p16INK4A mutants do not bind CDK4

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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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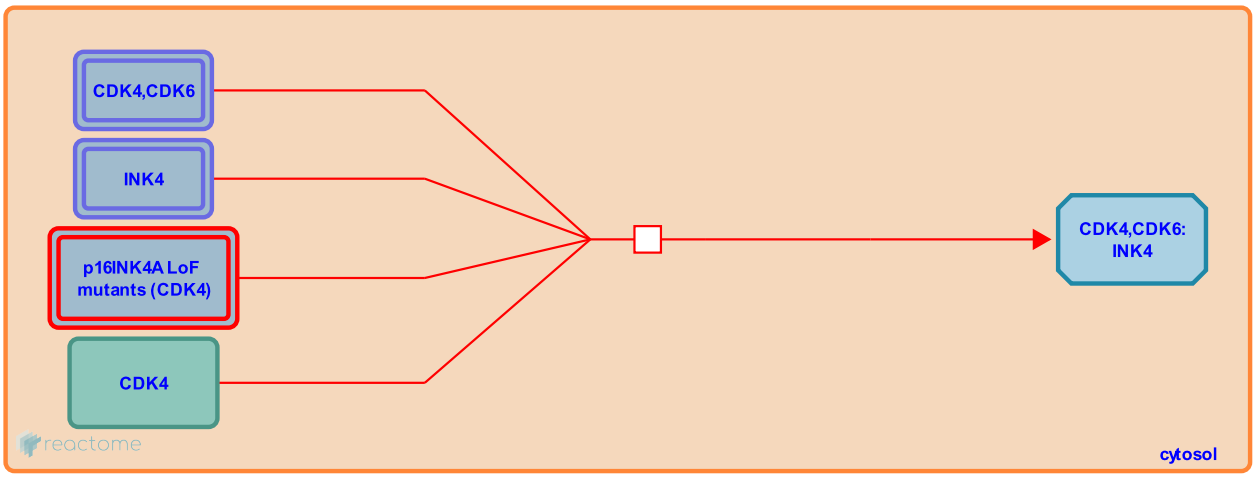
Stable identifier: R-HSA-9630792

Type: transition

Compartments: cytosol

Diseases: cancer



Wild type p16INK4A is able to form a complex with either CDK4 or CDK6 and prevent formation of catalytically active CDK complexes consisting of CDK4 or CDK6 and D-type cyclins (CCND). Several CDKN2A missense mutations found in cancer lead to amino acid substitutions in p16INK4A that impair binding of p16INK4A mutants to CDK4 while binding of these mutants to CDK6 is preserved. Functionally tested p16INK4A mutants that bind to CDK6 but not to CDK4 are:

p16INK4A R24P (Harland et al. 1997, Becker et al. 2001, Jones et al. 2007, McKenzie et al. 2010)
p16INK4A E88K (Ruas et al. 1999)
p16INK4A R112_L113insR (Ruas et al. 1999)

p16INK4A R24P is partially functional in inhibiting cellular proliferation (Jones et al. 2007), but its activity is severely reduced (Becker et al. 2001). Partial functionality in inhibition of cellular proliferation is also attributed to p16INK4A E88K (Ruas et al. 1999), but experimental evidence is lacking. The ability of p16INK4A R112_L113insR to inhibit cellular proliferation has not been tested.
A number of p16INK4A missense mutants have only been tested for their ability to bind to CDK4, but not CDK6. Mutants impaired in CDK4 binding whose binding to CDK6 has not been established include:

p16INK4A T18_A19dup (Kannengiesser et al. 2009)
p16INK4A G23D (Scaini et al. 2009, Kannengiesser et al. 2009, McKenzie et al. 2010)
p16INK4A G35A (Kannengiesser et al. 2009, McKenzie et al. 2010, Scaini et al. 2014)
p16INK4A G35V (Kannengiesser et al. 2009, McKenzie et al. 2010, Scaini et al. 2014)
p16INK4A A60R (Kannengiesser et al. 2009, McKenzie et al. 2010)
p16INK4A A60V (Kannengiesser et al. 2009, McKenzie et al. 2010)
p16INK4A G67_N71del (Kannengiesser et al. 2009)
p16INK4A D74Y (Kannengiesser et al. 2009)
p16INK4A T77P (Kannengiesser et al. 2009)
p16INK4A R80P (Kannengiesser et al. 2009)
p16INK4A L97R (Kannengiesser et al. 2009, McKenzie et al. 2010)
p16INK4A R99P (Kannengiesser et al. 2009, McKenzie et al. 2010)

p16INK4A G23D shows a reduced ability to prevent CDK4-mediated phosphorylation of RB1 (Scaini et al. 2009) and to inhibit cellular proliferation (Scaini et al. 2014). Impairment of ability to inhibit cellular proliferation was also demonstrated for p16INK4A G35A and p16INK4A G35V (Scaini et al. 2014), p16INK4A D74Y (Scaini et al. 2014), p16INK4A R80P (Jenkins et al. 2013) and p16INK4A R99P (Jenkins et al. 2013).
Based on sequence change similarity, the following p16INK4A mutants that have not been tested for their ability to bind to CDK4 or CDK6, but have been reported in cancer and predicted to be pathogenic (COSMIC database: Forbes et al. 2017) are annotated as candidates:

p16INK4A G23S
p16INK4A G23V
p16INK4A G35E
p16INK4A G35R
p16INK4A G35W
p16INK4A A60E
p16INK4A A60S
p16INK4A T77S
p16INK4A L97P

p16INK4A G23S and p16INK4A G23V show reduced ability to inhibit cellular proliferation (Scaini et al. 2014). p16INK4A G35E and p16INK4A G35R were shown to be markedly impaired in their ability to inhibit cellular proliferation, while p16INK4A G35W is somewhat impaired (Scaini et al. 2014). p16INK4A D74N (p16INK4A Asp74Ans) was not annotated because, while it is predicted to be pathogenic, it retains the ability to bind CDK4 and CDK6 (Yarbrough et al. 1999).
Mechanistic consequences of some p16INK4A mutations have not yet been elucidated. For example, substitution of alanine to proline at position 36, which is a consequence of a missense mutation in the exon 1alpha of CDKN2A, thus affecting only p16INK4A, results in expression of a mutant p16INK4A A36P protein. p16INK4A A36P retains the ability to bind to CDK4 (Becker et al. 2001, although not reproduced by McKenzie et al. 2010), but is not able to consistently inhibit CDK4-mediated phosphorylation of RB1 (Haferkamp et al. 2008), and is impaired in its ability to induce cell cycle arrest (Becker et al. 2001, Haferkamp et al. 2008). Another study shows that p16INK4A A36P retains cell cycle arrest-inducing ability, but is impaired in its ability to regulate intracellular oxidative stress (Jenkins et al. 2013).

Literature references

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Editions

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