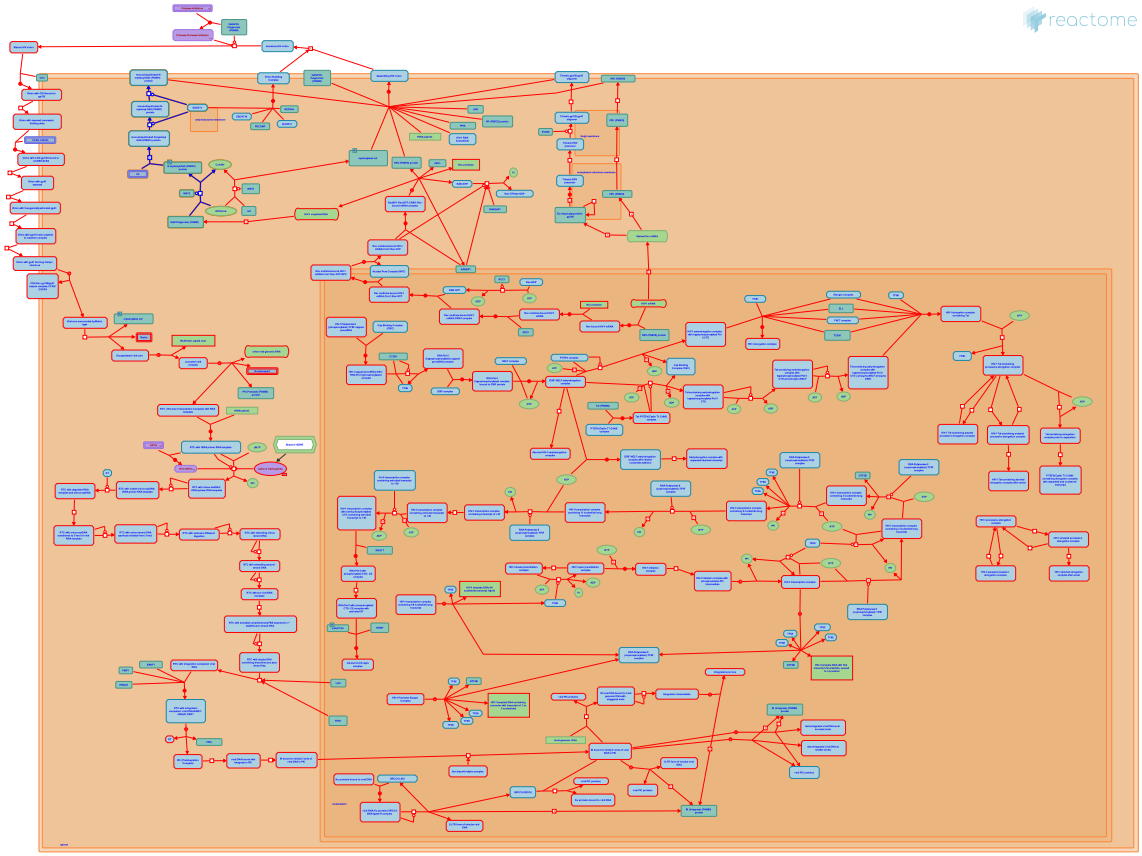
Membrane binding and targetting of GAG proteins



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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. ↗

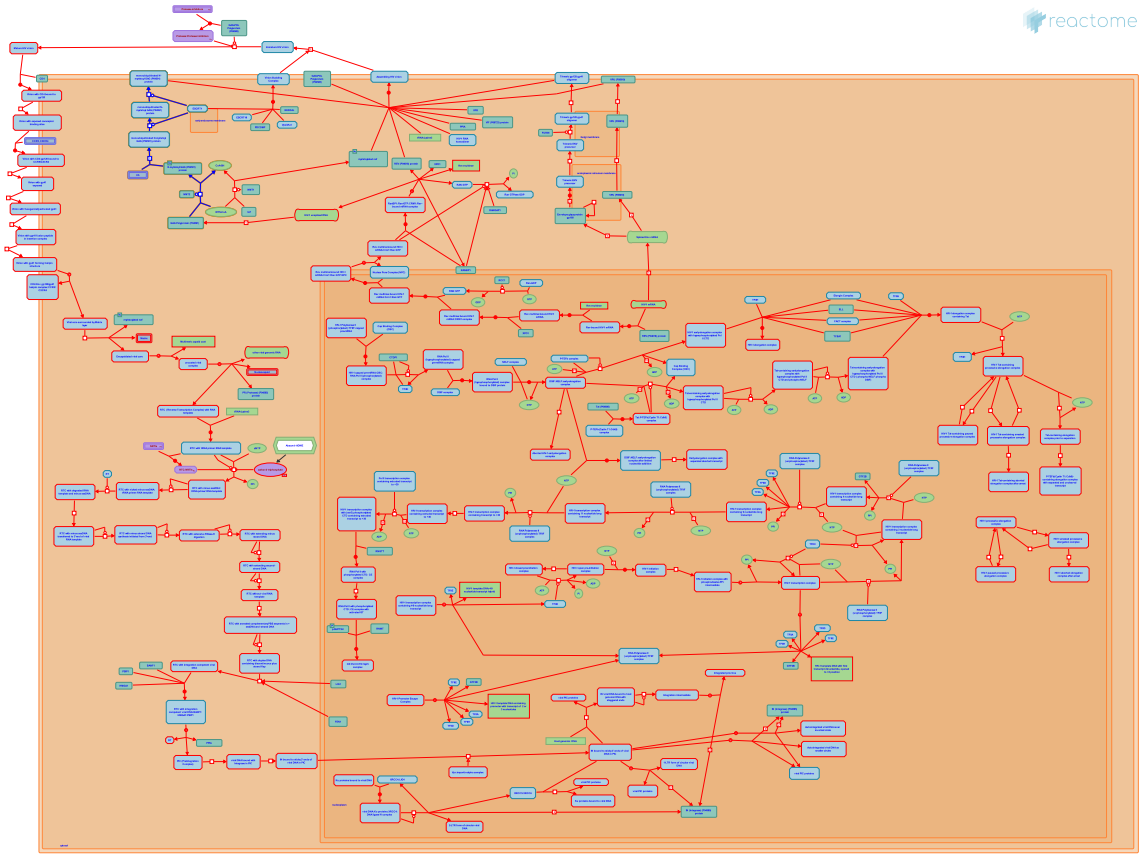
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Membrane binding and targetting of GAG proteins ↗

Stable identifier: R-HSA-174490

Diseases: Human immunodeficiency virus infectious disease



One of the mysteries of Gag protein involvement in HIV virion assembly is how the proteins are targeted to the proper membrane for budding. Infectious retroviruses do not bud from all of the available membrane surfaces within an infected cell, but primarily from the plasma membrane, which constitutes a small proportion of the total membrane surface in most cells. In polarized cells, the sites of budding are further restricted to the basolateral membrane.

Literature references

Resh, MD., Perlman, M. (2006). Identification of an intracellular trafficking and assembly pathway for HIV-1 gag. *Traffic, 7*, 731-45. ↗

Sundquist, WI., Morita, E. (2004). Retrovirus budding. *Annu Rev Cell Dev Biol, 20*, 395-425. ↗

Editions

2013-03-07	Authored	Gillespie, ME.
2013-05-21	Reviewed	Dube, M.

N-myristoylation of GAG polyprotein by NMT2

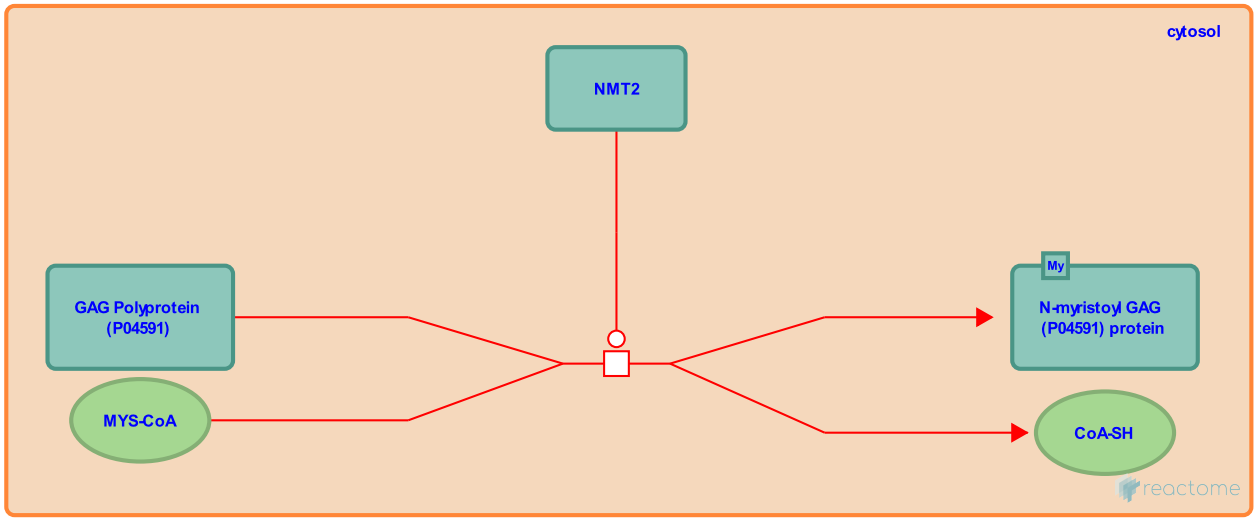
Location: Membrane binding and targetting of GAG proteins

Stable identifier: R-HSA-184392

Type: transition

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



The amino terminal glycine residue of HIV-1 Gag polyprotein is myristoylated (Henderson et al. 1992). Myristoylation of newly synthesized Gag occurs in the cytosol of the infected host cell, with myristoyl-CoA as the myristate donor and the host cell NMT2 enzyme as the catalyst. Human cells express two isoforms of N-myristoyl transferase (NMT) (Giang and Cravatt 1998). The argumant that the second isoform catalyzes this reaction is indirect, based on the the observations that a stable enzyme:substrate complex forms transiently during the reaction (Farazi et al. 2001), and that Gag polyprotein can be found complexed with NMT2 (but not NMT1) in HIV-1-infected human cells (Hill and Skowronski 2005).

Followed by: Monoubiquitination of N-myristoyl GAG polyprotein

Literature references

Skowronski, J., Hill, BT. (2005). Human N-myristoyltransferases form stable complexes with lentiviral nef and other viral and cellular substrate proteins. *J Virol, 79*, 1133-41.

Gordon, JI., Waksman, G., Farazi, TA. (2001). The biology and enzymology of protein N-myristoylation. *J Biol Chem, 276*, 39501-4.

Cravatt, BF., Giang, DK. (1998). A second mammalian N-myristoyltransferase. *J Biol Chem, 273*, 6595-8.

Editions

2013-03-07	Authored	Gillespie, ME.
2013-05-21	Reviewed	Dube, M.

Monoubiquitination of N-myristoyl GAG polyprotein ↗

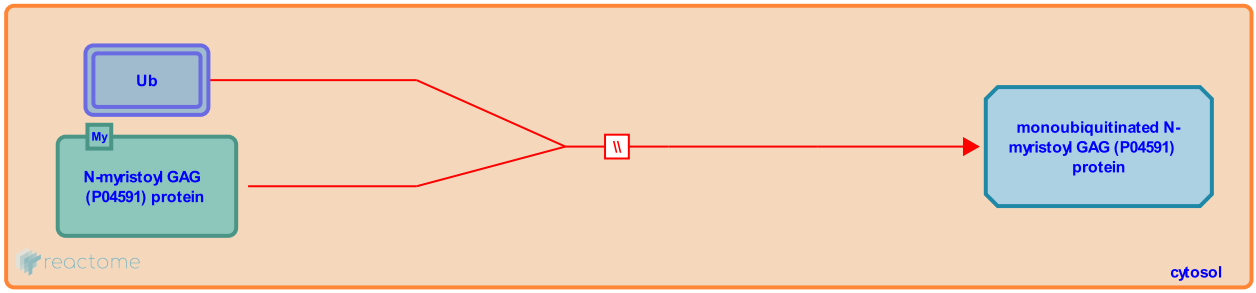
Location: Membrane binding and targetting of GAG proteins

Stable identifier: R-HSA-184323

Type: omitted

Compartments: cytosol

Diseases: Human immunodeficiency virus infectious disease



Cytosolic N-myristoyl Gag polyprotein is conjugated with a single molecule of ubiquitin. Conjugation is typically to one of two lysine residues in the p6 domain of Gag but can be to lysine residues in the MA, CA, NC, and SP2 domains of the protein. The specific host cell E2 and E3 proteins that mediate Gag ubiquitination have not been identified. The same studies that first identified the p6 ubiquitination sites in Gag also called the biological significance of Gag ubiquitination into question by demonstrating that Gag proteins in which the p6 ubiquitination sites had been removed by mutagenesis could still assemble efficiently into infectious viral particles (Ott et al. 1998, 2000). More recent work, however, has identified additional ubiquitination sites throughout the carboxyterminal region of the Gag polyprotein, and when all of these sites are removed by mutagenesis, both viral assembly involving the mutant Gag polyprotein and infectivity of the resulting viral particles are sharply reduced (Gottwein et al. 2006).

Preceded by: N-myristoylation of GAG polyprotein by NMT2

Followed by: Monoubiquitinated N-myristoyl GAG polyprotein is targeted to the late endosomal vesicle membrane by the ESCRT-I complex

Literature references

Ott, DE., Coren, LV., Oroszlan, S., Yoshinaka, Y., Henderson, LE., Johnson, DG. et al. (1998). Ubiquitin is covalently attached to the p6Gag proteins of human immunodeficiency virus type 1 and simian immunodeficiency virus and to the p12Gag protein of Moloney murine leukemia virus. *J Virol, 72*, 2962-8. ↗

Habermann, A., Jager, S., Gottwein, E., Krausslich, HG. (2006). Cumulative mutations of ubiquitin acceptor sites in human immunodeficiency virus type 1 gag cause a late budding defect. *J Virol, 80*, 6267-75. ↗

Ott, DE., Coren, LV., Gagliardi, TD., Chertova, EN., Schubert, U. (2000). Ubiquitination of HIV-1 and MuLV Gag. *Virology, 278*, 111-21. ↗

Editions

2013-03-07	Authored	Gillespie, ME.
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Monoubiquitinated N-myristoyl GAG polyprotein is targeted to the late endosomal vesicle membrane by the ESCRT-I complex ↗

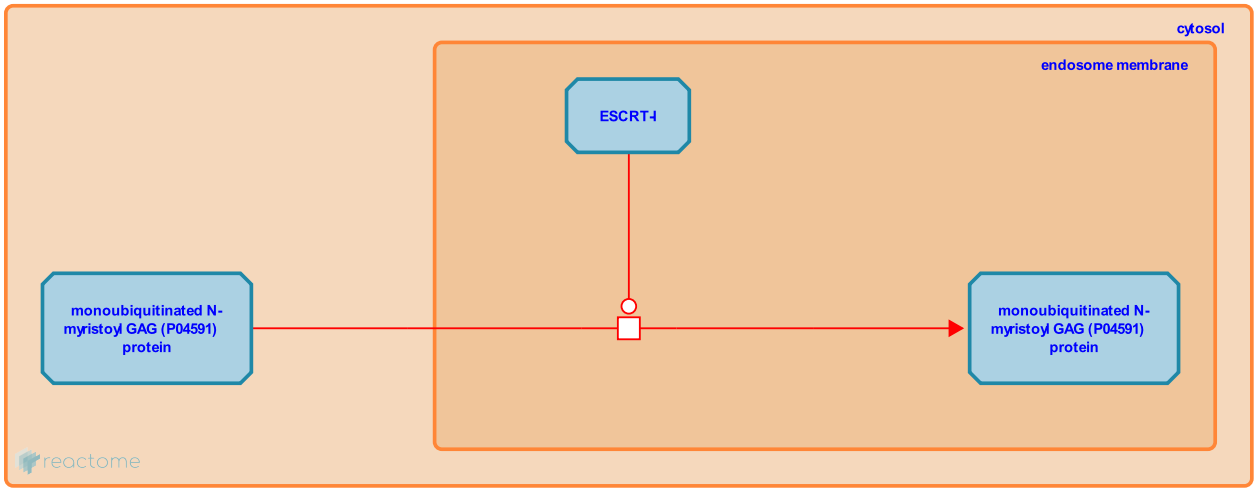
Location: Membrane binding and targetting of GAG proteins

Stable identifier: R-HSA-184269

Type: transition

Compartments: endosome membrane, cytosol

Diseases: Human immunodeficiency virus infectious disease



Monoubiquitinated N-myristoyl Gag polyprotein associates with the ESCRT-1 complex at an endosomal membrane (Eastman et al. 2005; Martin-Serrano et al. 2003; Stuchell et al. 2004).

Preceded by: Monoubiquitination of N-myristoyl GAG polyprotein

Followed by: Transport of GAG to the Plasma Membrane

Literature references

Ghaffarian, S., Stuchell, MD., Garrus, JE., Sundquist, WI., McKinnon, R., Muller, B. et al. (2004). The human endosomal sorting complex required for transport (ESCRT-I) and its role in HIV-1 budding. *J Biol Chem, 279*, 36059-71. ↗

Bieniasz, PD., Martin-Serrano, J., Zang, T. (2003). Role of ESCRT-I in retroviral budding. *J Virol, 77*, 4794-804. ↗

Chung, W., Bieniasz, PD., Eastman, SW., Martin-Serrano, J., Zang, T. (2005). Identification of human VPS37C, a component of endosomal sorting complex required for transport-I important for viral budding. *J Biol Chem, 280*, 628-36. ↗

Editions

2013-03-07	Authored	Gillespie, ME.
2013-05-21	Reviewed	Dube, M.

Transport of GAG to the Plasma Membrane ↗

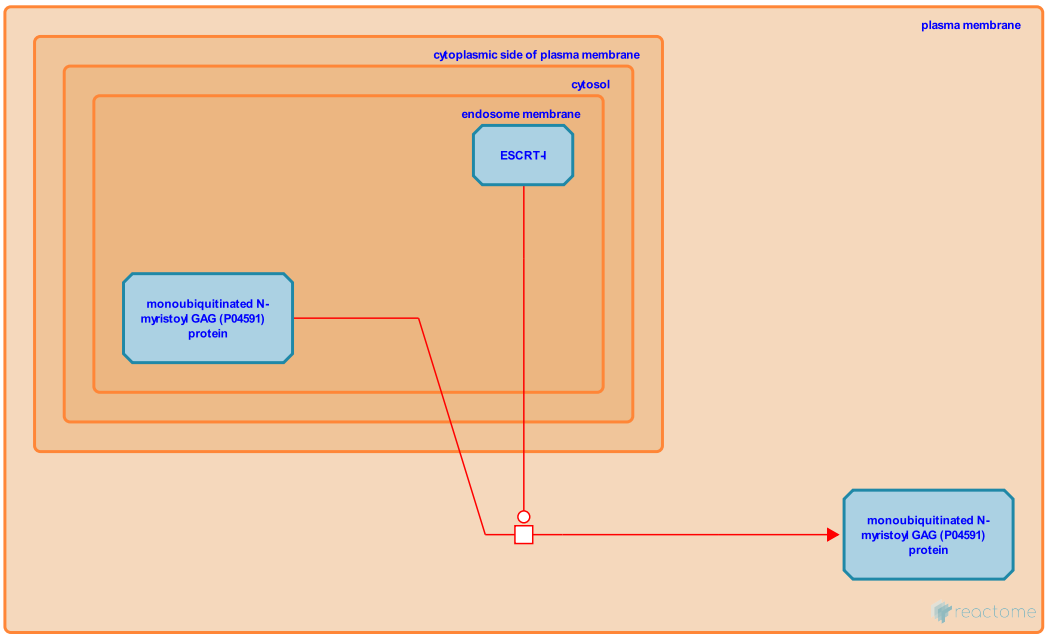
Location: Membrane binding and targetting of GAG proteins

Stable identifier: R-HSA-3149434

Type: transition

Compartments: plasma membrane

Diseases: Human immunodeficiency virus infectious disease



Assembling Gag molecules are largely derived from the rapidly diffusing cytoplasmic pool. Gag membrane targeting requires myristoylation and a subset of GAG molecules are shuttled to the plasma membrane in this way.

Preceded by: Monoubiquitinated N-myristoyl GAG polyprotein is targeted to the late endosomal vesicle membrane by the ESCRT-I complex

Literature references

Derse, D., Ono, A., Inlora, J., Chukkapalli, V. (2011). Gag localization and virus-like particle release mediated by the matrix domain of human T-lymphotropic virus type 1 Gag are less dependent on phosphatidylinositol-(4,5)-bisphosphate than those mediated by the matrix domain of HIV-1 Gag. *J. Virol., 85*, 3802-10. ↗

Editions

2013-03-07	Authored	Gillespie, ME.
2013-05-21	Reviewed	Dube, M.

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