained elevated levels of Ser473P-Akt (Fig. 4A). These data strongly suggest that a complex containing ILK and rictor recruits Akt and mediates Akt Ser473 phosphorylation, even when mTOR function is inhibited.

To further investigate the role of the ILK/rictor complex in the phosphorylation of Akt on Ser473, we engineered plasmids containing the V5-tagged NH2-terminal and COOH-terminal fragments of rictor shown to bind the ILK kinase domain in the yeast two-hybrid assay. The rictor fragments were transiently transfected into MDA-MB-231 cells and levels of Ser473P-Akt in ILK immunoprecipitates were evaluated. We observed a substantial reduction in the levels of phosphorylated Ser473P-Akt in ILK immunoprecipitates from cells expressing the NH2-terminal rictor fragment.
Importantly, the observation that genetic disruption of mTORC1 the ILK-rictor interaction may regulate Ser473 Akt phosphorylation. The amount of endogenous rictor in the ILK complex, suggesting that the terminal rictor fragment also resulted in a modest decrease in the phosphorylation of Akt on Ser 473. The expression of the NH2-terminal rictor fragment also resulted in a modest decrease in the phosphorylation requires ILK and rictor. Third, our data show, for the first time, that Akt is associated with a protein complex involved in regulation of its phosphorylation and that the ILK-rictor interaction is required for promoting Akt Ser473 phosphorylation in the ILK complex. Importantly, the observation that genetic disruption of mTORC1 and mTORC2 stimulates certain cancer cells to make available other kinases and kinase complexes to regulate Akt phosphorylation suggests that the ILK/rictor complex described here may play a role in the development of resistance to mTOR inhibitors and may also be involved in other aspects of cancer cell biology. These novel findings add to our understanding of the complex nature of regulation of Akt, a critical node in the regulation of cancer cell survival.

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