p16INK4A mutants do not bind CDK4,CDK6

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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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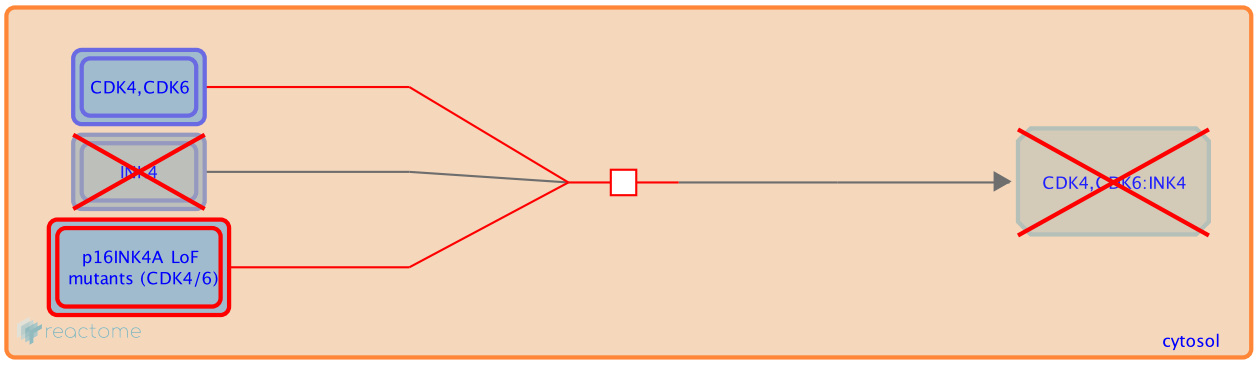
Stable identifier: R-HSA-9630795

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 both CDK4 and CDK6. Missense mutations in p16INK4A are recessive and are usually found in combination with genomic deletion or epigenetic silencing of the other CDKN2A allele (Kamb et al. 1994, Castellano et al. 1997, Liew et al. 1999). Inactivating mutations in the coding sequence of p16INK4A can also be accompanied with loss of heterozygosity (LOH) (Castellano et al. 1997, Kumar et al. 1999 , Liew et al. 1999). Functionally tested p16INK4A mutants that are unable to bind to either CDK4 or CDK6 or show little residual binding, and are unable to inhibit cellular proliferation are:

p16INK4A A20P (Ruas et al. 1999, Jones et al. 2007)

p16INK4A M53I (Harland et al. 1997, Walker et al. 1999, Becker et al. 2001)

p16INK4A P81L (Walker et al. 1999)

p16INK4A P81T (Kannengiesser et al. 2009, McKenzie et al. 2010)

p16INK4A D84G (Yarbrough et al. 1999)

p16INK4A D84H (Ruas et al. 1999)

p16INK4A D84N (Ruas et al. 1999)

p16INK4A D84V (Yarbrough et al. 1999)

p16INK4A D84Y (Ruas et al. 1999)

p16INK4A R87P (Walker et al. 1999, Yarbrough et al. 1999)

p16INK4A G101W (Walker et al. 1999, Kannengiesser et al. 2009, McKenzie et al. 2010, Scaini et al. 2014)

p16INK4A P114L (Harland et al. 1997)

p16INK4A V126D (Walker et al. 1999, Becker et al. 2001)

Based on the affected amino acid residue, the following p16INK4A missense 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 A20E

p16INK4A A20T

p16INK4A P81H

p16INK4A P81R

p16INK4A P81S

p16INK4A D84A

p16INK4A G101V

p16INK4A P114H

p16INK4A P114R

p16INK4A P114S

p16INK4A P114T

p16INK4A V126A

p16INK4A V126F

p16INK4A V126I

.p16INK4A P114S was shown to have a reduced binding to CDK4 (Kannengiesser et al. 2009) and a reduced ability to inhibit cellular proliferation (Scaini et al. 2014). p16INK4A A20S retains the ability to bind to CDK4 and CDK6 and to inhibit cellular proliferation (Yarbrough et al. 1999). p16INK4A R87W (Walker et al. 1999) and p16INK4A R87L (Yarbrough et al. 1999) retain the ability to bind to CDK4 and CDK6, but are unable to induce cell cycle arrest. Mutants p16INK4A A20S, p16INK4A R87W and p16INK4A R87L have not been annotated.

Some p16INK4A missense mutants are temperature sensitive, and their ability to bind to CDK4 and CDK6 can only be properly assessed at the physiological temperature of 37 degrees Celsius (Becker et al. 2001). Not controlling experimental temperature can be one source of inconsistencies when evaluating functionality of p16INK4A mutants, but many other variabilities in experimental systems and techniques can also influence the results of binding assays. A p16INK4A mutant with a preserved ability to bind to CDK4 and CDK6 may still not be able to inhibit their cyclin-dependent activation. However, the loss of CDK inhibitory function in p16INK4A mutants that do bind to CDK4 and CDK6 has not been tested directly.

Nonsense mutations in the second exon of the CDKN2A gene that lead to premature termination of p16INK4A mRNA translation are frequent in cancer. While the mRNAs of predicted p16INK4A truncation mutants can be detected, the truncated proteins cannot:

p16INK4A R58* (Castellano et al. 1997)

p16INK4A R80* (Fahham et al. 2010)

p16INK4A E88* (Castellano et al. 1997)

p16INK4A W110* (Castellano et al. 1997)

In addition, it was shown that the C-terminal half of p16INK4A is critical for binding to CDK4 and CDK6, and inhibition of cellular proliferation (Fahham et al. 2010).

The following nonsense and frameshift truncation mutants have not been functionally tested and are annotated as candidates:

p16INK4A E10*

p16INK4A S12*

p16INK4A W15*

p16INK4A E26*

p16INK4A E27*

p16INK4A E33*

p16INK4A Y44*

p16INK4A Q50*

p16INK4A E61*

p16INK4A E69*

p16INK4A C72*

p16INK4A P75*

p16INK4A E119*

p16INK4A E120*

The following recurrent frameshift truncations mutants that lack the C-terminal half of wild type p16INK4A and are therefore assumed to be unable to bind to CDK4 or CDK6 are also annotated as candidates:

p16INK4A S7fs*8

p16INK4A W15fs*1

p16INK4A L16fs*9

p16INK4A T18fs*15

p16INK4A T18fs*8

p16INK4A G23fs*3

p16INK4A A36fs*17

p16INK4A L37fs*16

p16INK4A N39fs*14

p16INK4A Y44fs*1

Literature references

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Editions

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