HHAT palmitoylates Hh N-terminal fragment

D'Eustachio, P., Liu, Y C., Rothfels, K.

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

03/05/2024

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. ↗

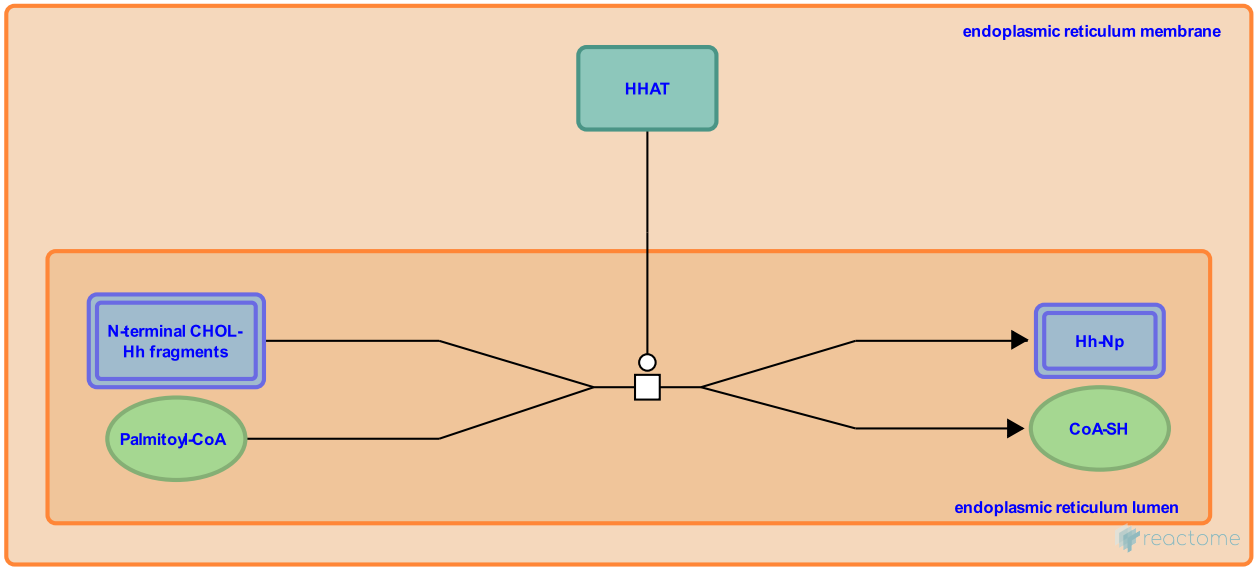
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

HHAT palmitoylates Hh N-terminal fragment ↗

Stable identifier: R-HSA-5358343

Type: transition

Compartments: endoplasmic reticulum lumen



In addition to being modified by cholesterol at its C-terminal end, the N-terminal fragment of Hh (Hh-Np) is also palmitoylated by the O-acyltransferase HHAT (Pepinsky et al, 1998; Charmoun et al 2001; Chen et al, 2004; Hardy and Resh, 2007). HHAT-mediated palmitoylation of Hh can be recapitulated in vitro and in vivo, and the cholesterol- and palmitoyl-modified N-terminal fragment represents the predominant secreted form of Hh in vivo (Buglino and Resh, 2008; Buglino and Resh, 2010; Taipale et al, 2000). Mutation or depletion of the HHAT enzyme and mutation of the palmitoyl acceptor cysteine in Hh itself abrogates palmitoylation of the ligand and reduces Hh signaling (Chen et al, 2004; Chamoun et al, 2001; Pepinsky et al, 1998; Callier et al, 2014).

Literature references

Rolland, A., Bernard, P., Callier, P., Antonarakis, SE., Nef, S., Faivre, L. et al. (2014). Loss of Function Mutation in the Palmitoyl-Transferase HHAT Leads to Syndromic 46,XY Disorder of Sex Development by Impeding Hedgehog Protein Palmitoylation and Signaling. *PLoS Genet., 10*, e1004340. ↗

Li, YJ., Xu, SM., Chuang, PT., Kawakami, T., Chen, MH. (2004). Palmitoylation is required for the production of a soluble multimeric Hedgehog protein complex and long-range signaling in vertebrates. *Genes Dev., 18*, 641-59. ↗

Resh, MD., Buglino, JA. (2010). Identification of conserved regions and residues within Hedgehog acyltransferase critical for palmitoylation of Sonic Hedgehog. *PLoS ONE, 5*, e11195. ↗

Milenkovic, L., Beachy, PA., Mann, RK., Cooper, MK., Scott, MP., Wang, B. et al. (2000). Effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine. *Nature, 406*, 1005-9. ↗

Pepinsky, RB., Galdes, A., Williams, KP., Garber, EA., Wen, D., Wang, EA. et al. (1998). Identification of a palmitic acid-modified form of human Sonic hedgehog. *J. Biol. Chem., 273*, 14037-45. ↗

Editions

2014-03-24	Authored	Rothfels, K.
2014-04-20	Edited	D'Eustachio, P.
2014-05-16	Reviewed	Liu, Y C.