# Phosphatidylinositol-4,5-bisphosphate 3-kinase 2.7.1.153

## 1 Nomenclature

**EC number**
2.7.1.153

**Systematic name**
ATP:1-phosphatidyl-1D-myo-inositol-4,5-bisphosphate 3-phosphotransferase

**Recommended name**
phosphatidylinositol-4,5-bisphosphate 3-kinase

**Synonyms**
P120-PI3K
PI3K
PI3K$\beta$
PI3K$\gamma$
PtdIns(4,5)P2 3-OH kinase
PtdIns-3-kinase p101
PtdIns-3-kinase p110
PtdInsP 3-OH$^-$kinase
class I PI3K
class I phosphoinositide 3-kinase
kinase (phosphorylating), phosphatidylinositol 4,5-diphosphate 3-
p101-PI3K
p110$\delta$
phosphatidylinositol (4,5)-bisphosphate 3-hydroxykinase
phosphatidylinositol 3-hydroxyl kinase
type I phosphoinositide 3-kinase

**CAS registry number**
103843-30-7

## 2 Source Organism

<1> *Drosophila melanogaster* [1]
<2> *Caenorhabditis elegans* [1]
<3> *Dictyostelium discoideum* [1]
<4> *mammalia* [1, 3]
<5> *Homo sapiens* [1, 2, 5]
<6> *Gallus gallus* [4]
<7> *Mus musculus* [6]

## 3 Reaction and Specificity

**Catalyzed reaction**

ATP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate = ADP + 1-phosphatidyl-1D-myo-inositol 3,4,5-trisphosphate

**Reaction type**

phospho-group transfer

**Natural substrates and products**

**S** Additional information <1, 2, 3, 4, 5, 6> (<1,2,3,4>, enzyme is involved in the synthesis of 3-phosphoinositides. Class I phosphoinositide 3-kinases are further subdivided into class IA and IB enzymes, which signal downstream of tyrosine kinase and heterotrimeric G protein-coupled receptors, respectively. All class I phosphoinositide 3-kinase members also bind to Ras, but the role of this interaction in physiological phosphoinositide 3-kinase signalling is not entirely clear [1]; <1,4>, enzyme can promote proliferation [1]; <1,2,3,4>, phosphoinositide 3-kinase and DNA synthesis [1]; <1,2,3,4>, phosphoinositide 3-kinase and apoptosis [1]; <4>, the adaptor subunits of the class IA enzymes bind phosphorylated Tyr residues, thereby linking the phosphoinositide 3-kinases catalytic subunit to tyr kinase signalling pathways [3]; <6>, enzyme is activated by binding of osteopontin to integrin $\alpha v\beta_3$ [4]; <5>, involvement of the enzyme in CD18-mediated adhesion of human neutrophils to fibrinogen [5]) [1, 3, 4, 5]

**P** ?

**Substrates and products**

**S** ATP + 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate <1, 2, 3, 4, 5, 6> (Reversibility: ? <1, 2, 3, 4, 5, 6> [1, 2, 3, 4]) [1, 2, 3, 4]

**P** ADP + 1-phosphatidyl-1D-myo-inositol 3,4,5-trisphosphate <1, 2, 3, 4, 5, 6> [1, 2, 3, 4]

**S** ATP + phosphatidylinositol <1, 2, 3, 4, 5> (Reversibility: ? <1, 2, 3, 4, 5> [1, 2, 3]) [1, 2, 3]

**P** ADP + phosphatidylinositol 3-phosphate <1, 2, 3, 4, 5> [1, 2, 3]

**S** ATP + phosphatidylinositol 4-phosphate <1, 2, 3, 4, 5> (Reversibility: ? <1, 2, 3, 4, 5> [1, 2, 3]) [1, 2, 3]

**P** ADP + phosphatidylinositol 4,5-diphosphate <1, 2, 3, 4, 5> [1, 2, 3]

**S** Additional information <4, 5> (<5>, p110$\delta$ does not phosphorylate the p85 adaptor but instead harbors an intrinsic autophosphorylation capacity [2]; <4>, enzyme interacts with active, GTP-bound Ras [3]) [2, 3]

**P** ?

**Inhibitors**

LY294002 <4, 5> [1, 2, 5]
wortmannin <4, 5> [1, 2, 5]

**Activating compounds**

platelet-derived growth factor <7> (<7>, stimulates synthesis of 1-phosphatidyl-1D-myo-inositol 3,4,5-trisphosphate [6]) [6]
Additional information <1> (<1>, stimulation of almost every receptor that induces tyrosine kinase activity also leads to class IA phosphatidylinositol-4,5-bisphosphate 3-kinase activation [1]) [1]

## 4 Enzyme Structure

**Subunits**

? <5> (<5>, x * 119471, p110$\delta$ subunit, can bind the p85 adaptor subunit, calculation from nucleotide sequence [2]) [2]
Additional information <1, 2, 3, 4> (<1,2,3,4>, class I phosphoinositide 3-kinases are heterodimers made up of an catalytic subunit, called p110, of about 110000 Da and an adaptor/regulatory subunit. Class I phosphoinositide 3-kinases are further subdivided into class Ia and IB enzymes, which signal downstream of tyrosine kinase and heterotrimeric G protein-coupled receptors, respectively [1,4]; <4>, three class IA p110 isoforms, p110$\alpha$, $\beta$ and $\delta$, which are encoded by three separate genes, at least seven adaptor proteins, which are generated by expression and alternative splicing of three different genes, namely p85$\alpha$, p85$\beta$ and p55$\gamma$. All these splice variants make functional complexes with p110 subunits [1,4]; <1>, a single type of catalytic/adaptor heterodimer: Dp110/p60 [1,4]; <2>, a single type of catalytic/adaptor heterodimer: AGE-1/AAP-1 [1,4]; <3>, three catalytic subunits: PIK1, PIK2 or PIK3 [1]) [1, 3]

## 5 Isolation/Preparation/Mutation/Application

**Source/tissue**

MCF-7 cell <5, 7> [1, 2, 6]
MOLT-4 cell <5, 7> [1, 2, 6]
leukocyte <4, 5> (<5>, p110$\delta$ is exclusively localized in leukocytes [2]) [1, 2]
neutrophil <5> [5]
Additional information <4> (<4>, all mammalian cell types investigated express at least one class IA isoform, class IB isoform is present only in mammals, where it shows a restricted tissue distribution, being abundant only in white blood cells [1]) [1]

**Localization**

cytosol <4> [1]

**Crystallization**

<4> [1]

**Cloning**

<5> (expression of P110$\delta$ in Sf9 insect cells [1]) [1]

## References

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[2] Vanhaesebroeck, B.; Welham, M.J.; Kotani, K.; Stein, R.; Warne, P.H.; Zvelebil, M.J.; Higashi, K.; Volinia, S.; Downward, J.; Waterfield, M.D.: P110$\delta$, a novel phosphoinositide 3-kinase in leukocytes. Proc. Natl. Acad. Sci. USA, **94**, 4330-4335 (1997)

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[4] Hruska, K.A.; Rolnick, F.; Huskey, M.; Alvarez, U.; Cheresh, D.: Engagement of the osteoclast integrin $\alpha_v\beta_3$ by osteopontin stimulates phosphatidylinositol 3-hydroxyl kinase activity. Endocrinology, **136**, 2984-2992 (1995)

[5] Metzner, B.; Heger, M.; Hofmann, C.; Czech, W.; Norgauer, J.: Evidence for the involvement of phosphatidylinositol 4,5-bisphosphate 3-kinase in CD18-mediated adhesion of human neutrophils to fibrinogen. Biochem. Biophys. Res. Commun., **232**, 719-723 (1997)

[6] Hawkins, P.T.; Jackson, T.R.; Stephens, L.R.: Platelet-derived growth factor stimulates synthesis of PtdIns(3,4,5)P3 by activating a PtdIns(4,5)P2 3-OH kinase. Nature, **358**, 157-159 (1992)