

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.

References

Cahilly-Snyder L, Yang-Feng T, Francke U, George DL. Molecular analysis and chromosomal mapping of amplified genes isolated from a transformed mouse 3T3 cell line. *Somat Cell Mol Genet* 1987;13(3):235-244.

Fakharzadeh SS, Trusko SP, George DL. Tumorigenic potential associated with enhanced expression of a gene that is amplified in a mouse tumor cell line. *EMBO J* 1991;10(6):1565-1569.

Momand J, Zambetti GP, Olson DC, George D, Levine AJ. The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation. *Cell* 1992;69(7):1237-1245.

Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. Amplification of a gene encoding a p53-associated protein in human sarcomas. *Nature* 1992;358(6381):80-83.

Barak Y, Juven T, Haffner R, Oren M. mdm2 expression is induced by wild type p53 activity. *EMBO J* 1993;12(2):461-468.

Oliner JD, Pieterpol JA, Thiagalingam S, Gyuris J, Kinzler KW, Vogelstein B. Oncoprotein MDM2 conceals the activation domain of tumour suppressor p53. *Nature* 1993;362(6423):857-860.

Perry ME, Piette J, Zawadzki JA, Harvey D, Levine AJ. The mdm-2 gene is induced in response to UV light in a p53-dependent manner. *Proc Natl Acad Sci USA* 1993;90(24):11623-11627.

Chen CY, Oliner JD, Zhan Q, Fornace AJ Jr, Vogelstein B, Kastan MB. Interactions between p53 and MDM2 in a mammalian cell cycle checkpoint pathway. *Proc Natl Acad Sci USA* 1994;91(7):2684-2688.

Jones SN, Roe AE, Donehower LA, Bradley A. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. *Nature* 1995;378(6553):206-208.

Montes de Oca Luna R, Wagner DS, Lozano G. Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p53. *Nature* 1995;378(6553):203-206.

Chen J, Wu X, Lin J, Levine AJ. mdm-2 inhibits the G1 arrest and apoptosis functions of the p53 tumor suppressor protein. *Mol Cell Biol* 1996;16(5):2445-2452.

Watanabe T, Ichikawa A, Saito H, Hotta T. Overexpression of the MDM2 oncogene in leukemia and lymphoma. *Leuk Lymphoma* 1996;21(5-6):391-397.

Haupt Y, Maya R, Kazanietz A, Oren M. Mdm2 promotes the rapid degradation of p53. *Nature* 1997;387(6630):296-299.

Honda R, Tanaka H, Yasuda H. Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. *FEBS Lett* 1997;420(1):25-27.

Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. *Nature* 1997;387(6630):299-303.

Schlott T, Reimer S, Jahns A, Ohlenbusch A, Ruschenburg I, Nagel H, Droese M. Point mutations and nucleotide insertions in the MDM2 zinc finger structure of human tumours. *J Pathol* 1997;182(1):54-61.

Freedman DA, Levine AJ. Nuclear export is required for degradation of endogenous p53 by MDM2 and human papillomavirus E6. *Mol Cell Biol* 1998;18(12):7288-7293.

Leveillard T, Gorry P, Niederreither K, Wasylyk B. MDM2 expression during mouse embryogenesis and the requirement of p53. *Mech Dev* 1998;74(1-2):189-193.

Momand J, Jung D, Wilczynski S, Niland J. The MDM2 gene amplification database. *Nucleic Acids Res* 1998;26(15):3453-3459.

Tao W, Levine AJ. P19(ARF) stabilizes p53 by blocking nucleocytoplasmic shuttling of Mdm2. *Proc Natl Acad Sci USA* 1999;96(12):6937-6941.

Bond GL, Hu W, Bond EE, Robins H, Lutzker SG, Arva NC, Bargonetti J, Bartel F, Taubert H, Wuerl P, Onel K, Yip L, Hwang SJ, Strong LC, Lozano G, Levine AJ. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. *Cell* 2004;119(5):591-602.

Sdek P, Ying H, Chang DL, Qiu W, Zheng H, Touitou R, Allday MJ, Xiao ZX. MDM2 promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma protein. *Mol Cell* 2005;20(5):699-708.

Duan W, Gao L, Wu X, Zhang Y, Otterson GA, Villalona-Calero MA. Differential response between the p53 ubiquitin-protein ligases Pirh2 and Mdm2 following DNA damage in human cancer cells. *Exp Cell Res* 2006;312(17):3370-3378.

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