Evasion of Oncogene Induced Senescence Due to p14ARF 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.

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Literature references


Reactome database release: 72

This document contains 1 pathway and 1 reaction (see Table of Contents)
In cell culture, p14ARF (CDKN2A transcript 4, CDKN2A-4, ARF), one of the two main protein products of the CDKN2A gene, contributes to oncogene induced 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 localized to 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 R21RfsTER47 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


Editions

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p14ARF mutant does not translocate to the nucleus

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