PP2A methylation by LCMT1

Janssens, V., Jupe, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

04/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

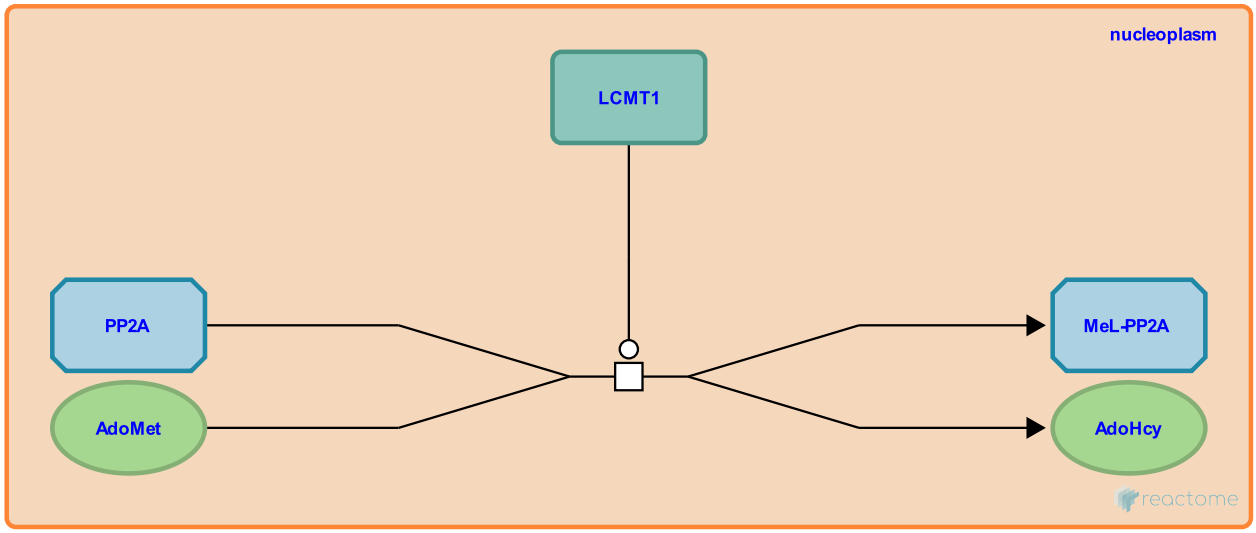
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

PP2A methylation by LCMT1 ↗

Stable identifier: R-HSA-8856945

Type: transition

Compartments: nucleoplasm



Reversible methylation of the PP2A C subunit is a highly conserved and essential regulatory mechanism (Lee et al. 1996). Methylation of the carboxy-termius of PP2A C enhances the affinity of the PP2A core enzyme for some regulatory subunits (Xing et al. 2008). Changes in PP2A methylation appear to regulate formation of PP2A complexes and alter the specificity of PP2A phosphatase activity (Mumby 2001). Blockade of PP2A methylation in yeast causes a set of phenotypes that are consistent with decreased formation of PP2A holoenzymes (Wu et al. 2000). Reversible methylation of PP2A is catalyzed by two highly conserved enzymes, a 38 kDa leucine carboxyl methyltransferase (LCMT1) (De Baere et al. 1999, Lee & Stock 1993) and a 42 kDa methylesterase (PPME1) (Lee et al. 1996, Ogris et al. 1999). PP2A carboxy-methylation by LCMT1 requires an active PP2A conformation and is significantly facilitated by the PP2A scaffold (or A) subunit (Stanevich et al. 2011, Stanevich et al. 2014). LCMT1 also methylates the PP2A-like phosphatases PP4 and PP6 (Hwang et al. 2016). PPME1 catalyzes removal of the methyl group, thus reversing the activity of LCMT1 (Lee et al. 1996). Overexpression of yeast PPME caused phenotypes similar to those associated with loss of the methyltransferase gene (Wu et al. 2000).

Methylation and demethylation are spatially separated within mammalian cells, as the majority of LCMT1 is cytoplasmic and PPME1 predominantly localizes in the nucleus (Longin et al. 2008). In mammalian cells, LCMT1 knockdown results in apoptotic cell death (Longin et al. 2007). In mice, LCMT1 or PPME1 knockout are lethal (Lee & Pallas 2007, Ortega-Gutiérrez et al. 2008). Methylation levels of PP2A change during the cell cycle, suggesting a critical role of methylation in cell-cycle regulation (Turowski et al. 1995, Lee & Pallas 2007). Regulation of PP2A methylation by LCMT1 and PPME1 plays a critical role in differentiation of neuroblastoma cells (Sontag et al. 2010). Decreased PP2A methylation in Alzheimer's and Parkinson's disease patients contributes to PP2A inactivation and increased phosphorylation of tau and alpha-synuclein (Sontag & Sontag 2014, Park et al. 2016). PPME1 may also inhibit PP2A by sequestration (Longin et al. 2004) and/or by evicting catalytic metal ions from the PP2A active site (Xing et al. 2008). As such, increased PPME1 expression suppresses PP2A tumor suppressive function and promotes oncogenic MAPK/ERK and AKT pathway activities in various cancer types (Kaur & Westermarck 2016). PPME1 may also protect PP2A from ubiquitin/proteasome degradation (Yabe et al. 2015).

Literature references

Merlevede, W., Janssens, V., De Baere, I., Goris, J., Derua, R., Van Hoof, C. et al. (1999). Purification of porcine brain protein phosphatase 2A leucine carboxyl methyltransferase and cloning of the human homologue. *Biochemistry, 38*, 16539-47. ↗

Editions

2016-02-12	Authored	Jupe, S.
2017-02-15	Reviewed	Janssens, V.
2017-02-15	Edited	Jupe, S.