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Gene Section
Mini Review

CDKN2a (cyclin dependent kinase 2a / p16)

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Identity

Hugo: CDKN2A
Other names: CDKN2a; p16; INK4; p16- INK4a; TP16; CDK4I; MTS1
Location: 9p21.3

DNA/RNA

Description

The gene encompasses 6.6 kb of DNA; 3 exons.

Transcription

471 nucleotides mRNA. The CDKN2 gene generates several transcript variants from different promoters. Each transcript differs in its first exon (E1), and utilizes alternate polyadenylation sites. E1-alpha, which is spliced into the common exons E2 and E3, gives rise to the p16-INK4 transcript. A putative DNA replication origin has been identified in close proximity of INK4/Arf locus that appears to transcriptionally repress p16 in a manner dependent on CDC6.

Protein

Description

156 amino acids; 16.5 kDa protein.

Expression

Moderately expressed in many organs as thymus, liver, pancreas, prostate, lung, or kidney.

Function

P16-INK4a interacts strongly with cyclin-dependent kinase 4 and cyclin-dependent kinase 6 and inhibits their ability to interact with cyclins D. P16-INK4a induces cell cycle arrest at G1 and G2/M checkpoints, blocking them from phosphorylating RB1 and preventing exit from G1 phase of the cell cycle. P16-INK4a could act as a negative regulator of normal cells proliferation.

Homology

Belongs to the cdkn2 cyclin-dependent kinase inhibitor family.

Implicated in

Cutaneous malignant melanoma 2 (CMM2)

Disease

Malignant melanoma arises de novo or from a preexisting benign nevus, which occurs most often in the skin but also may involve other sites.

Oncogenesis

Familial melanoma (comprising between 8 and 12% of all melanoma cases) is a genodermatosis transmitted as an autosomal dominant trait. CDKN2a has been identified as a major susceptibility gene for melanoma. However this gene accounts for a minority of familial melanoma. P16 is functionally inactivated by mutations or deletions, however, because many such mutations occur in exon 2, they can potentially also affect the alternative reading frame (ARF) protein.

Familial atypical multiple mole melanoma carcinoma syndrome (FAMMM)

Disease

Patients with the FAMMM syndrome are genetically loaded with an increased risk of developing melanoma

and other malignant neoplasms, for example, a pancreatic cancer.

Oncogenesis

FAMMM syndrome is an autosomal dominant disorder with variable incomplete penetrance of the clinical phenotypes. Germline mutations in the p16-INK4a gene were found in approximately 40% of the FAMMM syndrome.

Sporadic cancer

Disease

Defects in CDKN2a are involved in tumor formation in a wide range of tissues.

Prognosis

Aberrant p16 expression is associated with more aggressive behavior.

Oncogenesis

LOH on 9p21 is one of the most frequent genetic alterations identified in human cancer. However, point mutations of p16 on the other chromosome are relatively rare. Promoter methylation appears as the commonest mechanism of p16 gene inactivation.

Aging

Note: Expression of p16 increases markedly with aging in many human tissues. This finding has led to the proposal that p16 expression could be used as a biomarker of physiologic, as opposed to chronologic, age. It was suggested that an age-induced increase in p16 expression contributes to the decline of replicative potential of certain self-renewing compartments with aging.

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