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p85β increases phosphoinositide 3-kinase activity and accelerates tumor progression

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Class IA phosphoinositide 3-kinases (PI3K) are lipid kinases that generate 3-poly-phosphorylated phosphoinositides (PtdIns) at the plasma membrane; they are composed of a p85 regulatory subunit (p85α, p85β or p55γ, encoded by *PIK3R1, PIK3R2* or *PIK3R3*) and a 110 kDa catalytic subunit (p110α, p110β or p110δ, encoded by *PIK3CA, CB* or *CD*). p85α and p85β, as well as p110α and p110β, are ubiquitous and form heterodimeric complexes.[1] Whereas p85α (*PIK3R1*) is known to modulate p110α (*PIK3CA*) stability, intracellular localization and activation,[2] the effect of p85β (*PIK3R2*) on p110 is less well-understood.

p85β is expressed at lower levels than p85α in most human tissues; however, this was recently reported to be reversed in breast and colon carcinomas, in which p85α levels are lower than those of p85β. This change in p85 regulatory subunit usage correlates with increased PI3K pathway activation and tumor progression, as confirmed in mouse models.[3] Nonetheless, p85β effects could vary depending on cell genetic background, since its deletion in heterozygous *Pten*$^{+/-}$ mice does not alter the incidence of intestinal polyps.[4] Moreover, although p85β expression is lower than that of p85α in most normal tissues, it is physiologically high in neurons (www.genevestigator.com).

Increased PI3K activation is a frequent event in cancer.[1] Elevated p85β expression is a strategy for PI3K pathway enhancement that is not used by all cancer types; a review of microarray experiments deposited in Oncomine (www.oncomine.org) shows that *PIK3R2* mRNA expression is increased only in a few tumor types (although p85β can also be elevated by reduction of microRNA126 levels).[3] These tumors include colon and breast carcinomas. Other tumors use different strategies, sometimes more than one, to activate PI3K pathway. For example, bladder carcinomas show increased p110β expression (in approximately 90% of tumors), reduced *PTEN* expression (~50%), heterozygous *PTEN* deletion (~10%) and *PIK3CA* mutations (~15%), whereas lung carcinomas (squamous and small cell) frequently show *PIK3CA* amplification (~50 and ~20%, respectively). In contrast, pancreatic tumors show activating mutations in p85α (17%).[5] In endometrial cancer, several mutations have been identified that increase PI3K pathway activation, including *PTEN* loss (35–50%), *PIK3CA* mutation (30%) and *K-Ras* mutations (20%); mutations in *PIK3R1* (20%) and *PIK3R2* (5%) have also been reported in endometrial tumors.[6] Nonetheless, at difference from *PIK3R1* mutations, *PIK3R2* mutations do not concentrate in hotspots, and many are functionally silent. These genetic alterations could represent random mutations generated by defects in DNA mismatch repair (in ~20% of endometrial tumors). One of the *PIK3R2* mutations described in endometrial cancer produces a more active p85β mutant than the wild type protein,[6] suggesting that this mutation relieves p110 from p85β constraint, mimicking growth factor-induced p85β/p110α activation. Thus, as for *PIK3CA*, *PIK3R2* might show increased expression and mutation.

The study of the mechanism of p85β action showed that purified p85β/p110α phosphorylates its physiological substrate PtdIns (4,5)P_2 more efficiently than p85α/p110α; moreover, in transfected cells, increased p85β/p110α expression moderately enhanced PI3K activity in basal conditions. Nevertheless, both p85α/p110α- and p85β/p110α-expressing cells showed maximal PI3K activation only after growth factor addition, suggesting that despite basal activation, p85β/p110α responds to receptor stimulation.[3] These results imply a difference in the effects of p85α and p85β regulatory subunits on p110α. The complexity of p85 action on p110 is greater when we consider distinct p110 isoforms; for example, the cSH2 domain (found in all p85 forms) inhibits p110β but not p110α.[7] In addition to the effects on p110 activity, increased p85β expression is able to induce p110-independent migratory cell morphology.[3]

These results suggest that the p85β mode of action (compared with that of p85α) involves a different affinity for phosphoinositides and distinct inhibitory action on p110α, indicating that p85α and p85β control p110 in different ways (**Fig. 1**). p85β might also promote additional mechanisms of colon and breast tumor progression. For instance, p85α binds to PTEN (phosphatase and tensin homolog) and increases its phosphatase activity;[8] p85β also forms a complex with PTEN but could have a distinct effect on PTEN activity (**Fig. 1**). The p110-independent morphological change induced by p85β might be evidence that p85β acts as a scaffold for distinct cytoskeletal regulatory proteins than p85α, which also has a kinase-independent adaptor function.[9] Since p85β/p110β localizes to the nucleus,[10] p85β could regulate p110β nuclear function (**Fig. 1**). p85β thus modulates p110 activation and binds to

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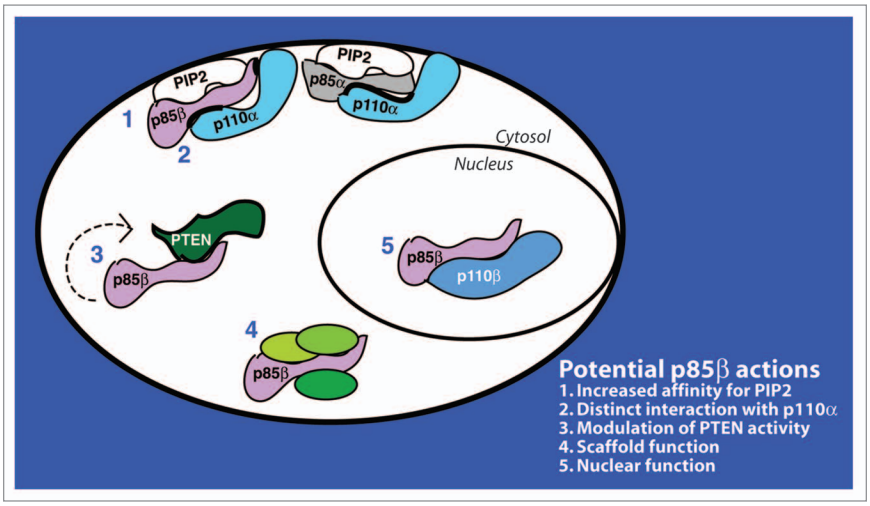

Figure 1. Potential mechanisms for p85β modulation of cell responses

membrane lipids; further study will clarify whether p85β functions as a scaffold, participates in PTEN activation or acts in the nucleus.

The selective increase on p85β regulatory subunit expression represents an unanticipated mechanism for PI3K activation and a novel strategy for tumor progression.

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