PORCN-inhibitor LGK974 prevents WNT ligand palmitoyltation and secretion

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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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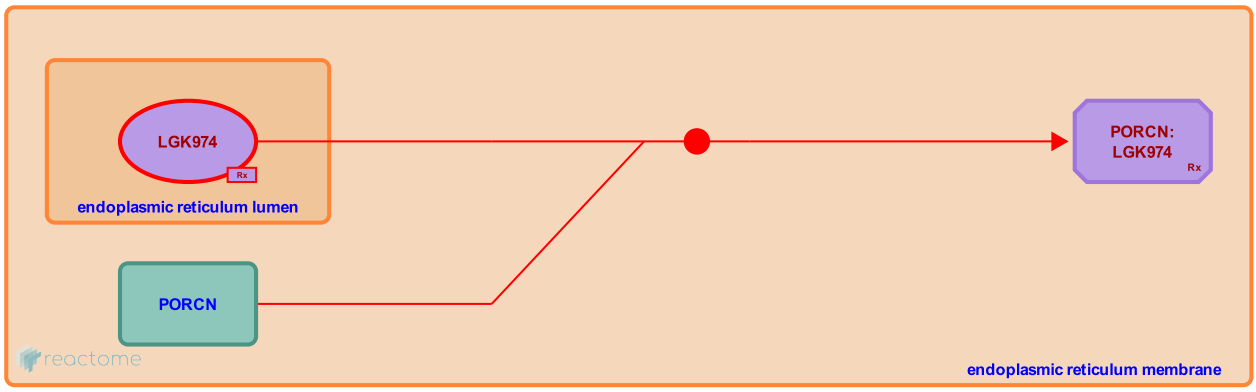
Stable identifier: R-HSA-5340560

Type: binding

Compartments: endoplasmic reticulum membrane

Diseases: cancer



Porcupine (PORCN) is an O-acyl-transferase that catalyzes the palmitoleoylation of WNT ligands at the conserved S209 (van den Heuvel et al, 1993; Kadowaki et al, 1996; Hofmann, 2000). This lipid modification is required for the trafficking of WNT ligands from the ER to the cell surface, and is also required for binding to the FZD receptors. In the absence of PORCN, WNT ligand accumulates in the ER and WNT signaling is abrogated (reviewed in MacDonald et al, 2009; Takada et al, 2006; Janda et al, 2012; Herr and Basler, 2012; Ching et al, 2008). PORCN is required for activity of all human WNT ligands (Proffitt et al, 2012; Najdi et al, 2012).

LGK974 is a small molecule inhibitor of PORCN that was identified in a screen for compounds that block WNT secretion (Liu et al, 2013). LGK974 potently blocks WNT signaling in vitro and in vivo and is in Phase I clinical trials (NCT01351103) for use in the treatment of WNT-dependent cancers.

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Editions

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