SnapShot: Lipid Kinases and Phosphatases

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Cell

Gene	Reaction(s) catalyzed in vitro	Reaction(s) catalyzed in vivo
PIK3C3	PI → PI(3)P	PI → PI(3)P
PIK3C2A	PI → PI(3)P, PI(4)P → PI(3,4)P_2, PI(4,5)P_2 → PI(3,4,5)P_3	PI → PI(3)P, PI(4)P → PI(3,4)P_2
PIK3C2B	PI → PI(3)P, PI(4)P → PI(3,4)P_2, PI(4,5)P_2 → PI(3,4,5)P_3	PI → PI(3)P
PIK3C2G	PI → PI(3)P, PI(4)P → PI(3,4)P_2	–
PIKFYVE	PI → PI(5)P, PI(3)P → PI(3,5)P_2	PI → PI(5)P, PI(3)P → PI(3,5)P_2
PIP4K2A	PI(3)P → PI(3,4)P_2 → PI(3,4,5)P_3, PI(5)P → PI(4,5)P_2	PI(5)P → PI(4,5)P_2
PIP4K2B	PI(3)P → PI(3,4)P_2, PI(5)P → PI(4,5)P_2	PI(5)P → PI(4,5)P_2
PIP4K2C	PI(5)P → PI(4,5)P_2	–
PIK3CA	PI → PI(3)P, PI(4)P → PI(3,4)P_2, PI(4,5)P_2 → PI(3,4,5)P_3	PI(4,5)P_2 → PI(3,4,5)P_3
PIK3CB	PI → PI(3)P, PI(4)P → PI(3,4)P_2, PI(4,5)P_2 → PI(3,4,5)P_3	PI(4,5)P_2 → PI(3,4,5)P_3
PIK3CD	PI → PI(3)P, PI(4)P → PI(3,4)P_2, PI(4,5)P_2 → PI(3,4,5)P_3	PI(4,5)P_2 → PI(3,4,5)P_3
PIK3CG	PI → PI(3)P, PI(4)P → PI(3,4)P_2, PI(4,5)P_2 → PI(3,4,5)P_3	PI(4,5)P_2 → PI(3,4,5)P_3
IPMK	PI(4,5)P_2 → PI(3,4,5)P_3	PI(4,5)P_2 → PI(3,4,5)P_3
PIP5K1A	PI → PI(5)P, PI(3)P → PI(3,4)P_2 → PI(3,4,5)P_3, PI(3)P → PI(3,5)P_2, PI(4)P → PI(4,5)P_2, PI(3,4)P_2 → PI(3,4,5)P_3	PI(4)P → PI(4,5)P_2
PIP5K1B	PI → PI(5)P, PI(3)P → PI(3,4)P_2 → PI(3,4,5)P_3, PI(3)P → PI(3,5)P_2, PI(4)P → PI(4,5)P_2, PI(3,4)P_2 → PI(3,4,5)P_3	PI(4)P → PI(4,5)P_2
PIP5K1C	PI(3)P → PI(3,4)P_2 → PI(3,4,5)P_3, PI(3)P → PI(3,5)P_2, PI(4)P → PI(4,5)P_2, PI(3,4)P_2 → PI(3,4,5)P_3	PI(4)P → PI(4,5)P_2
PI4K2A	PI → PI(4)P	PI → PI(4)P
PI4K2B	PI → PI(4)P	PI → PI(4)P
PI4KA	PI → PI(4)P	PI → PI(4)P
PI4KB	PI → PI(4)P	PI → PI(4)P
MTM1	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	PI(3)P → PI, PI(3,5)P_2 → PI(5)P
MTMR1	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	–
MTMR2	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	PI(3)P → PI
MTMR3	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	PI(3,5)P_2 → PI(5)P
MTMR4	PI(3)P → PI	PI(3)P → PI
MTMR6	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	PI(3,5)P_2 → PI(5)P
MTMR7	PI(3)P → PI	–
MTMR8	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	PI(3)P → PI
MTMR14	PI(3)P → PI, PI(3,5)P_2 → PI(5)P	PI(3)P → PI, PI(3,5)P_2 → PI(5)P
PTEN	PI(3)P → PI, PI(3,4)P_2 → PI(4)P, PI(3,5)P_2 → PI(5)P, PI(3,4,5)P_3 → PI(4,5)P_2	PI(3,4,5)P_3 → PI(4,5)P_2
TPTE2	PI(3)P → PI, PI(3,4)P_2 → PI(4)P, PI(3,5)P_2 → PI(5)P, PI(3,4,5)P_3 → PI(4,5)P_2	PI(4,5)P_2 → PI(4)P, PI(3,4)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2
TMEM55A	PI(4,5)P_2 → PI(5)P	–
TMEM55B	PI(4,5)P_2 → PI(5)P	PI(4,5)P_2 → PI(5)P
INPP4A	PI(3,4)P_2 → PI(3)P	PI(3,4)P_2 → PI(3)P
INPP4B	PI(3,4)P_2 → PI(3)P, PI(3,4,5)P_3 → PI(3,5)P_2	PI(3,4)P_2 → PI(3)P

Gene	Reaction(s) catalyzed in vitro	Reaction(s) catalyzed in vivo
PTPMT1	PI(5)P → PI	Phosphatidylglycerophosphate → Phosphatidylglycerol
FIG4	PI(3,5)P_2 → PI(3)P, PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(3,5)P_2 → PI(3)P
OCRL	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(4,5)P_2 → PI(4)P
INPP5B	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(4,5)P_2 → PI(4)P
INPP5D	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(3,4,5)P_3 → PI(3,4)P_2
INPP5E	PI(3,5)P_2 → PI(3)P, PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2
INPP5F	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(3,4,5)P_3 → PI(3,4)P_2
INPP5J	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(3,4,5)P_3 → PI(3,4)P_2
INPP5K	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(3,4,5)P_3 → PI(3,4)P_2
INPPL1	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2	PI(4,5)P_2 → PI(4)P, PI(3,4,5)P_3 → PI(3,4)P_2
SACM1L	PI(3)P → PI, PI(4)P → PI	PI(4)P → PI
SYNJ1	PI(3)P → PI, PI(4)P → PI, PI(4,5)P_2 → PI(4)P	PI(4,5)P_2 → PI(4)P
SYNJ2	PI(4,5)P_2 → PI(4)P	–
DGKA	DAG → PA	DAG → PA
DGKB	DAG → PA	DAG → PA
DGKG	DAG → PA	DAG → PA
DGKD	DAG → PA	DAG → PA
DGKE	DAG → PA	DAG → PA
DGKZ	DAG → PA	DAG → PA
DGKH	DAG → PA	DAG → PA
DGKQ	DAG → PA	DAG →PA
DGKI	DAG → PA	DAG → PA
DGKK	DAG → PA	DAG → PA
EIF2AK3	DAG → PA	DAG → PA
AGK	DAG → PA, MAG → LPA	DAG → PA , MAG → LPA
SPHK1	Sphingosine → Sphingosine 1-phosphate	Sphingosine → Sphingosine 1-phosphate
SPHK2	Sphingosine → Sphingosine 1-phosphate	Sphingosine → Sphingosine 1-phosphate
CERK	Ceramide → Ceramide 1-phosphate	Ceramide → Ceramide 1-phosphate
PPAP2A	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Ceramide, Sphingosine 1-phosphate → Sphingosine	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Ceramide, Sphingosine 1-phosphate → Sphingosine
PPAP2B	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Ceramide, Sphingosine 1-phosphate → Sphingosine	PA → DAG, LPA → MAG, Sphingosine 1-phosphate → Sphingosine
PPAP2C	PA → DAG, LPA → MAG, Ceramide 1-phosphate → Ceramide, Sphingosine 1-phosphate → Sphingosine	PA → DAG, LPA → MAG, Sphingosine 1-phosphate → Sphingosine
PPAPDC1A	PA → DAG, LPA → MAG, DGPP → PA	–
PPAPDC1B	PA → DAG, LPA → MAG, DGPP → PA	–
PPAPDC2	PSDP → PSMP, FDP → FMP, PA → DAG	PSDP → PSMP
LPIN1	PA → DAG	PA → DAG
LPIN2	PA → DAG	PA → DAG
LPIN3	PA → DAG	–
SGPP1	Sphingosine 1-phosphate → Sphingosine	Sphingosine 1-phosphate → Sphingosine

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This SnapShot presents the mammalian proteins that have been identified as enzymes that catalyze the phosphorylation or dephosphorylation of lipid substrates. We have included both the in vitro and in vivo reactions reported in the literature to highlight the importance of assessing the data from both sources.

We have limited the results from in vitro experiments to those published using full-length native or recombinant proteins; consequently, we have not included those reactions catalyzed by nonregulated, isolated catalytic domains. For the in vivo data, in addition to reports in which accurate measurements of the lipid substrates and products have been performed in cells, we have included the reactions identified using indirect measurements made using fluorescently tagged proteins expressed in cells that bind specifically to the lipid substrate and/or product in question.

The differences between the in vitro and in vivo reactions catalyzed by some lipid kinases and phosphatases further illustrates the importance of in vivo validation of enzyme reactions measured in the test tube.

Several reasons could explain differences in substrate specificity of a lipid kinase or phosphatase measured in a living cell or animal, compared to a test tube assay: (1) the cellular localization of the enzyme and, consequently, the access that the kinase or phosphatase has to its lipid substrate; (2) the unique membrane and protein environment in which the lipid substrate is presented to the enzyme; and (3) the presence of regulatory proteins and lipids in the cell that could determine which lipid substrates are engaged in vivo but that could be absent from an in vitro assay.

Furthermore, the technical challenges associated with accurately measuring the products of lipid kinase and phosphatase reactions in vivo could also contribute and, in some cases, could explain why similar in vivo data has not been reported.

Phospholipids are made up of different fatty acid moieties at the sn1 and sn2 position of the glycerol backbone and indeed can have acyl, alkyl, or alkenyl linkages; thus, for any given phospholipid, multiple molecular species exist that differ in the length and saturation of the fatty acid moieties. New methodologies in mass spectrometry are now revealing that the products of lipid kinase reactions measurable in vivo, such as PI(3,4,5)P_3, are limited to only a few molecular species, suggesting that the kinases and phosphatases that are responsible for PI(3,4,5)P_3 metabolism are selective for different molecular species.

Although this SnapShot has focused on the phosphatases that antagonize the actions of the lipid kinases, the products of the kinase reactions can in some cases be degraded by alternative activities. For example, sphingosine-1-phosphate can be degraded by a lysase activity. Furthermore, PI(4,5)P_2 and PA can be metabolized by phospholipase enzymes: phosphoinositide-specific phospholipase C hydrolyses PI(4,5)P_2 to generate DAG and inositol (1,4,5)P_3, and phospholipase A_1 and A_2 hydrolyse PA to generate LPA.

ABBREVIATIONS

PI, phosphatidylinositol; PI(3)P, phosphatidylinositol 3-phosphate; PI(4)P, phosphatidylinositol 4-phosphate; PI(5)P, phosphatidylinositol 5-phosphate; PI(3,4)P_2, phosphatidylinositol 3,4-bisphosphate; PI(3,5)P_2, phosphatidylinositol 3,5-bisphosphate; PI(4,5)P_2, phosphatidylinositol 4,5-bisphosphate; PI(3,4,5)P_3, phosphatidylinositol 3,4,5-trisphosphate; PA, phosphatidic acid; LPA, lyso-phosphatidic acid; DAG, diacylglycerol; MAG, monoacylglycerol; DGPP, diacylglycerol pyrophosphate; PSDP, presqualine diphosphate; PSMP, presqualine monophosphate; FDP, farnesyl diphosphate; FMP, farnesyl monophosphate.

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