

# AURKA phosphorylates PHLDA1

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01/04/2024

## 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

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Reactome database release: 88

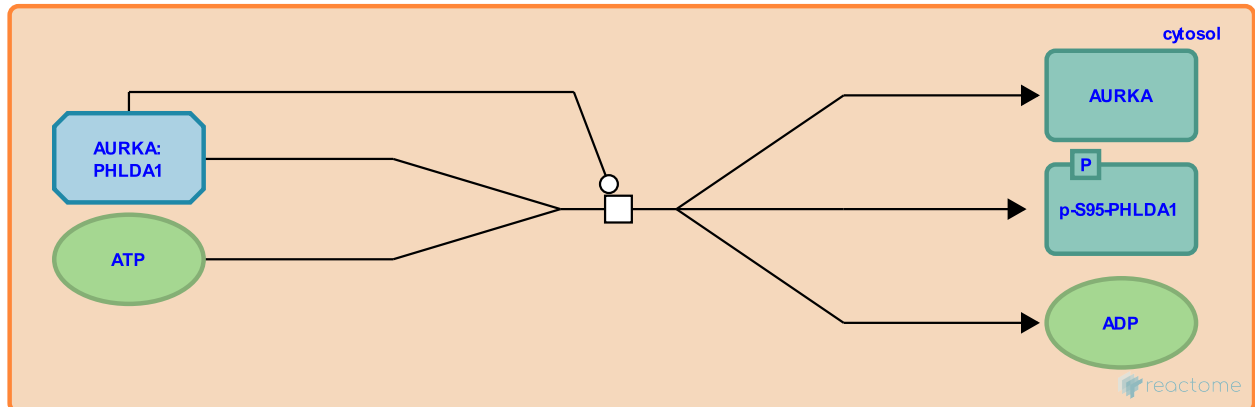
This document contains 1 reaction ([see Table of Contents](#))

## AURKA phosphorylates PHLDA1 [↗](#)

**Stable identifier:** R-HSA-8853444

**Type:** transition

**Compartments:** cytosol



Aurora kinase A (AURKA) phosphorylates PHLDA1 on serine residue S95. This residue is conserved in mouse and matches S98 in the recombinant mouse protein used for identification of the AURKA target site in PHLDA1. Although phosphorylation of AURKA on threonine residue T288 within the catalytic loop is needed for AURKA kinase activity (Walter et al. 2000), AURKA phosphorylation has not been specifically examined in the context of PHLDA1 phosphorylation and AURKA is therefore shown as unphosphorylated. AURKA-mediated phosphorylation promotes PHLDA1 ubiquitination by an unknown ubiquitin ligase, which triggers degradation of PHLDA1 and may contribute to the oncogenic role of AURKA in breast cancer. Unphosphorylated PHLDA1 contributes to AURKA ubiquitination and degradation but the identity of the ubiquitin ligase and cell cycle timing have not been determined (Johnson et al. 2011).

PHLDA1 is implicated as both a tumor suppressor and an oncogene. As a putative tumor suppressor, PHLDA1 may act by promoting cell death (Park et al. 1996, Neef et al. 2002, Hossain et al. 2003, Hayashida et al. 2006, Oberst et al. 2008) or inhibiting protein synthesis (Hinz et al. 2001). Higher levels of PHLDA1 in ERBB2 (HER2) positive breast tumors correlate with increased sensitivity to ERBB2 inhibitor, lapatinib (Li et al. 2014).

In estrogen receptor positive tumors, higher levels of PHLDA1 correlate with increased risk of cancer recurrence and distant metastases after hormone therapy, which may depend on the concomitant up-regulation of the NF-kappa B (NFKB) complex activity (Kastrati et al. 2015).

PHLDA1 has also been reported as a mediator of anti-apoptotic effect of IGF1 (Toyoshima et al. 2004). These studies suggest that PHLDA1 may have an oncogenic role in some settings.

Regulation of PHLDA1 expression has not been fully elucidated. PHLDA1 transcription may be directly stimulated by the activated estrogen receptor (Marchiori et al. 2008, Kastrati et al. 2015), possibly in cooperation with the NFKB complex (Kastrati et al. 2015). Indirectly, downregulation of microRNAs miR-181a and miR-181b in an estrogen and NFKB-dependent manner, increases stability of the PHLDA1 mRNA (Kastrati et al. 2015). Activation of ERK1 (MAPK3) or ERK2 (MAPK1) in response to ERBB2 or EGFR activation may also be involved in PHLDA1 up-regulation, possibly through a route that also involves JAK2 and STAT3 (Oberst et al. 2008, Li et al. 2014, Lyu et al. 2016). PHLDA1 may also be up-regulated in response to cellular stress such as heat shock (Hayashida et al. 2006), endoplasmic reticulum stress (Hossain et al. 2003) and oxidative stress (Park et al. 2013).

## Literature references

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## Editions

2016-01-29	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Shah, K.