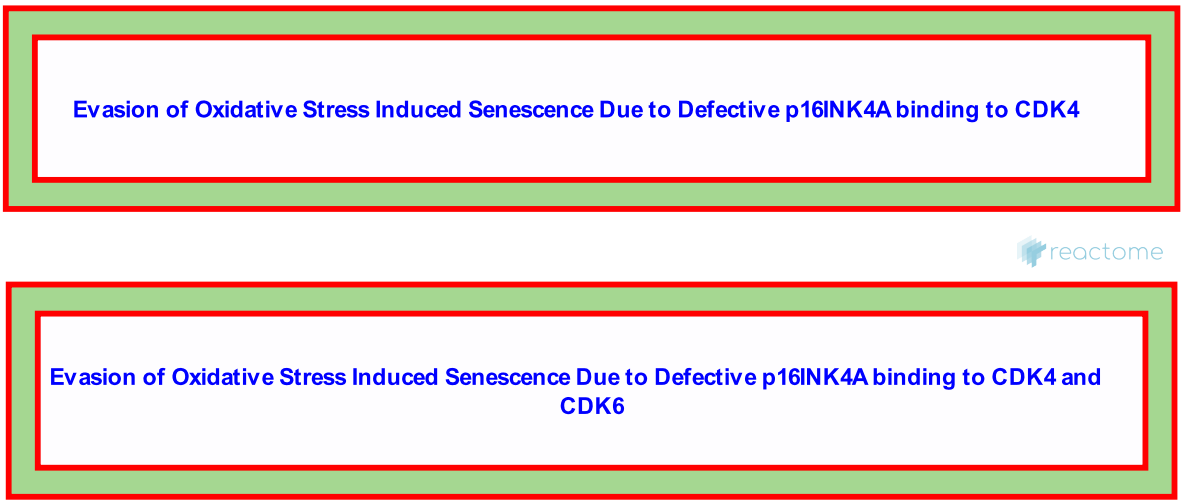
Evasion of Oxidative Stress Induced Senescence Due to p16INK4A Defects



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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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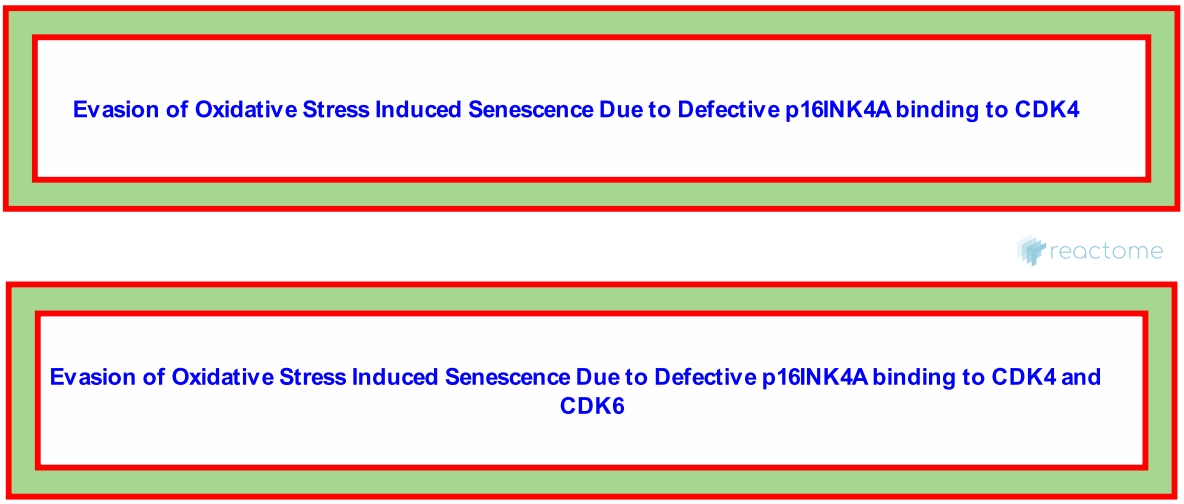
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Evasion of Oxidative Stress Induced Senescence Due to p16INK4A Defects ↗

Stable identifier: R-HSA-9632693

Diseases: cancer



The CDKN2A gene consists of four exons, exon 1beta, exon 1alpha, exon 2 and exon 3, going from the proximal to the distal gene end. There are two promoters in the CDKN2A gene locus. The promoter located between exons 1beta and 1alpha regulates transcription of the p16INK4A mRNA, which consists of exon 1alpha, exon 2 and exon 3 (only partially translated), and encodes a cyclin-dependent kinase inhibitor p16INK4A (also known as CDKN2A isoform 1, p16, INK4A, CDKN2A, CDK4I or MTS-1). The promoter located upstream of exon 1beta regulates transcription of the p14ARF mRNA, which consists of exon 1beta, exon 2 (partially translated) and exon 3 (untranslated). The p14ARF mRNA is translated in a different reading frame from the p16INK4A mRNA and produces the tumor suppressor ARF (also known as p14ARF or CDKN2A isoform 4), an inhibitor of MDM2 E3 ubiquitin ligase-mediated degradation of TP53 (p53).

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). Thus, p16INK4A prevents hyperphosphorylation of RB-family proteins, required for initiation of DNA replication in RB1-competent cells. Expression of p16INK4A increases in response to oxidative stress, leading to cellular senescence (programmed cell cycle arrest) under conditions of prolonged oxidative stress. Loss-of-function of p16INK4A frequently occurs in cancer, usually through loss of p16INK4A protein expression due to promoter hypermethylation or CDKN2A gene deletion (Merlo et al. 1995, Herman et al. 1995, Gonzalez-Zulueta et al. 1995, Wong et al. 1997, Witkiewicz et al. 2011, Shima et al. 2011, Tamayo-Orrego et al. 2016). Missense, nonsense and frameshift mutations in the CDKN2A locus can also impair p16INK4A function through expression of non-functional substitution mutants or truncated proteins (Kamb et al. 1994, Bartsch et al. 1995, Castellano et al. 1997). Germline intronic CDKN2A mutations that create aberrant splicing sites and result in expression of non-functional splicing variants of p16INK4A have been reported in familial melanoma (Harland et al. 2001, Harland et al. 2005). A CDKN2A gene mutation in the region encoding the 5'UTR of p16INK4A, reported in familial melanoma, creates a novel translation start codon and diminishes translation from the wild type start codon (Liu et al. 1999). However, mutations in the non coding regions of the CDKN2A gene are rare (Pollock et al. 2001).

p16INK4A defects enable cancerous cells to evade cell cycle arrest and senescence under prolonged oxidative stress (Tanaka et al. 1999, Chen 2000, Chen et al. 2004, Vurusaner et al. 2012, Rayess et al. 2012, LaPak and Burd 2014, Sharpless and Sherr 2015, Zhang et al. 2017). A cell cycle-independent role of p16INK4A in regulation of intracellular oxidative stress has been reported (Jenkins et al. 2011, Vurusaner et al. 2012, Jenkins et al. 2013).

Genomic deletions in the CDKN2A locus affect p14ARF, unless they are limited to exon 1alpha. The p14ARF promoter can also be hypermethylated in cancer, leading to loss of p14ARF expression. Some missense mutations occurring in exon 2 of the CDKN2A gene affect the p14ARF protein sequence. However, p14ARF mutants usually appear to be less functionally compromised than their p16INK4A counterparts. Most functional tests on p14ARF mutants examine the effect of mutations on MDM2 binding and TP53-mediated transcription of CDKN1A (p21), as well as sub-nuclear localization of p14ARF (Zhang and Xiong 1999, Schmitt et al. 1999, Eischen et al. 1999, Pinyol et al. 2000, Bostrom et al. 2001, Laud et al. 2006). Still, there are poorly explored functions of p14ARF that may be significantly affected in mutant p14ARF proteins detected in cancer (Itahana and Zhang 2008, Dominguez-Brauer et al. 2010).

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Itahana, K., Zhang, Y. (2008). Mitochondrial p32 is a critical mediator of ARF-induced apoptosis. *Cancer Cell, 13*, 542-53. ↗

Editions

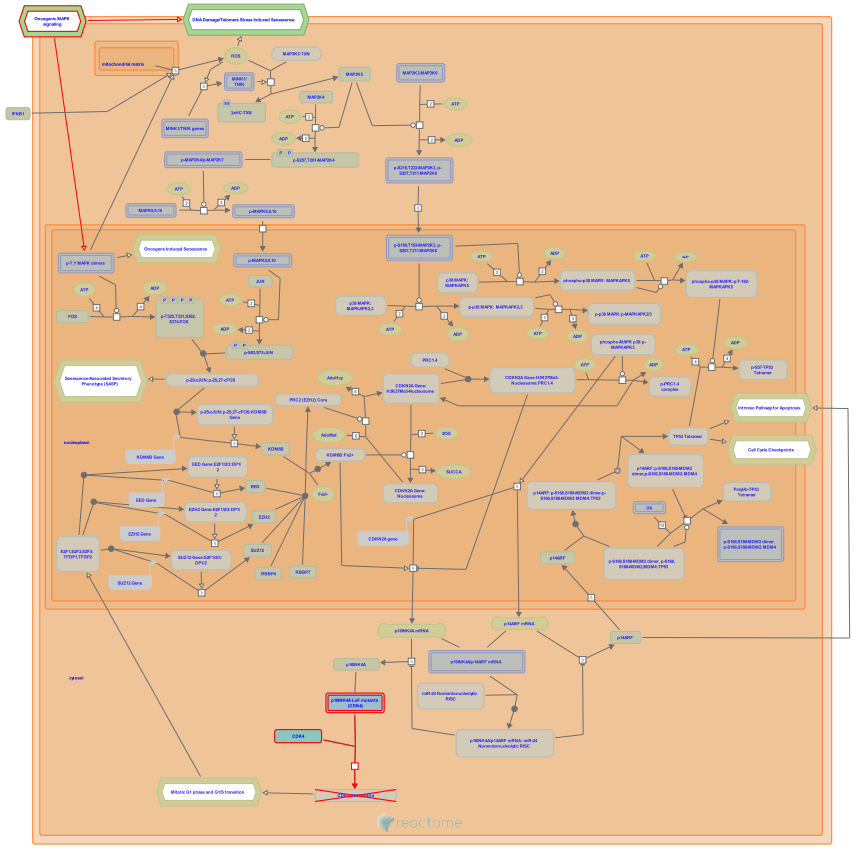
2018-12-24	Authored	Orlic-Milacic, M.
2019-04-23	Reviewed	Bennett, DC.
2019-05-07	Edited	Orlic-Milacic, M.
2019-06-03	Reviewed	Hayward, NK., Nathan, V.

Evasion of Oxidative Stress Induced Senescence Due to Defective p16INK4A binding to CDK4 ↗

Location: Evasion of Oxidative Stress Induced Senescence Due to p16INK4A Defects

Stable identifier: R-HSA-9632697

Diseases: cancer



Missense mutations and small indels in the CDKN2A gene, which result in amino acid changes in p16INK4A that impair its ability to bind to CDK4, interfere with p16INK4A-mediated, oxidative stress-induced, cellular senescence (Chen 2000, Vurusaner et al. 2012).
Loss-of-function mutations in p16INK4A can also contribute to cancer by interfering with p16INK4A-mediated inhibition of NFKB signaling (Becker et al. 2005).

Literature references

Chen, QM. (2000). Replicative senescence and oxidant-induced premature senescence. Beyond the control of cell cycle checkpoints. *Ann. N. Y. Acad. Sci., 908*, 111-25. ↗

Poli, G., Vurusaner, B., Basaga, H. (2012). Tumor suppressor genes and ROS: complex networks of interactions. *Free Radic. Biol. Med., 52*, 7-18. ↗

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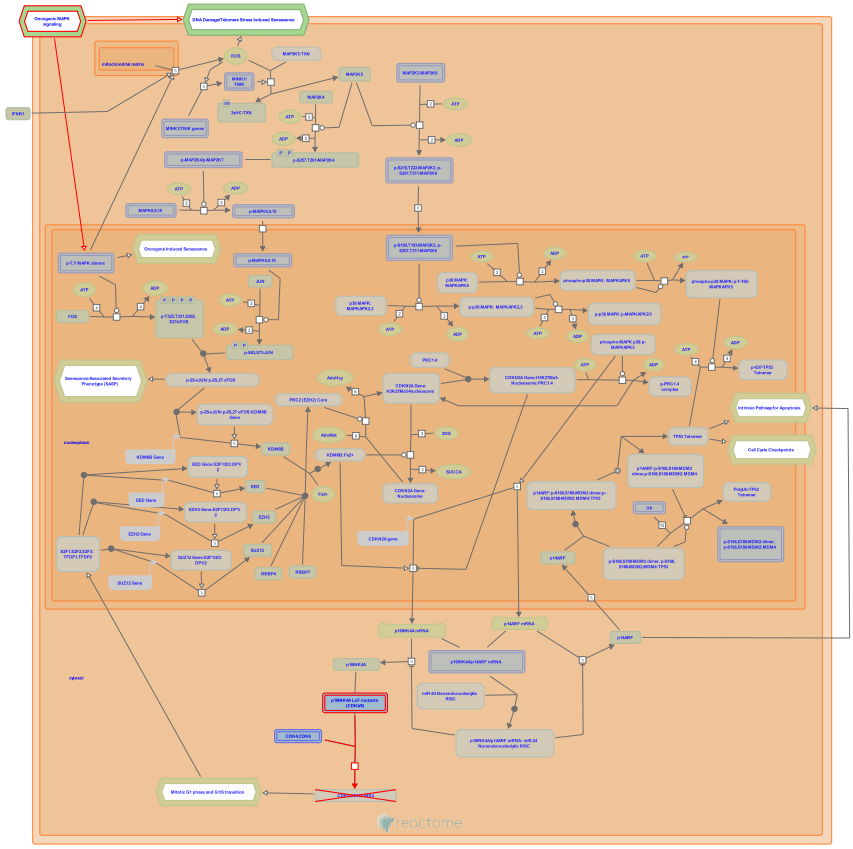
Evasion of Oxidative Stress Induced Senescence Due to Defective p16INK4A binding to CDK4 and CDK6 ↗

Location: Evasion of Oxidative Stress Induced Senescence Due to p16INK4A Defects

Stable identifier: R-HSA-9632700

Diseases: cancer



Missense and nonsense mutations in the CDKN2A gene that result in amino acid substitutions in p16INK4A or p16INK4A truncations, respectively, impairing its ability to bind to CDK4 and CDK6, interfere with p16INK4A-mediated induction of cellular senescence in response to oxidative stress (Chen 2000, Vurusaner et al. 2012).
Loss-of-function mutations in p16INK4A can also contribute to cancer by interfering with p16INK4A-mediated inhibition of NFKB signaling (Becker et al. 2005).

Literature references

Chen, QM. (2000). Replicative senescence and oxidant-induced premature senescence. Beyond the control of cell cycle checkpoints. *Ann. N. Y. Acad. Sci., 908*, 111-25. ↗

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