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Priority Report

Cancer Research

PIK3R1 (p85α) Is Somatically Mutated at High Frequency in Primary Endometrial Cancer

Mary E. Urick[1], Meghan L. Rudd[1], Andrew K. Godwin[3], Dennis Sgroi[4], Maria Merino[2], and Daphne W. Bell[1]

Abstract

Phosphoinositide 3-kinase (PI3K) is an important therapeutic target. Mutations in *PIK3CA*, which encodes p110α, the catalytic subunit of PI3K, occur in endometrioid endometrial cancers (EEC) and nonendometrioid endometrial cancers (NEEC). The goal of this study was to determine whether *PIK3R1*, which encodes p85α, the inhibitory subunit of PI3K, is mutated in endometrial carcinoma. We carried out exonic sequencing of *PIK3R1* from 42 EECs and 66 NEECs. The pattern of *PIK3R1* mutations was compared with the patterns of *PIK3CA*, *PTEN*, and *KRAS* mutations. The biochemical effect of seven *PIK3R1* mutations was examined by stable expression in U2OS cells, followed by coimmunoprecipitation analysis of p110α, and Western blotting of phospho-AKT^{Ser473} (p-AKT^{Ser473}). We found that *PIK3R1* was somatically mutated in 43% of EECs and 12% of NEECs. The majority of mutations (93.3%) were localized to the p85α-nSH2 and -iSH2 domains. Several mutations were recurrent. *PIK3R1* mutations were significantly ($P = 0.0015$) more frequent in *PIK3CA*-wild type EECs (70%) than in *PIK3CA* mutant EECs (18%). Introduction of wild-type p85α into U2OS cells reduced the level of p-AKT^{Ser473} compared with the vector control. Five p85α mutants, p85αdelH450-E451, p85αdelK459, p85αdelY463-L466, p85αdelR574-T576, and the p85αN564D positive control, were shown to bind p110α and led to increased levels of p-AKT^{Ser473}. The p85αR348X and p85αK511VfsX2 mutants did not bind p110α and showed no appreciable change in p-AKT^{Ser473} levels. In conclusion, our study has revealed a new mode of PI3K alteration in primary endometrial tumors and warrants future studies to determine whether *PIK3R1* mutations correlate with clinical outcome to targeted therapies directed against the PI3K pathway in EEC and NEEC. *Cancer Res; 71(12); 4061–7. ©2011 AACR.*

Introduction

Endometrial cancer kills approximately 74,000 women worldwide each year (1). Tumors are classified into 2 major subtypes, endometrioid endometrial cancers (EEC) and nonendometrioid endometrial cancers (NEEC; ref. 2). At diagnosis, the vast majority of endometrial tumors are EECs. Although many EECs are detected at an early stage and can be treated effectively with surgery, improved therapeutic strategies are needed for the treatment of recurrent and advanced-stage EECs (3, 4). NEECs represent a minority of tumors at presentation (4), but they are the most clinically aggressive subtype and cause a disproportionate fraction of all endometrial cancer–related deaths (5). Therefore, new therapeutic approaches to treat NEEC are needed.

The phosphoinositide 3-kinase (PI3K) signal transduction pathway represents an important therapeutic target (6). PI3K is a heterodimer composed of a catalytic subunit (p110α) encoded by *PIK3CA* and a regulatory subunit (p85α) encoded by *PIK3R1*. In quiescent cells, p85α binds to p110α and causes both stabilization and catalytic inhibition of p110α. Somatic mutations in *PIK3CA* occur in many tumor types, including endometrial cancer (7, 8), whereas somatic *PIK3R1* mutations are restricted to a few tumor types (9–12).

We recently showed that the ABD and C2 domains of p110α, which mediate binding to p85α, are frequently mutated in endometrial carcinomas (13). We therefore hypothesized that *PIK3R1* (p85α) itself might be mutated in endometrial tumors. Herein, we report that *PIK3R1* is somatically mutated in 43% of EECs and 12% of NEECs. Mutations preferentially localized to the p85α-iSH2 domain, which mediates binding to p110α. Several *PIK3R1* mutations promoted increased phosphorylation of AKT^{Ser473}. Collectively, our findings reveal a new mechanism by which the PI3K pathway is activated in endometrial cancer.

Authors' Affiliations: [1]Cancer Genetics Branch, National Human Genome Research Institute, and [2]National Cancer Institute, NIH, Bethesda, Maryland; [3]University of Kansas Medical Center, Kansas City, Kansas; and [4]Massachusetts General Hospital Cancer Center, Charlestown, Massachusetts

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M. E. Urick and M.L. Rudd contributed equally to this study.

Corresponding Author: Daphne W. Bell, Cancer Genetics Branch, National Human Genome Research Institute, NIH, Building 50, Room 5339, 50 South Drive, Bethesda, MD 20892. Phone: 301-594-9256; Fax: 301-594-1360; E-mail: belldaph@mail.nih.gov

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Materials and Methods

Clinical material

Primary tumor (42 EECs and 66 NEECs) and matched normal tissues were collected at resection, prior to treatment, and obtained with appropriate Institutional Review Board approval (13). A pathologist reviewed hematoxylin and eosin sections of tumors to verify histology and delineate regions of tissue composed of more than 70% tumor cells for macrodissection.

Genomic DNA extraction and identity testing

Genomic DNA was isolated from macrodissected tumor tissue or normal tissue by using the PUREGENE Kit (Gentra Systems). Matched tumor and normal DNAs were genotyped using the Coriell Identity Testing Kit.

PCR and sequencing

All coding exons of *PIK3R1* were amplified from tumor DNA, using the PCR, followed by nucleotide sequencing (see Supplementary Methods). Purified tumor cell populations were isolated from 3 tumors by using laser capture microdissection (LCM), followed by reverse transcriptase PCR (RT-PCR) and sequencing to determine whether there was monoallelic or biallelic expression of mutations (See Supplementary Methods).

Expression constructs

A retroviral expression construct containing full-length, wild-type *PIK3R1* cDNA in the pBABE vector (Addgene) was used to generate a series of *PIK3R1* mutant constructs by site-directed mutagenesis with the QuikChange II XL Site-Directed Mutagenesis Kit (Stratagene). Inserts were excised using *Bam*HI and *Sal*I and subcloned into the MYC-tagged pCMV-3Tag-7 expression vector (Agilent Technologies). The integrity of inserts was confirmed by Sanger sequencing.

Transfections, immunoprecipitation, and Western blotting

The osteosarcoma cell line U2OS was provided by Sean Lee (NIH); it was not subjected to an authentication test. U2OS cells were transfected with vector, wild-type, or mutant p85α expression constructs by using FuGENE-6 (Roche). Following hygromycin selection, pools of stably selected cells were serum starved in DMEM/0.5% FBS for 16 hours, followed by lysis and Western blotting (details in Supplementary Methods). For immunoprecipitation, lysates were incubated with MYC-tag Sepharose bead conjugates (Cell Signaling) overnight at 4°C. All Western blots were repeated in triplicate.

Results

Somatic *PIK3R1* mutations are frequent in primary EECs and NEECs

PIK3R1 was somatically mutated in 43% (18 of 42) of EECs and 12% (8 of 66) of NEECs ($P = 0.0004$, 2-tailed Fisher's exact test; Table 1 and Supplementary Fig. S1). Within the NEECs, 8% (4 of 46) of serous tumors and 20% (4 of 20) of clear cell tumors were mutated. We observed no significant correlations between *PIK3R1* mutations and tumor stage or grade (Supplementary Tables S3 and S4).

The distribution of *PIK3R1* mutations was nonrandom; 93.3% (28 of 30) of *PIK3R1* mutations, including 3 recurrent mutations, localized to the nSH2 and iSH2 domains of p85α that mediate binding to p110α (Fig. 1). Fifty percent (15 of 30) of all coding mutations localized within the proximal region (residues 434–475) of the iSH2 domain, including a series of 10 overlapping in-frame deletions defined by 3 shortest regions of overlap (SRO1–SRO3; Fig. 1).

All somatic *PIK3R1* mutations seemed to be heterozygous. To determine whether the mutations were truly heterozygous or if the wild-type allele was contributed by contaminating normal cells, we used LCM to isolate purified tumor cell populations from 3 cases (T88, T100, and T120), followed by RT-PCR and sequencing. Expression of both mutant and wild-type alleles was observed, confirming heterozygosity in tumor cells (Supplementary Fig. S2).

In EECs, *PIK3R1* mutations frequently coexist with *PTEN* and *KRAS* mutations but tend to be mutually exclusive with *PIK3CA* mutations

PIK3R1 and *PIK3CA* mutations are mutually exclusive in glioblastoma multiforme but coexist in colorectal cancer (10, 11, 14). We previously determined the mutational status of *PIK3CA*, *PTEN*, and *KRAS* in our endometrial tumors (13). When these results were merged with those from our analysis of *PIK3R1* mutations, we found that 95% (40 of 42 cases) of EECs, and 41% (27 of 66) of NEECs had somatically mutated 1 or more of the 4 genes (Fig. 2). We evaluated the patterns of mutations among EECs because all 4 genes were mutated at high frequency in these tumors. There was no significant difference in the frequency of *PIK3R1* mutations between *PTEN* mutant (48%, 16 of 33 tumors) and *PTEN* wild-type EECs (22%, 2 of 9 tumors), or between *KRAS* mutant (50%, 9 of 18 tumors) and *KRAS* wild-type EECs (37%, 9 of 24 tumors). In contrast, *PIK3R1* mutations were significantly ($P = 0.0015$) more frequent in *PIK3CA* wild-type EECs (70%, 14 of 20) than in *PIK3CA* mutant EECs (18%, 4 of 22).

Ten tumors (4 EECs and 6 NEECs) had coexisting *PIK3R1* and *PIK3CA* mutations (Table 2). Strikingly, the proportion of truncating mutants of *PIK3R1* that coexisted with *PIK3CA* mutants (63%, 7 of 11 truncations) was significantly higher ($P = 0.010$) than the proportion of missense mutations or in-frame insertions/deletions of *PIK3R1* (12%, 2 of 17 mutations) that coexisted with *PIK3CA* mutations.

A subset of p85α mutants leads to increased phosphorylation of AKT^{Ser473} *in vitro*

We transfected U2OS osteosarcoma cells with constructs expressing either wild-type or mutant *PIK3R1* to determine the biochemical effects of p85α mutants on phosphorylation of AKT^{Ser473}, an important PI3K substrate. We used U2OS cells because they express low endogenous levels of phospho-AKT^{Ser473} (p-AKT^{Ser473}; ref. 15). Seven p85α mutants present in endometrial tumors were analyzed: p85αdelK459 and p85αdelY463-L466, which define SRO2 and SRO3;

Table 1. Somatic *PIK3R1* mutations in primary endometrial tumors

Case no.	Histology	Mutated exon/intron	*PIK3R1* nucleotide change[a]	Predicted p85α amino acid change[b]	Predicted effect on protein
EECs					
T85	Endometrioid	Exon 12/intron 12	c.1730_1745+3delGAGACCAATACTTGATGTA	delR577_M582insK[c]	In-frame insertion and deletion
T88	Endometrioid	Exon 8	c.C1042T	R348X	Premature truncation
T93	Endometrioid	Exon 10	c.1351_1356delGAATAT	delE451_Y452	In-frame deletion
T93	Endometrioid	Exon 10	c.1373_1375delAAA	delK459	In-frame deletion
T95	Endometrioid	Exon 10	c.1369_1383delCAAGAAAAAAGTCGA	delQ457_R461	In-frame deletion
T100	Endometrioid	Exon 10	c.1348_1353delCATGAA	delH450_E451	In-frame deletion
T104	Endometrioid	Exon 12	c.1719_1727delGAGAAAGAC	delR574_T576	In-frame deletion
T106	Endometrioid	Intron 10	c.1426–13A>G	Q475_E476insIMLQ[c]	In frame insertion
T119	Endometrioid	Exon 8	c.C1072T	R358X	Premature truncation
T119	Endometrioid	Exon 10	c.1386_1387insTATG	D464VfsX2	Premature truncation
T120	Endometrioid	Exon 12	c.1719_1727delGAGAAAGAC	delR574_T576	In-frame deletion
T122	Endometrioid	Exon 11	c.1529_1530delAA	K511VfsX2	Premature truncation
T124	Endometrioid	Exon 15	c.2103_2104insAGAA	L702RfsX48	Frameshift and extended protein
T124	Endometrioid	Intron 7/exon 8	c.1020–13_c.1026delGTTTTCATTTCAGGGAAGAA	Not determined	–
T126	Endometrioid	Intron 10	c.1426–9_1426–32delTATGACATTATCTTTTTAAAATTA	Q475_E476insVLQ[c]	In-frame insertion
T126	Endometrioid	Exon 12	c.1624_1626delAGA	delR542	In-frame deletion
T128	Endometrioid	Exon 10	c.1365_1382delGTTTCAAGAAAAAAGTCG	delF456_R461	In-frame deletion
T129	Endometrioid	Exon 11	c.C1494A	C498X	Premature truncation
T129	Endometrioid	Exon 10	c.1399_1425+2delTATGAAGAATATACCCGCACATCCCAGGT	delD434_Q475[c]	In-frame deletion
T130	Endometrioid	Exon 10	c.1367_1382delTTCAAGAAAAAAGTCGAinsCT	delF456_R461insS	In-frame deletion/insertion
T132	Endometrioid	Exon 10	c.1386_1397delATATGATAGATT	delY463_L466	In-frame deletion
T134	Endometrioid	Exon 11	c.G1483T	E495X	Premature truncation
T137	Endometrioid	Exon 10	c.1425+2T>G	delD434_Q475[c]	In-frame deletion
NEECs					
T3	Serous	Intron 10	c.1426–21C>A	Not determined	–
T3	Serous	Intron 8	c.1119–25C>A	Not determined	–
T21	Clear cell	Exon 10	c.1386_1387delAT	Y463X	Premature truncation
T28	Serous	Exon 12	c.A1690G	N564D	Nucleotide substitution
T61	Clear cell	Exon 10	c.1358_1390delACACTCAGTTTCAAGAAAAAAGTCGAGAATATG	delT454_D464	In-frame deletion
T74	Serous	Exon 7	c.C1002G	Y334X	Premature truncation
T77	Clear cell	Exon 6	c.C901T	R301X	Premature truncation
T79	Serous	Exon 8	c.C1042T	R348X	Premature truncation
T113	Clear cell	Exon 10	c.1372_1373insA	S460KfsX5	Premature truncation
T113	Clear cell	Exon 12	c.A1643G	D548G	Nucleotide substitution

[a]Nucleotide positions are based on transcript ENST00000396611.

[b]Amino acid positions are based on protein ENSP00000379855.

[c]The predicted protein change was determined by sequencing RT-PCR products to determine any effect of the mutated intronic bases on splicing.

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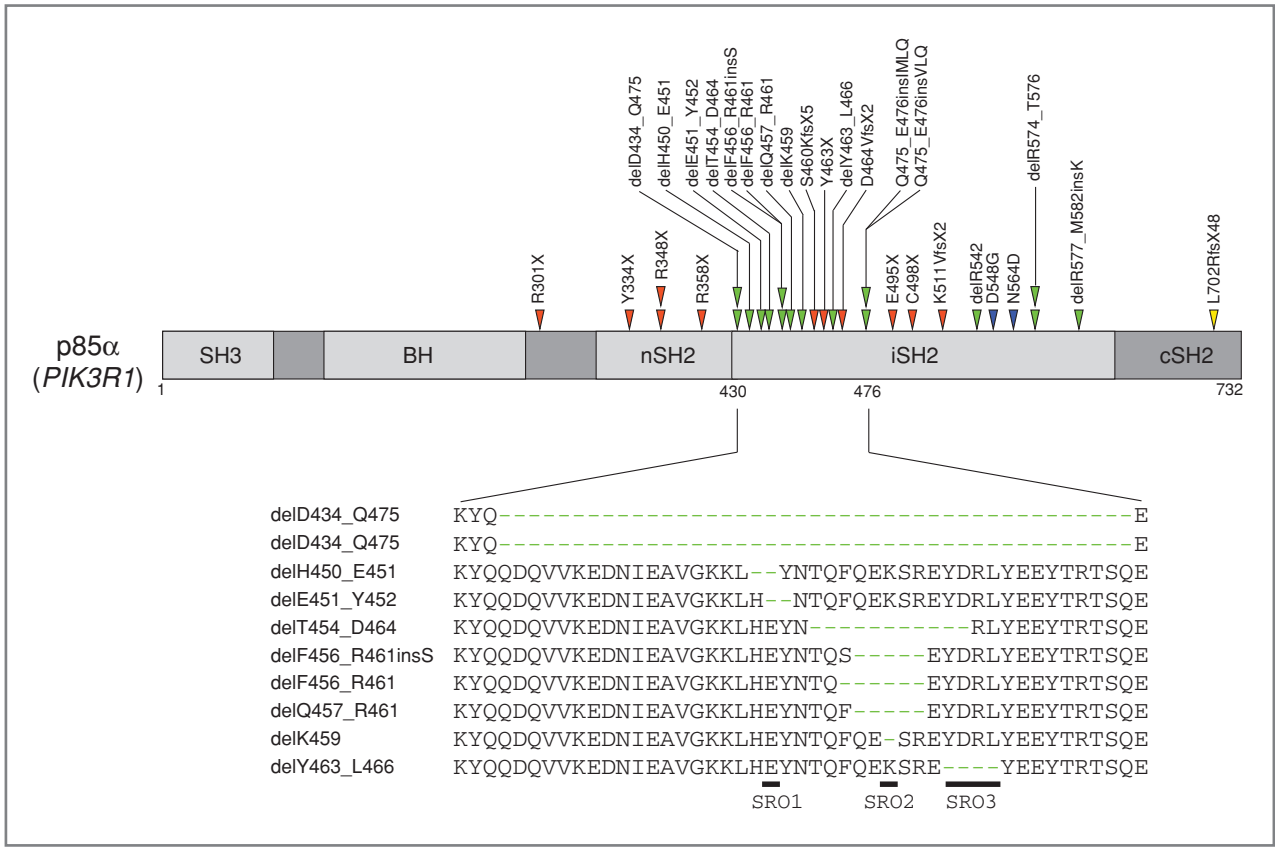

Figure 1. p85α (*PIK3R1*) mutations in primary endometrial carcinomas. Top, schematic representation of the p85α protein showing positions of somatic mutations relative to functional domains. Each arrowhead represents a single mutation: nonsense mutations and frameshift mutations (red arrowheads); in-frame insertions and deletions (green arrowheads); missense mutations (blue arrowheads); frameshift mutation that extends the protein (yellow arrowhead). Bottom, overlapping somatic in-frame deletions (dashed lines) within the proximal iSH2 domain. Three SROs between deletions are indicated (black bars).

p85αR348X and p85αdelR574-T576, which were recurrent mutations in our study; p85αK511VfsX2, the most carboxy-terminal truncation mutant; and p85αdelH450-E451 and p85αN564D, which were present in endometrial tumors as well as in other tumor types (10, 11). p85αN564D served as a positive control because it is known to increase PI3K activity (10).

Coimmunoprecipitation of p110α and MYC-tagged p85α mutants showed that all mutants retained the ability to bind p110α except for p85αR348X and p85αdelK511VfsX2 (Fig. 3A). Western blotting showed the expected low endogenous level of p-AKT^{Ser473} in U2OS cells transfected with the vector control (Fig. 3B). As noted previously (10), and consistent with the inhibitory effect of wild-type p85α on the PI3K pathway, introduction of wild-type p85α into U2OS cells reduced the level of p-AKT^{Ser473} compared with vector alone (Fig. 3B). In contrast to wild-type p85α, stable expression of 5 p85α mutants (p85αdelH450-E451, p85αdelK459, p85αdelY463-L466, p85αdelR574-T576, and p85αN564D) led to increased levels of p-AKT^{Ser473} compared with vector control (Fig. 3B). Only the p85αR348X and p85αK511VfsX2 mutants did not exhibit appreciable changes in p-AKT^{Ser473} levels compared with vector control. Ribosomal protein S6, an important downstream target of AKT and mTOR, exhibited a similar phosphorylation pattern to AKT^{Ser473} (Fig. 3B).

Discussion

To our knowledge, this is the first report of somatic *PIK3R1* (p85α) mutations in endometrial carcinoma. The high frequency and nonrandom distribution of these mutations strongly suggests that mutations of *PIK3R1* may be examples of "driver" mutations (16) that confer a selective advantage in endometrial tumorigenesis. In support of this idea, we show that stable expression of several p85α mutants leads to functional activation of the PI3K pathway, as evidenced by increased phosphorylation of AKT^{Ser473}. Our present findings have relevance not only to endometrial cancer but also to other tumor types; one of the mutants (p85αdelH450-E451) that we have shown to promote AKT^{Ser473} phosphorylation has also been found in a glioblastoma (14).

Analysis of 2 in-frame deletion mutants that correspond to the 2 shortest regions of overlapping deletion within the proximal p85α-iSH2 domain (p85αdelK459 and p85αdelY463-L466) showed that each promotes phosphorylation on AKT^{Ser473}. On the basis of this finding, we predict that the additional overlapping in-frame deletions are also likely to have altered biochemical properties. Although we have not determined the mechanism by which these deletions promote AKT phosphorylation, we speculate that it might result from

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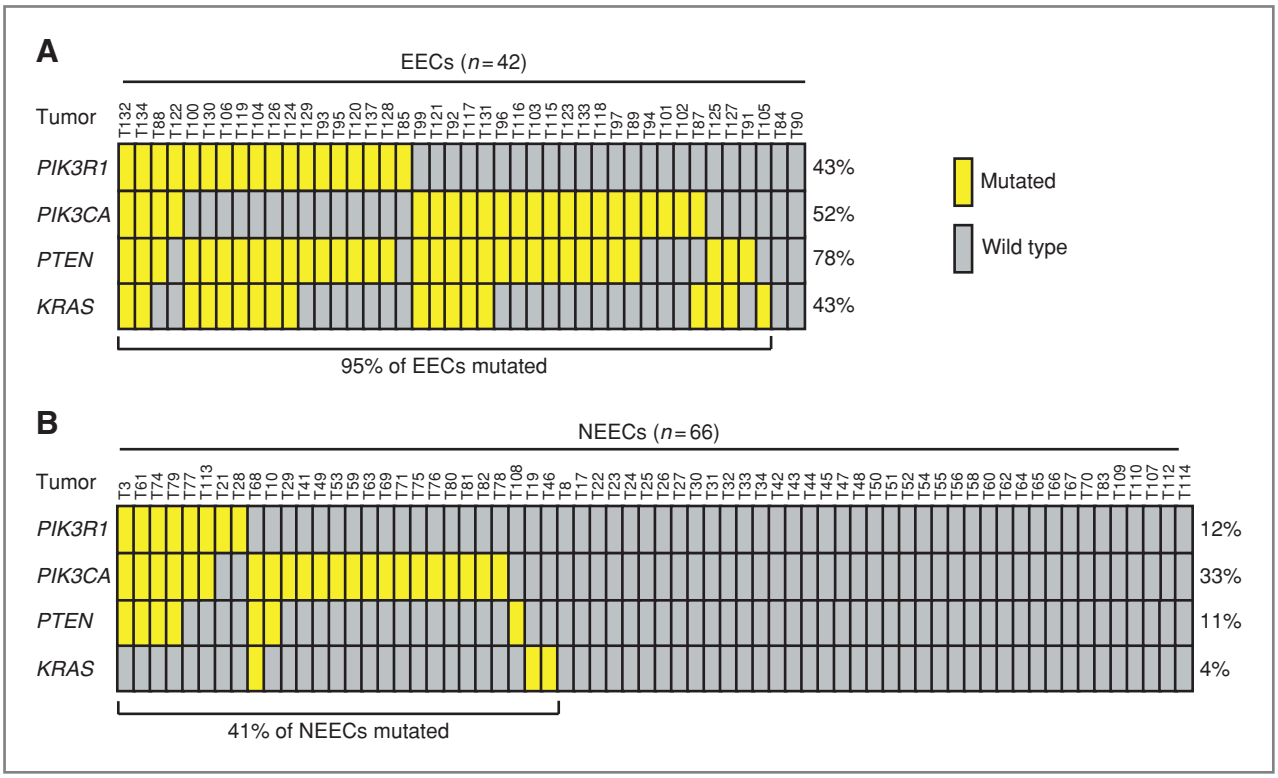

Figure 2. *PIK3R1*, *PIK3CA*, *PTEN*, and *KRAS* mutational status in primary endometrial carcinomas. The mutation pattern is shown for (A) 42 EECs and (B) 66 NEECs. Columns represent individual tumors (T). Somatically mutated tumors (yellow bars) are distinguished from tumors with no detectable somatic mutation (gray bars). The mutation frequency for individual genes is shown (at right).

altered interactions between the mutant forms of p85α and the cell membrane, as structural studies have suggested that residues 447 to 561 of p85α form contact with lipid membranes (17) and/or from altered interactions between the p85α-iSH2 domain and the p110α-ABD domain (18).

An excess of p85α-nSH2 and -iSH2 truncation mutants was observed in endometrial tumors that had coexisting mutations in *PIK3CA*. We therefore hypothesize that these truncating mutants of p85α are not functionally equivalent to p110α mutants. In support of this idea, the p85αR348X and

Table 2. Endometrial tumors with coexisting p85α and p110α mutants

Case no.	Histology	p85α mutant	p110α mutant[a]
EECs			
T88	Endometrioid	R348X	R88Q[b], F667L
T122	Endometrioid	K511VfsX2	H1047R[b]
T132	Endometrioid	delY463_L466	M1004I
T134	Endometrioid	E495X	E545K[b], M1043V[b]
NEECs			
T3	Serous	Intronic	E81K
T61	Clear cell	delT454_D464	E453A
T74	Serous	Y334X	H1047Y[b], R93Q, K111N[b]
T77	Clear cell	R301X	H1047R[b]
T79	Serous	R348X	T1025A
T113	Clear cell	S460KfsX5, D548G	A222V, E365K[b]

[a]From Rudd and colleagues (13).
[b]Activating mutants of p110α.

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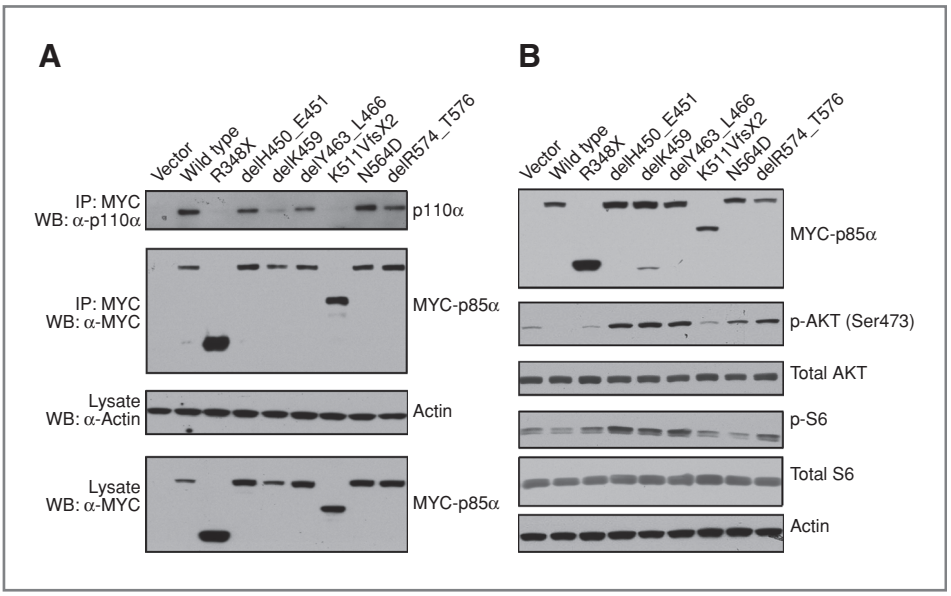

Figure 3. Increased phosphorylation on AKT^{Ser473} following exogenous expression of p85α mutants in U2OS cells. A, coimmunoprecipitation of p110α with p85α mutants. All mutants bound p110α except p85αR348X and p85αK511VfsX2. IP, immunoprecipitation; WB, Western blotting. B, Western blots of U2OS osteosarcoma cells stably transfected with MYC-tagged expression constructs encoding either vector only, wild-type p85α, or mutant forms of p85α found in endometrial tumors. The p85αN564D mutant served as a positive control because it promotes increased p-AKT^{Ser473} levels compared with wild-type p85α (10).

p85αK511VfsX2 truncations, which coexist with p110α mutations, did not bind to p110α or increase p-AKT^{Ser473} levels when stably expressed in U2OS cells. In the case of the p85αR348X mutant, this is consistent with previous observations that this protein fails to bind p110α (10). Because the p85αR301X and p85αY334X mutants, which also coexisted with p110α mutations, truncate p85α amino terminal to residue 348, we predict that these mutants also do not bind p110α or hyperphosphorylate AKT. Exactly how the truncating mutants of p85α, which coexist with p110α mutants, affect p85α function remains to be determined. Nonetheless, their effect on structurally important domains, their preferential co-occurrence with p110α mutations, and the recurrent nature of the R348X mutant here and in colorectal cancers (10) strongly suggest that these are likely to be driver mutations that contribute to endometrial tumorigenesis. Because the majority of somatic *PIK3R1* mutations uncovered in NEECs were truncation mutants, of uncertain functional significance, future studies will be critical to elucidate the contribution of p85α disruption to this tumor subtype.

In conclusion, we have identified a new mode of PI3K alteration in primary endometrial tumors. Targeted therapies directed against the PI3K pathway have already entered clinical trials for patients with endometrial cancer (19–21). Our findings indicate that it will be important to consider the mutational status of *PIK3R1* as molecular correlates associated with clinical outcome are sought. Finally, given our observation that not all p85α mutants are functionally equivalent, future studies will be critical to understand the biochemical properties of the complete spectrum of *PIK3R1* mutations present in endometrial carcinoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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