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

Sandra Herrero-Gonzalez and Antonio Di Cristofano

Summary: Cheung and colleagues identify PIK3R1 and PIK3R2, the genes encoding the α and β isoforms of the phosphatidylinositol 3-kinase (PI3K) p85 regulatory subunit, as additional mutation targets in endometrial cancer, and describe a novel mechanism leading to PTEN loss. Cancer Discovery. 1(2):106–7. ©2011 AACR.

Commentary on Cheung et al., p. 170(8).

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).

Given the range of biological processes controlled by PI3K, it is not surprising that mutations that lead to aberrant activation of the PI3K cascade are frequent events in human cancers (5). In particular, type I, estrogen-related, endometrial cancer (EC) appears to harbor mutations in PI3K pathway members with a particularly high prevalence (6). Previous reports had established high mutation rates for both PTEN and the gene encoding the α isoform of p110, PIK3CA (7). In this issue of Cancer Discovery, Cheung and colleagues (8) present an extremely comprehensive analysis of more than 200 primary ECs that validates the notion of PTEN haploinsufficiency and describes a novel mechanism leading 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 this 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.

It was previously shown that p85α interacts with and increases PTEN activity (10). Cheung and colleagues (8) now show that expression of wild-type p85α, but not p85β, increases PTEN protein levels through stabilization. Expression of the p85α E160* truncation mutant, which cannot bind PTEN, leads instead to reduced levels of PTEN protein due to increased ubiquitination and degradation. It appears that p85α binds
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.

Published online July 18, 2011.

**REFERENCES**

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

Sandra Herrero-Gonzalez and Antonio Di Cristofano


Updated version  Access the most recent version of this article at: http://cancerdiscovery.aacrjournals.org/content/1/2/106

Cited articles  This article cites 12 articles, 7 of which you can access for free at: http://cancerdiscovery.aacrjournals.org/content/1/2/106.full#ref-list-1

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.