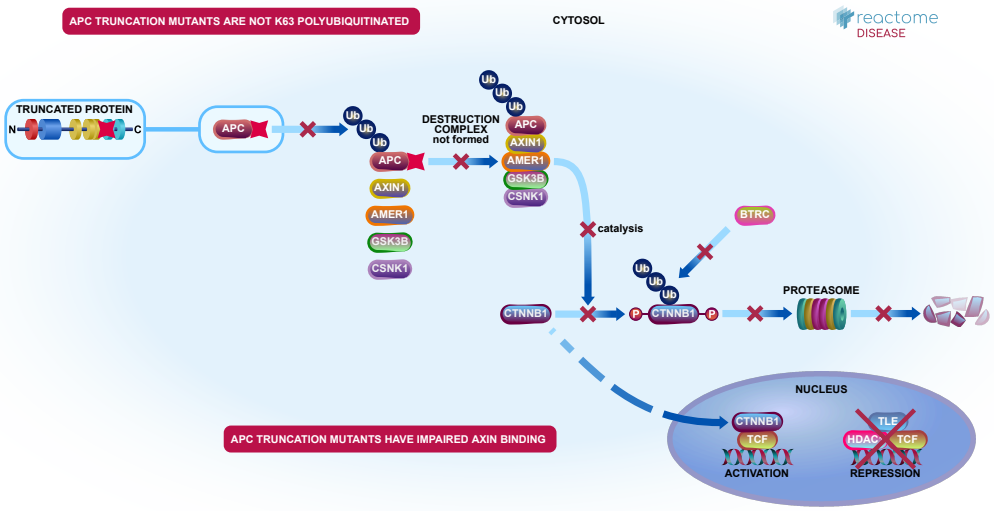
Signaling by APC mutants



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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. ↗

Reactome database release: 88

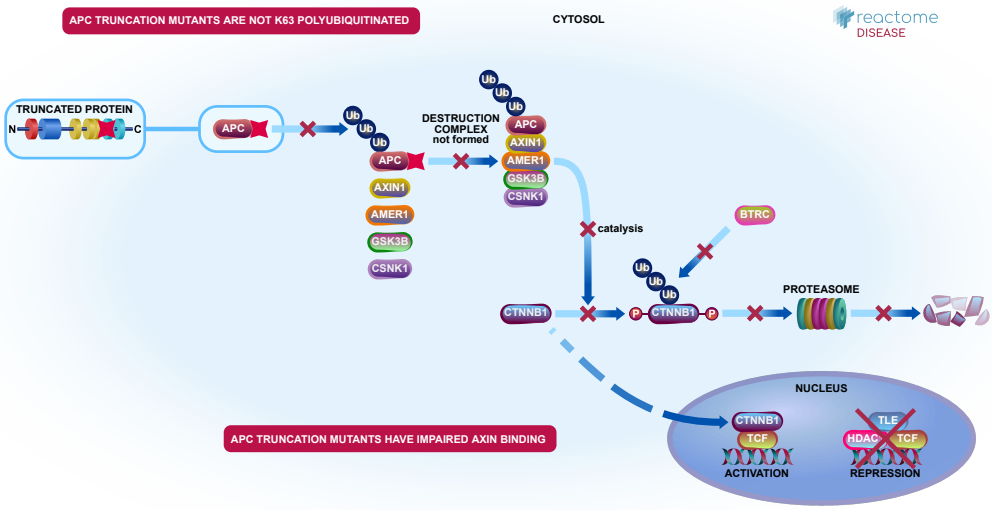
This document contains 3 pathways (see Table of Contents)

Signaling by APC mutants ↗

Stable identifier: R-HSA-4839744

Compartments: cytosol

Diseases: cancer



APC is a large and central component of the destruction complex, which limits signaling in the absence of WNT ligand by promoting the ubiquitin-mediated degradation of beta-catenin. APC interacts with numerous components of the destruction complex, including AXINs (AXIN1 and AXIN2), GSK3s (GSK3alpha and GSK3beta), CK1, PP2A and beta-catenin, and these interactions are critical for the phosphorylation and degradation of beta-catenin (reviewed in Saito-Diaz et al, 2013). APC is itself the target of phosphorylation and K63 ubiquitination in the absence of WNT signaling and these modifications are required for its interactions with other components of the destruction complex (Tran and Polakis, 2012; Ha et al, 2004; reviewed in Stamos and Weis, 2013).

More than 85% of sporadic and hereditary colorectal tumors carry loss-of-function mutations in APC. Most of the mutations are frameshifts and result in truncated proteins that lack the SAMP motifs and the 15 and 20 aa repeats that are implicated in binding AXIN and regulating beta-catenin binding and degradation (Miyoshi et al, 1992; Nagase and Nakamura, 1993; reviewed in Segditas and Tomlinson, 2006). Cancers expressing truncated APC have high levels of cytoplasmic beta-catenin and deregulated expression of WNT target genes (Korinek et al, 1997). Approximately 15% of the colorectal tumors with wild-type APC harbor phosphodegron mutations of beta-catenin; interestingly, mutations in APC and beta-catenin are mutually exclusive events. Similar to APC-mutant tumors, beta-catenin is stabilized in these tumors and constitutive WNT target activation is detected (Morin et al, 1997; reviewed in Polakis, 2000).

Literature references

Nagase, H., Nakamura, Y. (1993). Mutations of the APC (adenomatous polyposis coli) gene. *Hum. Mutat., 2*, 425-34. ↗

Barker, N., Clevers, HC., Morin, PJ., Kinzler, KW., Vogelstein, B., Korinek, V. et al. (1997). Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. *Science, 275*, 1787-90. ↗

Polakis, P., Tran, H. (2012). Reversible modification of adenomatous polyposis coli (APC) with K63-linked polyubiquitin regulates the assembly and activity of the ?-catenin destruction complex. *J. Biol. Chem., 287*, 28552-63. ↗

Stamos, JL., Ha, NC., Tonozuka, T., Choi, HJ., Weis, WI. (2004). Mechanism of phosphorylation-dependent binding of APC to beta-catenin and its role in beta-catenin degradation. *Mol Cell, 15*, 511-21. ↗

Polakis, P. (2000). Wnt signaling and cancer. *Genes Dev., 14*, 1837-51. ↗

Editions

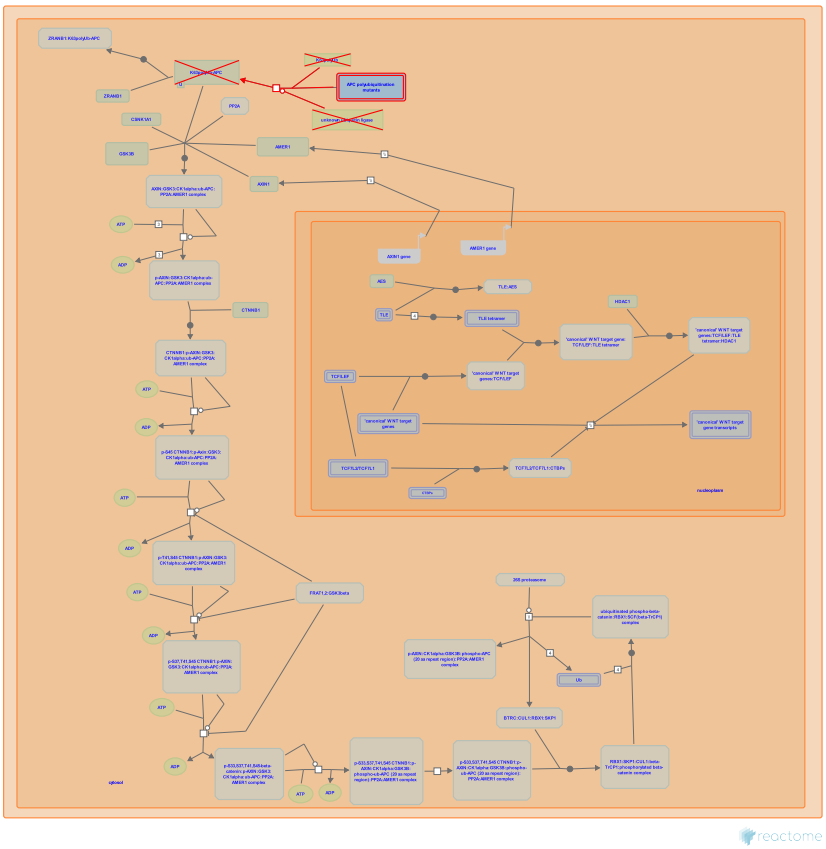
2013-11-01	Authored	Rothfels, K.
2014-04-03	Edited	Matthews, L.
2014-05-12	Reviewed	Salahshor, S.
2014-05-22	Reviewed	Woodgett, J.

APC truncation mutants are not K63 polyubiquitinated ↗

Location: Signaling by APC mutants

Stable identifier: R-HSA-5467333

Diseases: cancer



APC has been shown to be reversibly modified with K63-linked polyubiquitin chains. This modification is required for the assembly of the destruction complex and subsequent degradation of beta-catenin in the absence of WNT ligand. K63-polyubiquitination of APC is lacking in a number of colorectal cancer cell lines expressing truncated forms of APC, and these lines have aberrantly high beta-catenin levels and WNT pathway activation (Tran and Polakis, 2012).

Literature references

Polakis, P., Tran, H. (2012). Reversible modification of adenomatous polyposis coli (APC) with K63-linked polyubiquitin regulates the assembly and activity of the ?-catenin destruction complex. *J. Biol. Chem., 287*, 28552-63. ↗

Editions

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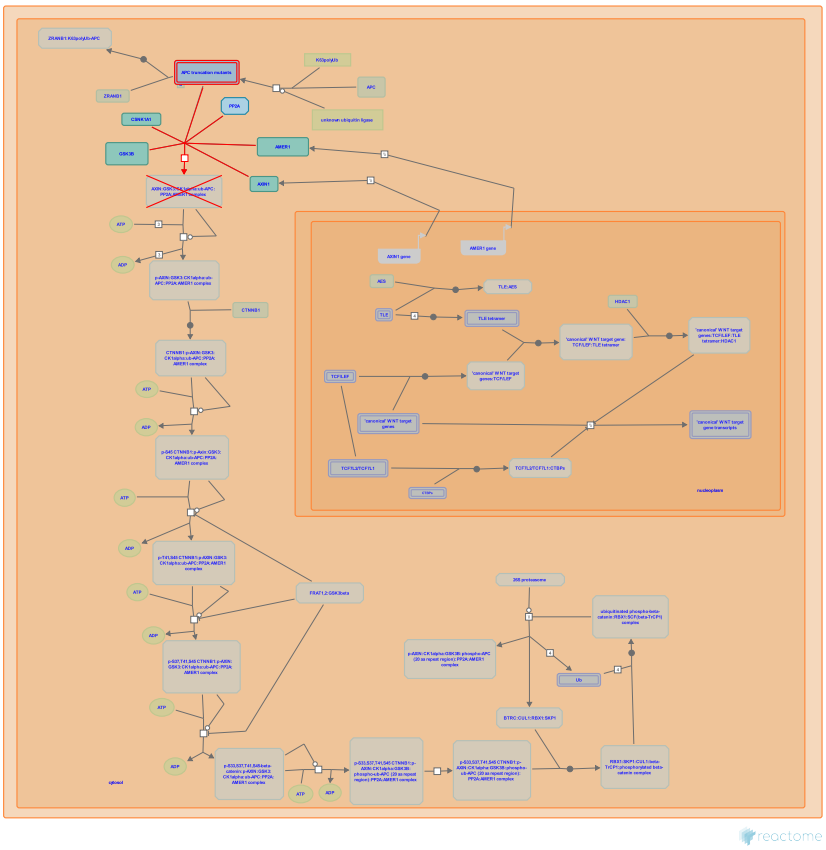
APC truncation mutants have impaired AXIN binding ↗

Location: Signaling by APC mutants

Stable identifier: R-HSA-5467337

Diseases: cancer



Mutations in the APC tumor suppressor gene are common in colorectal and other cancers and cluster in the central mutation cluster region (MCR) of the gene (Miyoshi et al, 1992; Nagase and Nakamura, 1993; Dihlmann et al, 1999; reviewed in Bienz and Clevers, 2000). These mutations generally result in truncated proteins that destabilize the destruction complex and result in elevated WNT pathway activation (reviewed in Polakis, 2000).

Literature references

Nagase, H., Nakamura, Y. (1993). Mutations of the APC (adenomatous polyposis coli) gene. *Hum. Mutat., 2*, 425-34. ↗

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Gebert, J., Herfarth, C., Siermann, A., von Knebel Doeberitz, M., Dihlmann, S. (1999). Dominant negative effect of the APC1309 mutation: a possible explanation for genotype-phenotype correlations in familial adenomatous polyposis. *Cancer Res., 59*, 1857-60. ↗

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Editions

2014-01-17	Authored	Rothfels, K.
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2014-05-12	Reviewed	Salahshor, S.
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