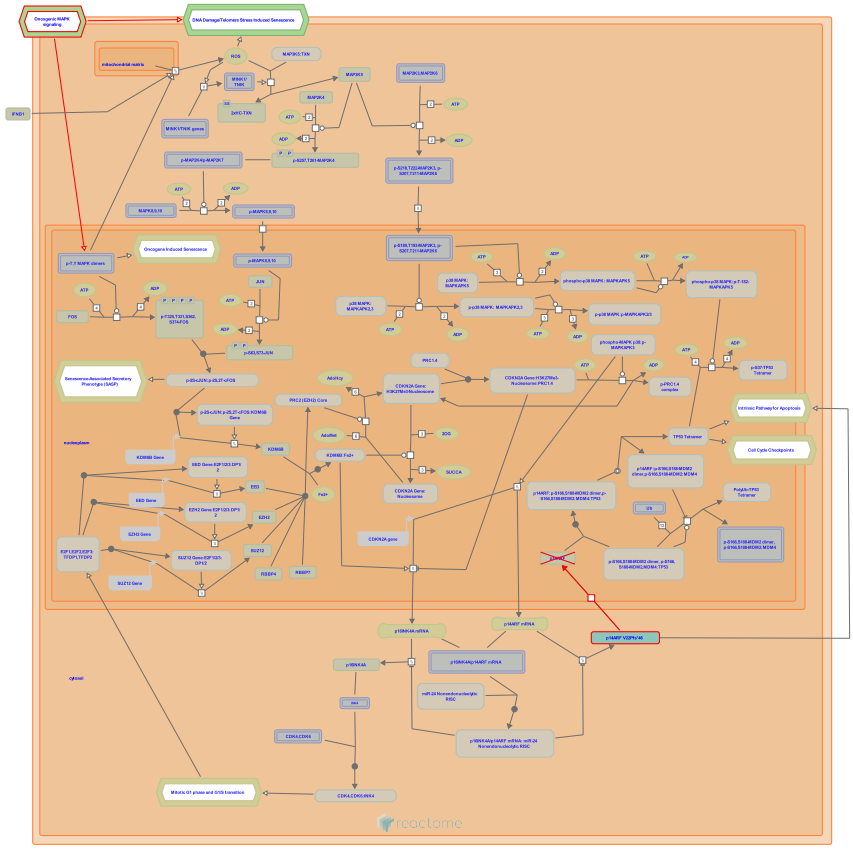
Evasion of Oxidative Stress Induced Senescence Due to p14ARF Defects



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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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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Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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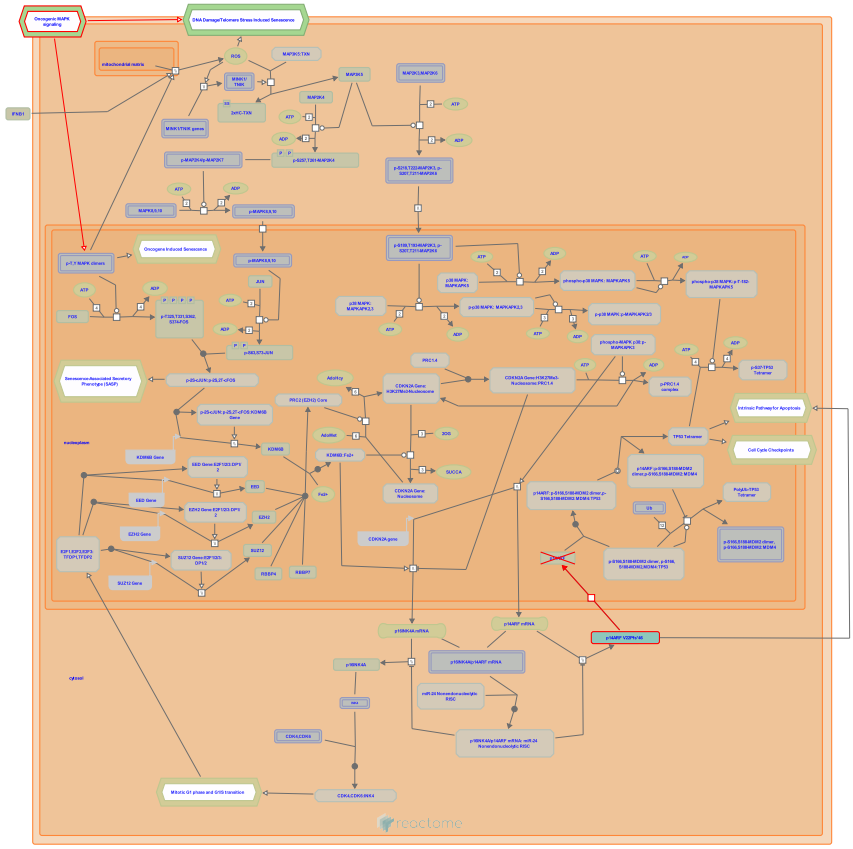
Stable identifier: R-HSA-9646304

Diseases: cancer



One of the two main protein products of the CDKN2A gene, p14ARF (CDKN2A transcript 4, CDKN2A-4, ARF), contributes to oxidative stress induced cellular senescence by stabilizing TP53 (p53). The function of p14ARF in p53 stabilization through sequestration of MDM2, a p53 ubiquitin ligase, depends on the nuclear localization of p14ARF and its ability to interact with MDM2. The nuclear localization signal and the MDM2 interaction domain map to the first 15 amino acids of the N-terminus of p14ARF. This region is encoded by the p14ARF-specific exon 1beta of CDKN2A. An independent MDM2-binding domain is localized at the C-terminus of p14ARF (Lohrum et al. 2000). Insertion of 16 nucleotides in exon 1beta results in a frameshift truncation of p14ARF, responsible for a familial melanoma syndrome in which the p16INK4A product of the CDKN2A gene is unaffected. This mutation is rare and has so far been reported in one family only. The mutant protein, p14ARF V22Pfs*46 has the nucleotide localization signal and the N-terminal MDM2 interaction region preserved, but is unable to translocate from the cytosol to the nucleus, possibly due to aberrant conformation (Rizos, Puig et al. 2001), and also lacks the C-terminal MDM2 interaction region. Relocation of wild type p14ARF to the cytosol has been observed in melanoma (Rizos, Darmanian et al. 2001) and aggressive thyroid papillary carcinoma (Ferru et al. 2006). Genomic deletion of exon 1beta, with exons 1alpha, 2 and 3 intact, has been reported in about 30% of melanoma cases with genomic deletions involving the CDKN2A locus (Freedberg et al. 2008). Several different familial melanoma germline mutations map to the exon 1beta splice donor site (Harland et al. 2005).
The ability of p14ARF to localize to the nucleolus also plays a role in p14ARF-mediated stabilization of p53. Mutations in exon 2 of the CDKN2A gene can lead to missense mutations in p14ARF that affect its nucleolar localization and p53 stabilization, but the exact mechanism has not been fully elucidated (Zhang and Xiong 1999, reviewed by Fontana et al. 2019).

Literature references

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Editions

2019-06-28	Authored	Orlic-Milacic, M.
2019-07-08	Reviewed	Rizos, H.
2019-07-16	Edited	Orlic-Milacic, M.
2019-08-12	Reviewed	Bennett, DC.
2019-08-14	Edited	Orlic-Milacic, M.

p14ARF mutant does not translocate to the nucleus ↗

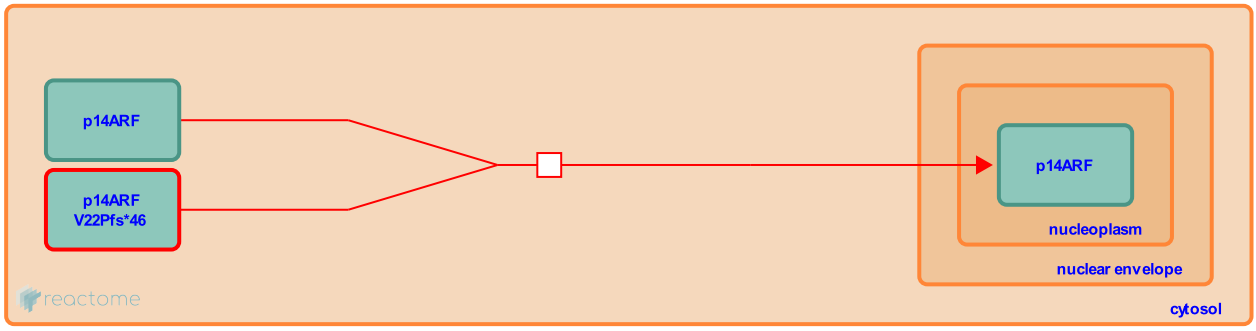
Location: Evasion of Oxidative Stress Induced Senescence Due to p14ARF Defects

Stable identifier: R-HSA-9646295

Type: transition

Compartments: cytosol

Diseases: cancer



A germline mutation affecting exon 1beta of the CDKN2A locus is associated with a familial melanoma syndrome. The mutation represents an insertion of 16 nucleotides (CGGCCCGCCGCGAGTG) between coding bases 60 and 61 in exon 1beta. This insertion results in a frameshift, starting at arginine codon at position 21 of p14ARF, with the first amino acid changed being valine at position 22, and ending with a premature stop codon at position 67. The mutant protein p14ARF V22Pfs*46 (p14ARF 60ins16) is unable to translocate to the nucleus and stabilize TP53 (Rizos, Puig et al. 2001).

Literature references

Puig, S., Milà, M., Darmanian, AP., Badenas, C., Kefford, RF., Rizos, H. et al. (2001). A melanoma-associated germline mutation in exon 1beta inactivates p14ARF. *Oncogene, 20*, 5543-7. ↗

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