The Enigma of p53

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This perspective will focus on the physiological impact of wild-type and mutant p53 activities. In particular, the tissue-specific nature of activation of p53 targets and their subsequent effects on cell behavior will be discussed. Because mutations in p53 are common in human cancers, the regulation and physiological consequences of mutant p53 proteins will also be discussed.

p53, A SHORT-LIVED PROTEIN TRANSCRIPTION FACTOR

p53 is a potent transcription factor that binds two repeats of a specific DNA sequence (5'-RRRCWWGYYY-3') as a tetramer and activates hundreds of genes—many in a tissue- and cell-specific manner (El-Deiry et al. 1992; Hoh et al. 2002). Most often this sequence is within 10 kb of the promoter but sometimes occurs further away at enhancers. p53 is stabilized and activated in response to numerous cellular signals that often sense DNA damage, stress, and inappropriate oncogene activation (which will be termed the stress response in this review) (Biegging et al. 2014). These p53-regulated genes have numerous functions from killing cells (*Puma*, *Noxa*, *Bax*) to arresting the cell cycle (*p21*, *Btg2*, *Ptprv*) and initiating senescence (*p21*, *Pml*, *Pai-1*) to altering the metabolic state (*TIGAR*, *Soc-2*, *DRAM*) for cell survival (Aubrey et al. 2016). Why does p53 activate so many genes? And how does it decide which genes to activate when? Answers to these questions remain elusive.

As with most transcription factors, p53 is normally a very short-lived protein (it has a 10- to 20-min half-life). In normal cells, p53 is kept at very low levels by two critical inhibitors Mdm2 and Mdm4 (Pant and Lozano 2014). Mdm2 encodes an E3 ubiquitin ligase that targets p53 for polyubiquitination and proteasomal degradation. Mdm4 on the other hand has a RING domain that lacks E3 ligase function but forms a heterodimer with Mdm2 to inhibit p53 activity. Mdm4 likely functions as an E4 ligase to enhance processivity of Mdm2 (Pant and Lozano 2014). Loss of either *Mdm2* or *Mdm4* in mice leads to embryo lethal phenotypes that are completely dependent on p53 as deletion of *p53* rescues these phenotypes (Jones et al. 1995; Montes de Oca Luna et al. 1995; Parant et al. 2001). In the central nervous system (CNS), a combination of *Mdm2* and *Mdm4* loss leads to more detrimental phenotypes, suggesting that both cooperate to inhibit p53 function at least in some cell types (Francoz et al. 2006;

Xiong et al. 2006). Furthermore, disruption of the Mdm2–Mdm4 interaction is also an embryo lethal event, indicating that the Mdm2/4 heterodimer is the most potent inhibitor of p53 (Huang et al. 2011; Pant et al. 2011). That being said, an Mdm2 that lacks E3 ligase activity but retains binding to Mdm4 is not embryonic lethal, indicating that the ability to bind the transactivation domain is sufficient to keep p53 levels low under physiological conditions (Tollini et al. 2014). However, these mice are extremely sensitive to irradiation and die because p53 levels cannot return to baseline quickly enough. Thus, the Mdm proteins are essential inhibitors of p53 activity, but the levels required to maintain p53 at low physiological levels are less than those required to inhibit p53 levels after a stress response.

NUMEROUS *Mdm2* ALLELES DEFINE p53 PHYSIOLOGICAL OUTCOMES

Mice heterozygous for *Mdm2* or *Mdm4* are normal. However, a low dose of ionizing radiation, which causes DNA damage, kills *Mdm2*^{+/-} and *Mdm4*^{+/-} mice but not controls in a p53-dependent manner (Terzian et al. 2007). *Mdm2* *Mdm4* double heterozygous mice, which express slightly more p53 (because of haploinsufficiency of these two inhibitors), suffer lethal developmental defects 30% of the time or hematopoietic failure within 2–3 wk after birth (70%). None survive beyond this age. The observation that *Mdm2*^{+/-} *Mdm4*^{+/-} *p53*^{+/-} mice are alive and well indicates how exquisitely Mdm2 and Mdm4 regulate p53 levels (Terzian et al. 2007).

Studies of hypomorphic *Mdm2* alleles have also defined important tissue specificities. Mice inheriting a hypomorphic and a null allele of *Mdm2* express ~30% of Mdm2 levels and show increased p53 activity. These mice are small, lymphopenic, and radiosensitive (Mendrysa et al. 2003). Another hypomorphic *Mdm2* allele (which contains a 184-bp deletion and retains the *Neomycin* gene

in intron 1 in feedback loop defective mice) with decreased Mdm2 levels also exhibits unique p53-dependent pathologies: increased skin pigmentation of the epidermis, reduction of seminiferous tubules and decreased spermatocytes in testis, and decreased number of ovarian follicles (Pant et al. 2016). None of the defects is rescued by deletion of the p53 target *p21*, but the reproductive phenotypes are rescued by *Puma* loss. Thus, deletion of a single downstream target of p53 (*Puma*) could revert a p53-dependent phenotype. The skin phenotype appears to be driven by KitL signaling. *KitL* is another p53 target expressed in melanocytes and is linked to their migration and accumulation (Zeron-Medina et al. 2013). These studies show for the first time that depletion of a single p53 target can bypass the effects of p53 and further implicate tissue-specific nature of the p53 response in vivo.

Deletion of *Mdm2* using an *Mdm2* floxed allele and a tamoxifen-inducible universally expressed CreER transgene resulted in numerous pathologies in adult mice, which included extensive absence of white pulp in the spleen, erythroid depletion in the bone marrow, villus atrophy in the intestine, and tubular proteinuria and fibrosis in the kidney (Table 1; Zhang et al. 2014). Importantly, all phenotypes were obviated by *p53* loss highlighting the near-universal importance of Mdm2 in maintaining appropriate levels of p53 in vivo. An analysis of p53 transcriptional activity showed a varied response depending on tissue type (Table 1). Surprisingly, *p21* was elevated almost 200-fold in the kidney compared with seven- and 12-fold in liver and spleen, respectively. As an aside, *p21* is always up-regulated by p53 in response to numerous signals and serves as a great marker for p53 transcriptional activation. *Puma*, another p53 transcriptional target, was elevated 18-fold in the kidney but was not elevated in the liver. Global loss of *Mdm2* also resulted in apoptosis and senescence phenotypes that varied by tissue type (Table 1).

Besides affecting normal developmental/physiological functions, minor changes in the levels of Mdm2 and Mdm4 also affect tumor phenotypes. Haploinsufficiency at *Mdm2* or *Mdm4* loci delays tumor onset in mice carrying an *Eμ-myc* transgene (Alt et al. 2003; Terzian et al. 2007), and decreased *Mdm2* levels delay intestinal tumors in *Apc^{min/+}* mice (Mendrysa et al. 2006). In addition, a single-nucleotide polymorphism in the *Mdm2*

promoter that increases the levels of *Mdm2* also contributes to cancer risk (Bond et al. 2004; Post et al. 2010). Last, transgenic mice that have high levels of Mdm2 or Mdm4 are also prone to develop multiple cancers, indicating that Mdm2 and Mdm4 directly impact tumor development (Jones et al. 1998; Xiong et al. 2010).

p53 RESPONDS TO DNA DAMAGE/STRESS

An abnormal physiological state (that likely differs by cell type) is sensed by p53 and results in p53 activation and cellular outcomes (Biegging et al. 2014). Numerous upstream signals activate p53 and include DNA damage, telomere erosion, oxidative stress, hypoxia, and hyperproliferative signals. For these reasons, p53 was labeled the guardian of the genome (Lane 1992). As indicated above, the Mdm proteins keep p53 at low levels normally. However, in response to DNA damage and a myriad of other signals that sense abnormal cell behavior, p53 is phosphorylated, acetylated, and sumoylated and these posttranslational modifications unleash a tissue-specific transcriptional program.

THE p53 TUMOR SUPPRESSOR PATHWAY

In 1990, the wild-type sequence of p53 was finally determined, and it was shown to inhibit transformation in vitro (Finlay et al. 1989). At the same time, mutations in *Tp53* with concomitant loss of heterozygosity were identified in colorectal cancers (Baker et al. 1989). p53 mutations were subsequently identified in the germline of individuals with a rare cancer syndrome, the Li-Fraumeni syndrome (Malkin et al. 1990). And last, mice with deletion of the *p53* gene developed a variety of cancers that vary depending on the background of the animal (Donehower et al. 1992; Jacks et al. 1994; Donehower and Lozano 2009).

DNA sequencing of thousands of human tumors has revealed that *Tp53* is the most often mutated tumor suppressor (Hainaut and Pfeifer 2016). Decreased p53 levels by either deletion or mutation or increased levels of the p53 inhibitors Mdm2 and Mdm4 lead to tumor development in a mutually exclusive relationship (Wasylishen and Lozano 2016).

Table 1. Phenotypes of *Mdm2^{FM/-} CAG-CreER* mice upon activation of Cre

Tissue	Phenotype ^a	Cdkn1a (p21)	Bbc3 (Puma)	Apoptosis	Senescence ^b
Spleen	Absence of white pulp	11.9 ± 4.20	2.11 ± 0.96	pos	neg
Bone marrow	Erythroid depletion ^c	NA	NA	NA	NA
Intestine	Villus atrophy, apoptotic crypts	NA	NA	pos	NA
Kidney	Protein casts, tubule dilation	184.56 ± 56.3	18.21 ± 5.32	pos	pos
Liver	Increased AST, fibrosis	6.80 ± 1.37	0.91 ± 0.27	pos	pos
Heart	Fibrosis	37.07 ± 12.76	7.37 ± 2.31	neg	pos
Cerebrum		16.21 ± 2.68	3.13 ± 0.48	pos	pos
Cerebellum		21.59 ± 4.58	2.46 ± 0.41	neg	NA
Retina		20.58 ± 7.08	6.97 ± 1.58	pos	pos

NA, not available; pos, positive; neg, negative; AST, aspartate aminotransferase.

^aAs observed by morphology for two different treatments.

^bAt least two cytokines/chemokines were elevated.

^cErythroid depletion occurs in Diamond-Blackfan anemia and is due to elevated p53 activity.

However, the most common alterations at the p53 locus are missense mutations (~75%) that occur in the DNA binding domain and disrupt interactions with DNA and thus transcriptional activity. These missense mutations are of two kinds: structural and conformational. Importantly for this discussion, most p53 missense mutations do not disrupt the amino and carboxyl domains of p53. These are the domains through which cells signal to p53. For example, phosphorylation at the amino terminus disrupts interactions with Mdm2/4 (Loughery and Meek 2013). Tetramerization of the carboxyl terminus forces conformational changes in the DNA binding domain that facilitate DNA binding (D'Abramo et al. 2016).

Modeling of the hotspot p53 mutations in mice have yielded several observations, the most important of which is that mutant p53 has a gain-of-function phenotype (Lang et al. 2004; Olive et al. 2004; Brosh and Rotter 2009; Freed-Pastor and Prives 2012). Tumor cells expressing a stable mutant p53 have a more aggressive and highly metastatic phenotype. Another important observation from the mouse models is that, similar to the half-life of wild-type p53, mutant p53 is an unstable protein under normal physiological conditions. Some tumors expressing only mutant p53 did not have a detectable p53 protein by immunohistochemistry, leading to the hypothesis that tumor-specific events stabilized p53 (Lang et al. 2004). As proof of concept, homozygosity of the *p53R172H* allele rescued the *Mdm2*-null lethal phenotype and resulted in increased levels of p53 mutant protein, increased tumor incidence, and increased metastasis (Terzian et al. 2008). Several p53-activating stress responses such as DNA damage and reactive oxygen species (ROS) also stabilize the p53 mutant protein in vivo (Suh et al. 2011). Thus, it appears that signals that regulate p53 via the amino and carboxyl termini also regulate mutant p53. An important question that needs to be addressed is what signals stabilize the p53 mutant protein in tumors.

These signals may be constitutive and result in a stable p53 protein in all cells of the tumors (Fig. 1). But these signals may also be intermittent, resulting in p53 stability only in some tumor cells at any one time, leading to

tumor heterogeneity. The timing of p53 mutation and stabilization is critical. In ovarian cancer, for example, p53 mutation appears to be an early and probably the first event resulting in a stable mutant protein in all cells (Perets et al. 2013). In colorectal cancers, on the other hand, p53 mutations are late and correlate to a change in the behavior of tumor cells to a more aggressive and invasive one (Fearon and Vogelstein 1990). So what stabilizes mutant p53 in tumors? Many of these signals are likely the same mechanisms that stabilize wild-type p53. Inflammatory signals, DNA damage, hypoxia, and ROS are all likely to contribute to stabilization of mutant p53 proteins. Nonetheless, some p53 mutant mice develop tumors that do not have a stable p53 protein and these likely resemble tumors with deletions of *p53* (Lang et al. 2004).

Further studies are needed to understand how mutant p53 is stabilized, as a growing number of studies suggest tumor cells are addicted to mutant p53 (Alexandrova et al. 2015). Undermining the signals that stabilize mutant p53 (e.g., hsp90) may have important therapeutic consequences.

CONCLUSION

p53 is a master regulator of a tissue-specific transcriptional program that alters the behavior of cells killing some and stopping others from proliferation. Because of these tumor suppressive activities, p53 is the most often altered gene and pathway. I will venture to say that all tumor cells have undermined the p53 pathway by some mechanism. Studies to understand how p53 is regulated will lead to important therapeutic options, as has already happened with the development of Mdm2 inhibitors that are being tested in clinical trials (Cheek and Lane 2016; Wang et al. 2016). A deeper understanding of how mutant p53 leads to more aggressive highly invasive phenotypes in vivo is important, as is an understanding of the signals that stabilize mutant p53 proteins.

REFERENCES

- Alexandrova EM, Yallowitz AR, Li D, Xu S, Schulz R, Proia DA, Lozano G, Dobbstein M, Moll UM. 2015. Improving survival by exploiting tumour dependence on stabilized mutant p53 for treatment. *Nature* **523**: 352–356.
- Alt JR, Greiner TC, Cleveland JL, Eischen CM. 2003. Mdm2 haplo-insufficiency profoundly inhibits Myc-induced lymphomagenesis. *EMBO J* **22**: 1442–1450.
- Aubrey BJ, Strasser A, Kelly GL. 2016. Tumor-suppressor functions of the TP53 pathway. *Cold Spring Harb Perspect Med* **6**: a026062.
- Baker SJ, Fearon ER, Nigro JM, Hamilton SR, Preisinger AC, Jessup JM, van Tuinen P, Ledbetter DH, Barker DF, Nakamura Y, et al. 1989. Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science* **244**: 217–221.
- Biegging KT, Mello SS, Attardi LD. 2014. Unravelling mechanisms of p53-mediated tumour suppression. *Nat Rev Cancer* **14**: 359–370.
- Bond GL, Hu W, Bond EE, Robins H, Lutzker SG, Arva NC, Bargonetti J, Bartel F, Taubert H, Wuerl P, et al. 2004. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. *Cell* **119**: 591–602.

Figure 1. Numerous stress signals stabilize both wild-type and mutant p53. Wild-type p53 activates numerous transcriptional targets many in a cell-specific manner. Mutant p53, on the other hand, is transcriptionally inactive but binds other transcription factors to alter gene expression. When stabilized, mutant p53 shows gain-of-function activities. Some signals are constitutive (e.g., genomic instability) and lead to p53 stability in all tumor cells. Other signals (e.g., hypoxia) may result in only some cells having a mutant p53. ROS, reactive oxygen species.

- Brosh R, Rotter V. 2009. When mutants gain new powers: News from the mutant p53 field. *Nat Rev Cancer* **9**: 701–713.
- Cheok CF, Lane DP. 2016. Exploiting the p53 pathway for therapy. *Cold Spring Harb Perspect Med* **6**: a026310.
- D'Abramo M, Besker N, Desideri A, Levine AJ, Melino G, Chillemi G. 2016. The p53 tetramer shows an induced-fit interaction of the C-terminal domain with the DNA-binding domain. *Oncogene* **35**: 3272–3281.
- Donehower LA, Lozano G. 2009. 20 years studying p53 functions in genetically engineered mice. *Nat Rev Cancer* **9**: 831–841.
- Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CA Jr, Butel JS, Bradley A. 1992. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature* **356**: 215–221.
- El-Deiry WS, Kern SE, Pietenpol JA, Kinzler KW, Vogelstein B. 1992. Definition of a consensus binding site for p53. *Nat Genet* **1**: 45–49.
- Fearon ER, Vogelstein B. 1990. A genetic model for colorectal tumorigenesis. *Cell* **61**: 759–767.
- Finlay CA, Hinds PW, Levine AJ. 1989. The p53 proto-oncogene can act as a suppressor of transformation. *Cell* **57**: 1083–1093.
- Francoz S, Froment P, Bogaerts S, De Clercq S, Maetens M, Doumont G, Bellefroid E, Marine JC. 2006. Mdm4 and Mdm2 cooperate to inhibit p53 activity in proliferating and quiescent cells in vivo. *Proc Natl Acad Sci* **103**: 3232–3237.
- Freed-Pastor WA, Prives C. 2012. Mutant p53: One name, many proteins. *Genes Dev* **26**: 1268–1286.
- Hainaut P, Pfeifer GP. 2016. Somatic TP53 mutations in the era of genome sequencing. *Cold Spring Harb Perspect Med* **6**: a026179.
- Hoh J, Jin S, Parrado T, Edington J, Levine AJ, Ott J. 2002. The p53MH algorithm and its application in detecting p53-responsive genes. *Proc Natl Acad Sci* **99**: 8467–8472.
- Huang L, Yan Z, Liao X, Li Y, Yang J, Wang ZG, Zuo Y, Kawai H, Shadfan M, Ganapathy S, et al. 2011. The p53 inhibitors MDM2/MDMX complex is required for control of p53 activity in vivo. *Proc Natl Acad Sci* **108**: 12001–12006.
- Jacks T, Remington L, Williams BO, Schmitt EM, Halachmi S, Bronson RT, Weinberg RA. 1994. Tumor spectrum analysis in p53-mutant mice. *Curr Biol* **4**: 1–7.
- Jones SN, Roe AE, Donehower LA, Bradley A. 1995. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. *Nature* **378**: 206–208.
- Jones SN, Hancock AR, Vogel H, Donehower LA, Bradley A. 1998. Overexpression of Mdm2 in mice reveals a p53-independent role for Mdm2 in tumorigenesis. *Proc Natl Acad Sci* **95**: 15608–15612.
- Lane DP. 1992. Cancer. p53, guardian of the genome. *Nature* **358**: 15–16.
- Lang GA, Iwakuma T, Suh YA, Liu G, Rao VA, Parant JM, Valentin-Vega YA, Terzian T, Caldwell LC, Strong LC, et al. 2004. Gain of function of a p53 hot spot mutation in a mouse model of Li–Fraumeni syndrome. *Cell* **119**: 861–872.
- Loughery J, Meek D. 2013. Switching on p53: An essential role for protein phosphorylation? *BioDiscovery* **8**: 1.
- Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, et al. 1990. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* **250**: 1233–1238.
- Mendrysa SM, McElwee MK, Michalowski J, O'Leary KA, Young KM, Perry ME. 2003. *mdm2* is critical for inhibition of p53 during lymphopoiesis and the response to ionizing irradiation. *Mol Cell Biol* **23**: 462–472.
- Mendrysa SM, O'Leary KA, McElwee MK, Michalowski J, Eisenman RN, Powell DA, Perry ME. 2006. Tumor suppression and normal aging in mice with constitutively high p53 activity. *Genes Dev* **20**: 16–21.
- Montes de Oca Luna R, Wagner DS, Lozano G. 1995. Rescue of early embryonic lethality in *mdm2*-deficient mice by deletion of p53. *Nature* **378**: 203–206.
- Olive KP, Tuveson DA, Ruhe ZC, Yin B, Willis NA, Bronson RT, Crowley D, Jacks T. 2004. Mutant p53 gain of function in two mouse models of Li–Fraumeni syndrome. *Cell* **119**: 847–860.
- Pant V, Lozano G. 2014. Limiting the power of p53 through the ubiquitin proteasome pathway. *Genes Dev* **28**: 1739–1751.
- Pant V, Xiong S, Iwakuma T, Quintas-Cardama A, Lozano G. 2011. Heterodimerization of Mdm2 and Mdm4 is critical for regulating p53 activity during embryogenesis but dispensable for p53 and Mdm2 stability. *Proc Natl Acad Sci* **108**: 11995–12000.
- Pant V, Xiong S, Chau G, Tsai K, Shetty G, Lozano G. 2016. Distinct downstream targets manifest p53-dependent pathologies in mice. *Oncogene* doi: 10.1038/onc.2016.111.
- Parant J, Chavez-Reyes A, Little NA, Yan W, Reinke V, Jochemsen AG, Lozano G. 2001. Rescue of embryonic lethality in Mdm4-null mice by loss of Trp53 suggests a nonoverlapping pathway with MDM2 to regulate p53. *Nat Genet* **29**: 92–95.
- Perets R, Wyant GA, Muto KW, Bijron JG, Poole BB, Chin KT, Chen JY, Ohman AW, Stepule CD, Kwak S, et al. 2013. Transformation of the fallopian tube secretory epithelium leads to high-grade serous ovarian cancer in Brca;Tp53;Pten models. *Cancer Cell* **24**: 751–765.
- Post SM, Quintas-Cardama A, Pant V, Iwakuma T, Hamir A, Jackson JG, Maccio DR, Bond GL, Johnson DG, Levine AJ, et al. 2010. A high-frequency regulatory polymorphism in the p53 pathway accelerates tumor development. *Cancer Cell* **18**: 220–230.
- Suh YA, Post SM, Elizondo-Fraire AC, Maccio DR, Jackson JG, El-Naggar AK, Van Pelt C, Terzian T, Lozano G. 2011. Multiple stress signals activate mutant p53 in vivo. *Cancer Res* **71**: 7168–7175.
- Terzian T, Wang Y, Van Pelt CS, Box NF, Travis EL, Lozano G. 2007. Haploinsufficiency of Mdm2 and Mdm4 in tumorigenesis and development. *Mol Cell Biol* **27**: 5479–5485.
- Terzian T, Suh YA, Iwakuma T, Post SM, Neumann M, Lang GA, Van Pelt CS, Lozano G. 2008. The inherent instability of mutant p53 is alleviated by Mdm2 or p16INK4a loss. *Genes Dev* **22**: 1337–1344.
- Tollini LA, Jin A, Park J, Zhang Y. 2014. Regulation of p53 by Mdm2 E3 ligase function is dispensable in embryogenesis and development, but essential in response to DNA damage. *Cancer Cell* **26**: 235–247.
- Wang S, Zhao Y, Aguilar A, Bernard D, Yang C. 2016. Targeting the MDM2-p53 protein–protein interaction for new cancer therapy: Progress and challenges. *Cold Spring Harb Perspect Med* **6**: a026245.
- Wasylishen AR, Lozano G. 2016. Attenuating the p53 pathway in human cancers: Many means to the same end. *Cold Spring Harb Perspect Med* **6**: a026211.
- Xiong S, Van Pelt CS, Elizondo-Fraire AC, Liu G, Lozano G. 2006. Synergistic roles of Mdm2 and Mdm4 for p53 inhibition in central nervous system development. *Proc Natl Acad Sci* **103**: 3226–3231.
- Xiong S, Pant V, Suh YA, Van Pelt CS, Wang Y, Valentin-Vega YA, Post SM, Lozano G. 2010. Spontaneous tumorigenesis in mice overexpressing the p53-negative regulator Mdm4. *Cancer Res* **70**: 7148–7154.
- Zeron-Medina J, Wang X, Repapi E, Campbell MR, Su D, Castro-Giner F, Davies B, Peterse EF, Sacilotto N, Walker GJ, et al. 2013. A polymorphic p53 response element in KIT ligand influences cancer risk and has undergone natural selection. *Cell* **155**: 410–422.
- Zhang Y, Xiong S, Li Q, Hu S, Tashakori M, Van Pelt C, You MJ, Pagoon L, Lozano G. 2014. Tissue-specific and age-dependent effects of global Mdm2 loss. *J Pathol* **233**: 380–391.

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