E-cadherin degradation by PS1:NCSTN (Gamma-secretase)

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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.
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Literature references

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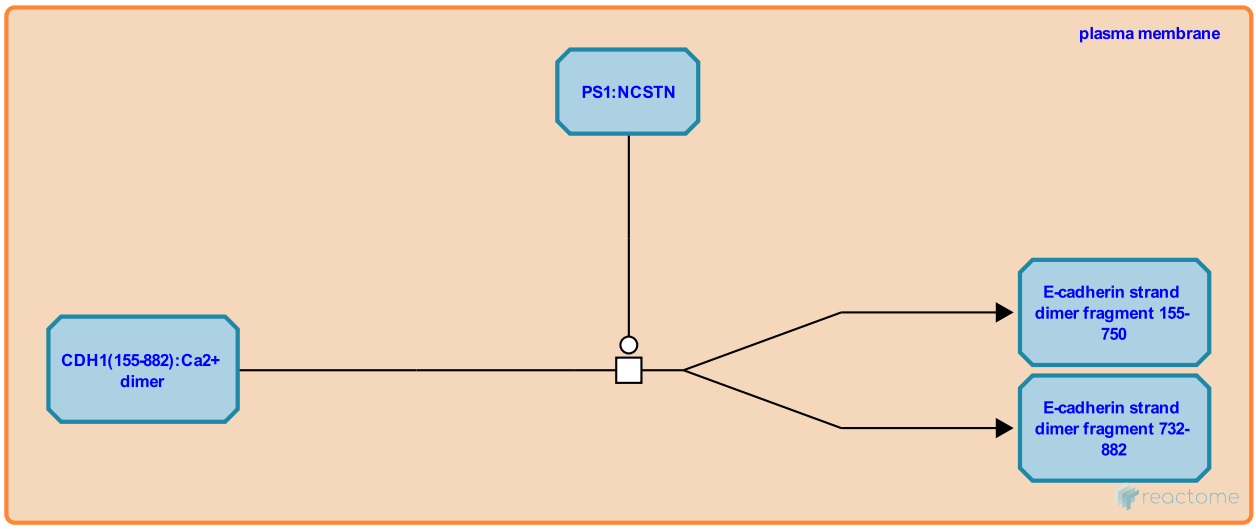
Stable identifier: R-HSA-2534206

Type: transition

Compartments: plasma membrane

Inferred from: E-cadherin strand dimer degradation by PS1 (Homo sapiens)



E-cadherin (CDH1) localizes to the lateral membrane of differentiated epithelia, providing the structural foundation for adherens junctions, multiprotein complexes that link cell-cell contacts to the actin cytoskeleton and various signaling molecules (Perez-Moreno et al. 2003, Baum & Georgiou 2011). The extracellular domain has five cadherin-type repeat ectodomain (EC) modules; the most membrane-distal EC mediates binding with CDH1 on adjacent cells (Boggon et al. 2002). Calcium ions bind between the EC domains of two CDH1 peptides to form a dimer with a rod-like conformation (Boggon et al. 2002) which is required for cell-cell interaction (Gumbiner 1996, Patel et al. 2006). The cytoplasmic tail of E-cadherin binds to the armadillo repeat protein beta-catenin, a target of the Wnt signaling pathway and a cofactor for TCF/LEF-mediated transcription (Gavard & Mège 2005). Beta-catenin in turn binds alpha-catenin, which interacts with the actin microfilament network, actin and the actin-binding proteins vinculin, formins, alpha-actinin, zonula occludin protein, and afadin (Bershadsky 2004). Cell–cell adhesions also contain desmosomes, which link cell contacts to intermediate filaments, and nectin-based, calcium-independent adhesions, which are linked to actin (Takai & Nakanishi 2003, Yin and Green 2004). The critical importance of E-cadherin to normal development and tissue function is demonstrated by embryonic lethal E-cadherin gene mouse knockouts (Larue et al. 1994). Loss of cadherin-based cell-cell adhesion is a hallmark of carcinogenesis, correlating with tumour progression, allowing cells to escape normal growth control signals, resulting in loss of differentiation and increased cell proliferation associated with invasive behaviour (Frixen et al. 1991, Capaldo & Macara 2007). Full-length 120-kDa CDH1 protein is cleaved in the ectodomain close to the plasma membrane by a number of metalloproteases, generating an extracellular 38-kDa C-terminal fragment (CTF) termed CTF1 which can be further processed by a gamma-secretase-like activity to a soluble 33-kDa CTF2 (Marambaud et al. 2002, Roy & Berx 2008). MMP3, MMP7 (Noë et al. 2001, canine MMPs), MMP9 (Symowicz et al. 2007), plasmin (Ryniers et al. 2002, canine plasmin), Kallikrien 7 (Johnson et al. 2007), ADAM10 (Maretzky et al. 2005) and ADAM15 (Najy et al. 2008) all cleave CDH1 extracellularly, close to the transmembrane region. Presenilin-1 (Marambaud et al. 2002), the catalytic subunit of gamma-secretase (Herreman et al. 2003, Li et al. 2003), cleaves CDH1 producing a soluble 33-kDa fragment termed CTF2. Caspase-3 (Steinhusen et al. 2001) and calpain-1 (Rios-Doria et al. 2003) cleave E-cadherin in its cytoplasmic part releasing an intracellular 37 kDa C-terminal fragment.

Editions

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