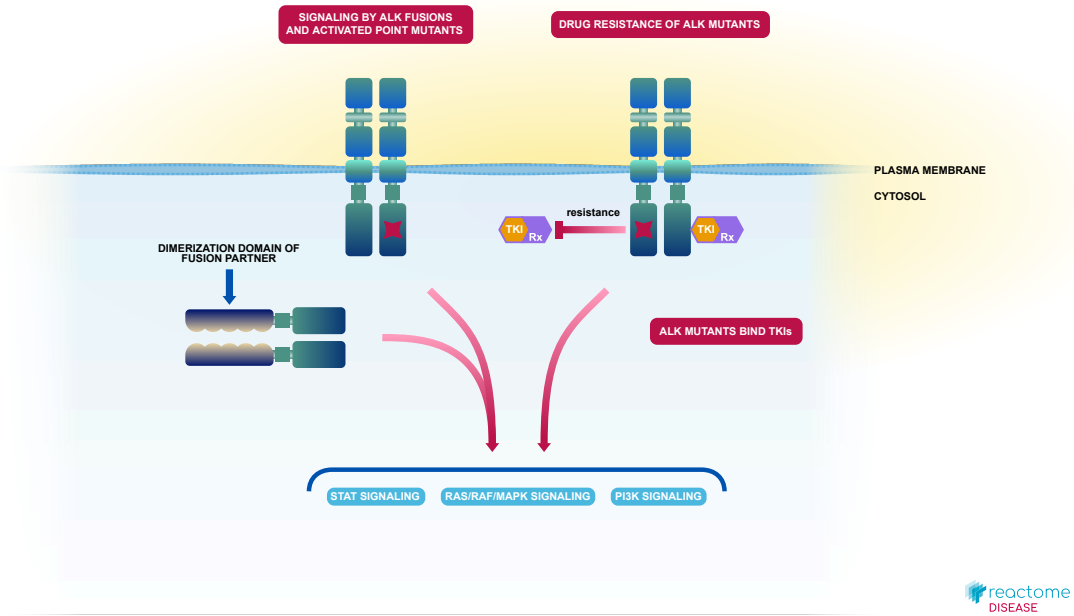
Signaling by ALK in cancer



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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).

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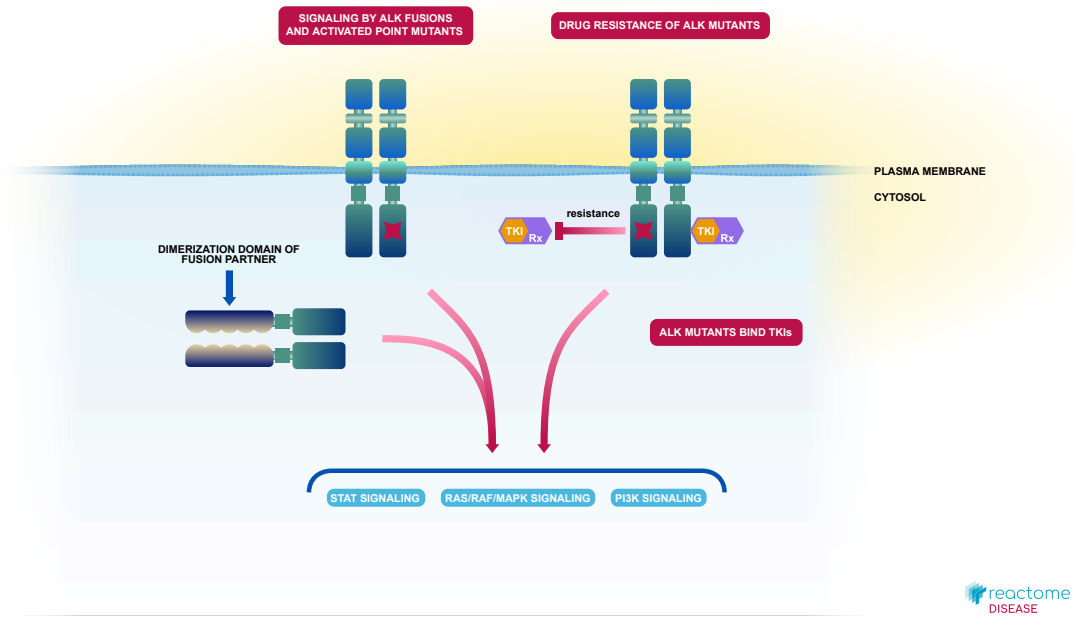
Signaling by ALK in cancer ↗

Stable identifier: R-HSA-9700206

Diseases: cancer



Anaplastic lymphoma kinase (ALK) was first identified in the context of an oncogenic fusion with nucleophosmin (NPM) in anaplastic large cell lymphoma (ALCL) (Morris et al, 1994). NPM-ALK fusions occur in approximately 75-80% of ALCL cases and at lower frequencies in other cancers, including non-small cell lung cancer, neuroblastoma and inflammatory myofibroblastic tumors (IFTs) (Morris et al, 1994; Shiota et al, 1994; reviewed in Della Corte et al, 2018; Werner et al, 2017).

In addition to NPM, fusions of ALK with nearly 30 other 5' partners have since been identified, although these tend to occur at lower frequencies in the cancers in which they appear (reviewed in Chiarle et al, 2008; Della Corte et al, 2018; Roskoski, 2013; Hallberg and Palmer, 2016). In general, ALK fusions combine the 5' end of the partner gene which contributes a dimerization domain with the intracellular portion of the ALK receptor including the kinase domain, and lead to constitutive signaling by virtue of the partner-domain mediated dimerization (reviewed in Roskoski, 2013; Della Corte et al, 2018).

In addition to translocation events that lead to fusion proteins, the ALK gene also contributes to oncogenesis as a result of gene amplification and overexpression events, as well as being subject to activating missense mutations (reviewed in Della Corte et al, 2018; Hallberg and Palmer, 2016).

Oncogenic ALK activity can be targeted with tyrosine kinase inhibitors, although resistance often arises due to secondary mutations or activation of bypass pathways (reviewed in Roskoski, 2013; Della Corte et al, 2018; Hallberg and Palmer, 2016; Werner et al, 2017; Lovly and Pao, 2012).

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Editions

2021-03-22	Authored	Rothfels, K.
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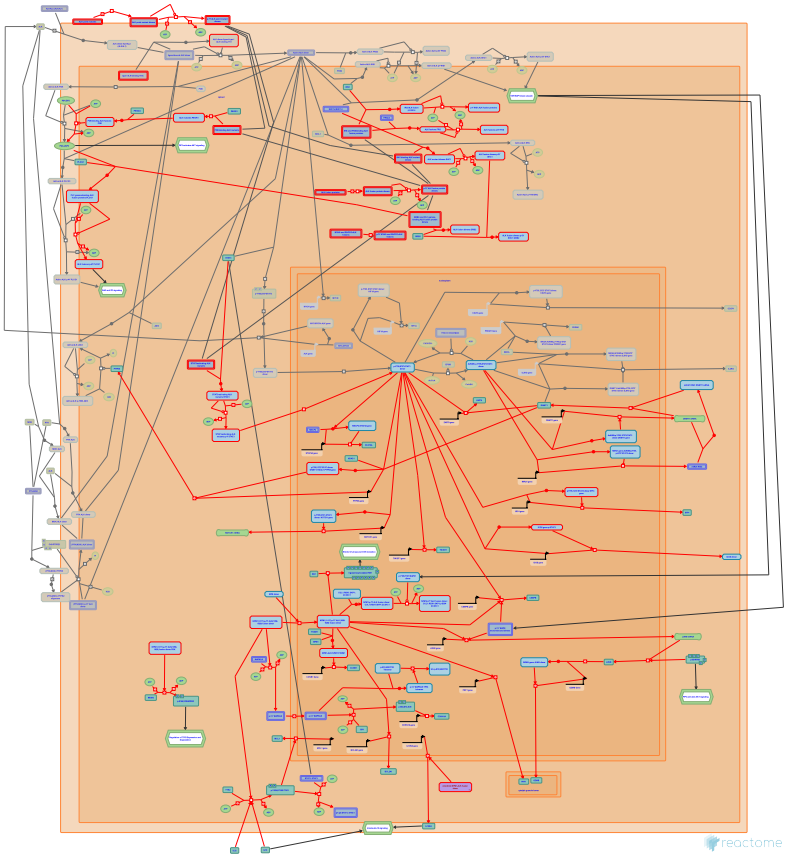
Signaling by ALK fusions and activated point mutants ↗

Location: Signaling by ALK in cancer

Stable identifier: R-HSA-9725370

Diseases: cancer



ALK is activated in a range of cancers as a result of amplification or overexpression, fusion event or activating point mutations, resulting, in general, in constitutive activation of intracellular signaling. The major pathways initiated downstream of activated ALK are STAT3 and, to a lesser extent, STAT5 signaling and signaling through the MAP kinase, PI3K/AKT and PLC gamma cascades (reviewed in Della Corte et al, 2018; Hallberg and Palmer, 2013; Hallberg and Palmer, 2016; Chiarle et al, 2008).

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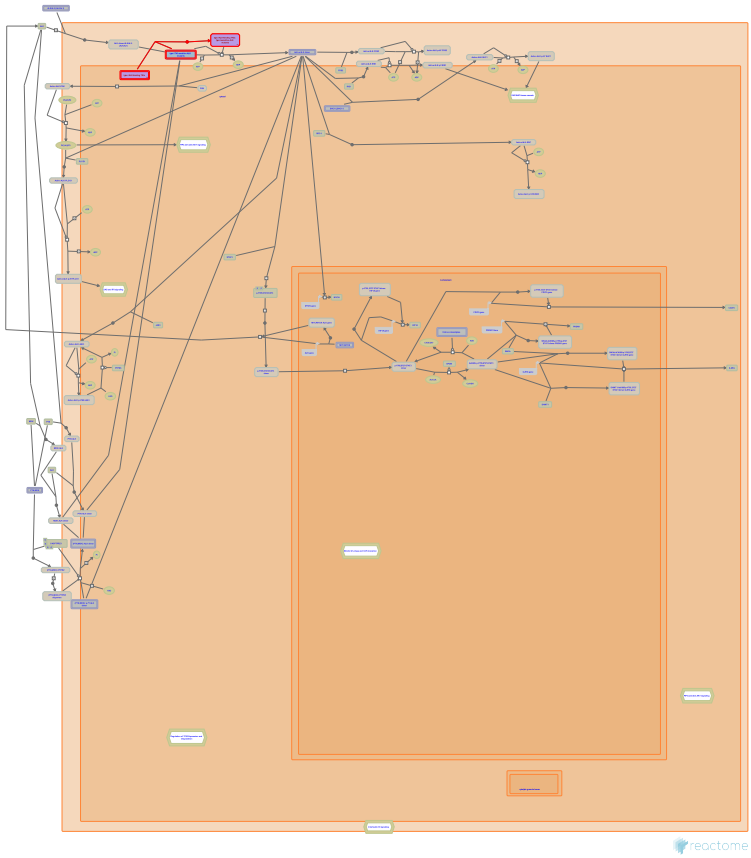
ALK mutants bind TKIs ↗

Location: Signaling by ALK in cancer

Stable identifier: R-HSA-9700645

Diseases: cancer



Aberrant signaling by activated forms of ALK can be inhibited by tyrosine kinase inhibitors (TKIs). ALK, like other tyrosine kinase receptors, is activated through a series of phosphorylation and conformational changes that move the receptor from the inactive form to the fully activated form. Type II TKIs bind to the inactive form of the receptor at a site adjacent to the ATP-binding cleft, while type I TKIs bind to the active form (reviewed in Roskoski, 2013). Type I inhibitors crizotinib, brigatinib, alectinib, ceritinib and lorlatinib are all approved for treatment of ALK-dependent cancer. Development of resistance to TKIs is not uncommon, however, either through acquisition of secondary mutations or through activation of bypass pathways that remove the dependence on ALK signaling (reviewed in Lovly and Pao, 2012; Lin et al, 2017; Della Corte et al, 2018).

Literature references

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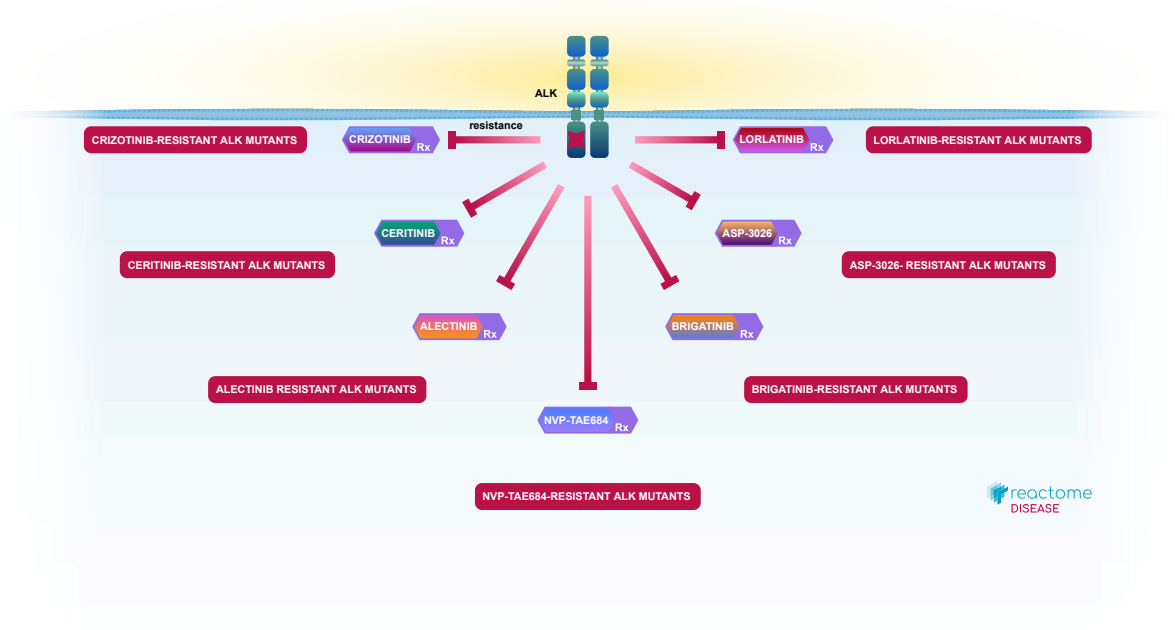
Drug resistance of ALK mutants ↗

Location: Signaling by ALK in cancer

Stable identifier: R-HSA-9700649

Diseases: cancer



Aberrant ALK activity arises through fusions, point mutations, overexpression or amplifications and has been shown to be an oncogenic driver in a number of cancers including anaplastic large cell lymphoma (ALCL), non-small cell lung cancer (NSCLC), inflammatory myofibroblastic tumors (IMTs) neuroblastomas and more (reviewed in Della Corte et al, 2018; Lin et al, 2017). As a result, ALK is a promising therapeutic target for inhibition with tyrosine kinase inhibitors. Crizotinib, ceritinib, brigatinib, alectinib and lorlatinib are all approved for the treatment of ALK-driven cancers, however resistance commonly develops either as a result of accumulating secondary mutations, or through activation of bypass pathways that remove the dependence on ALK signaling (reviewed in Della Corte et al, 2017; Roskoski, 2013; Lin et al, 2017).

Literature references

Troiani, T., Viscardi, G., Morgillo, F., Fasano, M., Martinelli, E., Ciardiello, F. et al. (2018). Role and targeting of anaplastic lymphoma kinase in cancer. *Mol. Cancer, 17*, 30. ↗

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