

## Gene Section

### Mini Review

# MDM2 (transformed mouse 3T3 cell double minute 2, p53 binding protein)

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### Identity

**Hugo:** MDM2

**Other names:** HDMX; hdm2

**Location:** 12q15

### DNA/RNA

#### Description

The gene encompasses 33 kb of DNA; 12 exons.

#### Transcription

2.3 kb nucleotides mRNA. 1476 b open reading frame.

### Protein

#### Description

491 amino acids; 90 kDa protein.

#### Expression

Expression of MDM2 during embryogenesis was studied in mice. During 14.5 to 18.5 days of prenatal development, the nasal respiratory epithelium expresses high levels of MDM2 RNA and protein in both wild type and p53 null embryos. MDM2 expression during development is tissue-specific and is independent of p53. The *mdm2* basal mRNA expression appears relatively moderate in most organs in adult mice.

MDM2 gene was overexpressed in some types of leukemias and lymphomas. Overexpression was significantly more frequent in the low-grade type of B-cell non-Hodgkin's lymphoma (B-NHL) than in the intermediate/high grade types of lymphoma and the overexpression was also significantly more frequent in the advanced rather than the earlier stages of B-cell chronic lymphocytic leukemia (B-CLL).

### Localisation

MDM2 protein was found in nucleus and cytoplasm.

### Function

MDM2 was originally cloned from transformed Balb/c3T3 cell line called 3T3DM and was identified as an amplified oncogene in murine cell lines. MDM2 was shown to be amplified in approximately 30% of osteosarcomas and soft tissue tumors and was subsequently found to act as an ubiquitin ligase promoting proteasome dependent degradation of p53. MDM2 is also a transcriptional target of p53 such that p53 activity controls the expression and protein level of its own negative regulator, providing for an elegant feedback loop. MDM2 inhibits the G1 arrest and apoptosis functions of the p53 tumor suppressor protein. The MDM2-p53 complex also inhibits p53 mediated transactivation.

MDM2 knockout mouse embryos died during development and deletion of the p53 gene rescues MDM2 null embryos. These studies suggested that p53 is lethal in the absence of MDM2 during mouse development and MDM2 is a critical regulator to control p53 activity.

In addition, MDM2 involves nuclear export of p53 protein. Interaction between the p53 and MDM2 is not sufficient to mediate p53 degradation. The p53-MDM2 complex must be shuttled from the nucleus to the cytoplasm in order for p53 degradation.

Besides, the MDM2 protein also promotes RB (retinoblastoma) protein degradation in a proteasome-dependent manner in human tumor cell lines. MDM2 overexpression contributes to cancer development in part by destabilizing RB.

Interaction between MDM2 and the tumor suppressor genes p53 and Rb lead to deregulate cell proliferation

and apoptosis. MDM2 is a key factor in human tumorigenesis.

Both MDM2 and Pirh2 (RCHY1) proteins are p53 ubiquitin-protein E3 ligases promoting for degradation of p53 protein. However, MDM2 operates in a distinct manner from Pirh2 in response to DNA damage in cancer cells. MDM2 protein is reduced or absent in the p53 null cells compared to the p53 positive cells, Whereas, Pirh2 expression is not affected by the status of p53.

A single nucleotide polymorphism (SNP309) found in the MDM2 promoter is shown to increase the affinity of the transcriptional activator Sp1, resulting in higher levels of MDM2 RNA and protein and the subsequent attenuation of the p53 pathway. In humans, SNP309 is shown to associate with accelerated tumor formation in both hereditary and sporadic cancers.

### Homology

The MDM2 gene has been identified in various organisms including mammals, amphibians and fishes. It belongs to the ring finger ubiquitin protein E3 ligase family, containing Conserved RING-finger Domain.

## Mutations

**Note:** MDM2 mutations are uncommon. Point mutations were reported in human cancers.

## Implicated in

### Soft tissue tumors and osteosarcomas

#### Disease

A set of data of MDM2 amplification based on 3889 samples from tumors or xenografts from 28 tumor types from previously published sources was collected. The overall frequency of MDM2 amplification in these human tumors was 7%. Gene amplification was observed in 19 tumor types, with the highest frequency observed in soft tissue tumors (20%), osteosarcomas (16%) and esophageal carcinomas (13%).

#### Oncogenesis

MDM2 is amplified in many cancers. Because the MDM2 is an ubiquitin-protein ligase that promotes p53 protein degradation, the increased MDM2 protein could play an important role in tumorigenesis, especially in the development of soft tissue tumors, osteosarcomas and esophageal carcinomas.

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