The phosphatidylinositol 3-kinase (PI3K) enzyme is an obligate heterodimer composed of a regulatory subunit (p85) and a catalytic subunit (p110) (1). The inter-SH2 domain of p85 binds to both the adapter-binding domain and the C2 domain of p110, causing its stabilization and catalytic inhibition, respectively (2). Once recruited to the membrane by the interaction of p85 with a variety of receptors, p110 is activated through a conformational switch and produces phosphatidylinositol 3,4,5-trisphosphate (PIP3), which functions as a cellular second messenger. PIP3 recruits kinases containing a pleckstrin homology domain to the cell membrane, where they are activated. These kinases, the most important of which is AKT, control a multitude of pathways, including cell growth, survival, and metabolism (3). The tumor suppressor lipid phosphatase PTEN hydrolyzes PIP3 to PIP2, thus acting as a functional antagonist of PI3K (4).

The activation of PI3K is necessary and sufficient to overcome the inhibitory control of p85 over p110; however, one specific mechanism that leads to constitutive PI3K activation is the finding that PIK3R2 is also frequently mutated in EC, because the mutation rate so far reported in any tumor type was negligible.

Most EC PTEN mutations are in heterozygosity, and about half of the PTEN- tumors show complete loss of protein expression, supporting the notion that epigenetic and postranslational mechanisms contribute to PTEN loss during neoplastic transformation. Furthermore, PTEN heterozygous mutations frequently coexist with PIK3CA, PIK3R1, and PIK3R2 mutations, and in this case a lower percentage of tumors shows complete loss of PTEN protein, strongly suggesting that activation of PI3K is necessary and sufficient to overcome the activity of the remaining PTEN allele.

These compelling genetic data seem to seriously undermine the notion of PTEN haploinsufficiency by providing evidence of mechanisms that bypass the need for total PTEN loss to activate PI3K downstream signaling.

A second key finding in the article by Cheung and colleagues (8) comes from the analysis of the effect exerted by PIK3R1 and PIK3R2 mutations on PI3K signaling. Based on the current knowledge of p85’s role in controlling p110 activation, it is not unexpected that most PIK3R1 and PIK3R2 mutations are gain-of-function and work by removing the inhibitory control of p85 over p110; however, one specific PIK3R1 mutant, E160*, unexpectedly uncovers a different mechanism that leads to constitutive PI3K activation. This notion, supported by an initial analysis of the correlation between EC genetic alterations and cell line response to mTOR, PI3K, and mitogen-activated protein kinase inhibitors, will now open the way to a more rational combination of targeted therapies in advanced EC patients.
PTEN as a homodimer, and binding of the mutant p85α to the wild-type protein impairs the ability of the dimer to interact with and protect PTEN.

Although these data, combined with the finding of PIK3R1 mutations, may contribute one additional mechanism explaining loss of PTEN protein in PTEN wild-type or heterozygous tumors, more stringent validation is now necessary using in vivo models to convincingly prove that p85α protects PTEN from proteasomal degradation in a physiologically relevant system. For example, it would be interesting to reevaluate the data presented by Luo and colleagues (11) showing that loss of one Pik3r1 allele increases the number of intestinal polyps but decreases prostate cell proliferation, and has no effect on T-cell hyperproliferation in Pten−/− mice, by comparing the levels of Pten protein in these different tissues showing opposite behavior. Along the same lines, it is important to point out that the levels of Pten protein do not seem to change in the liver of 6-month-old conditional Pik3r1 mutants (12).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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New Routes to Old Places: PIK3R1 and PIK3R2 Join PIK3CA and PTEN as Endometrial Cancer Genes

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