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Review

MDM2 beyond cancer: podoptosis, development, inflammation, and tissue regeneration

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Summary. Murine double minute (MDM)-2 is an intracellular molecule with diverse biological functions. It was first described to limit p53-mediated cell cycle arrest and apoptosis, hence, gain of function mutations are associated with malignancies. This generated a rationale for MDM2 being a potential therapeutic target in cancer therapy. Meanwhile, several additional functions and pathogenic roles of MDM2 have been identified that either enforce therapeutic MDM2 blockade or raise caution about potential side effects. MDM2 is also required for organ development and tissue homeostasis because unopposed p53 activation leads to p53-overactivation-dependent cell death, referred to as podoptosis. Podoptosis is caspase-independent and, therefore, different from apoptosis. The mitogenic role of MDM2 is also needed for wound healing upon tissue injury, while MDM2 inhibition impairs re-epithelialization upon epithelial damage. In addition, MDM2 has p53-independent transcription factor-like effects in nuclear factor-kappa beta (NFκB) activation. Therefore, MDM2 promotes tissue inflammation and MDM2 inhibition has potent anti-inflammatory effects in tissue injury. Here we review the biology of MDM2 in the context of tissue development, homeostasis, and injury and discuss how the divergent roles of MDM2 could be used for certain therapeutic purposes. MDM2 blockade had mostly anti-inflammatory and anti-mitotic effects that can be of additive therapeutic efficacy in inflammatory and hyperproliferative disorders such as certain cancers or lymphoproliferative autoimmunity, such as systemic lupus erythematosus or crescentic glomerulonephritis.

Key words: Malignancy, Tumor, Nutlin, Cell cycle, Lupus, Podoptosis

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Introduction

Murine double minute (MDM)-2 is an intracellular protein with diverse functions that contributes to wound healing, carcinogenesis, and tissue inflammation. MDM2 is an attractive therapeutic target for numerous diseases for a number of reasons: First, MDM2 is an E3 ubiquitin ligase that negatively regulates p53 mainly by ubiquitin-mediated degradation (Clegg et al., 2008), and as such MDM2 suppresses coordinated cell cycle arrest or cell death and promotes cell survival and growth (Vazquez et al., 2008). Second, cell-type-specific deletion of MDM2 recovers p53 and induces cell-type-specific cell death (Grier et al., 2006). Third, MDM2 is strongly expressed in epithelial organs (Fig. 1). Hence, gain-of-function mutations represent an alternative mechanism to disrupt the p53 pathway in early cancer development (Vazquez et al., 2008; Eischen and Lozano, 2009), and finally, MDM2 blockade with suitable antagonists was shown to block tumor growth in a number of models (Vassilev et al., 2004; Shangary and

Wang, 2009). This review gives an overview on the expression and functional roles of MDM2 in homeostasis and disease.

The classical paradigm: MDM2 counterbalances p53

MDM2 has oncoprotein functions based on its role as negative regulator of tumor suppressor protein p53, which is one of the central regulators of the cell cycle (Manfredi, 2010; Thomasova et al., 2012). MDM2 acts as E3 ubiquitin ligase and directs p53 towards proteasomal degradation (Eischen and Lozano, 2014). In addition, MDM2 promotes p53 export from nucleus to cytoplasm and can also block the transcriptional activity of p53 by binding directly to the N-terminal transactivation domain of p53, which prevents the interaction of p53 with the basal transcriptional machinery (Momand et al., 1992; Chen et al., 1993; Oliner et al., 1993; Zhao et al., 2014). Furthermore, MDM2 is a p53 target gene, because p53 activation upregulates MDM2 mRNA expression, which in turn leads to p53 degradation, i.e. a negative feedback loop (Clegg et al., 2008; Eischen and Lozano, 2009; Marine and Lozano, 2010).

MDM2 and p53 regulate the cell cycle

The cell cycle is a unidirectional pathway, which can lead to 1. Cell hypertrophy (when arrested at cell cycle check points), to 2. Cell division (when completing the M-phase), or to 3. Cell death (when mitosis occurs despite significant DNA damage, which can lead to cell death, referred to as "mitotic catastrophe") (Mulay et al., 2013). Dysregulation of the cell cycle can lead to cell loss and tissue atrophy or to hyperplastic lesions and cancer (Steinbeck, 2004; Maddika et al., 2007; Verduzco and Amatruda, 2011; Mirzayans et al., 2012).The balance of p53 and MDM2 integrates numerous signaling pathways that regulate the cell cycle. The cell cycle itself is executed by multiple proteins including the cyclins, cyclin kinases, and cyclin kinase inhibitors (Thomasova and Anders, 2015). The "guardian of the genome", p53, facilitates cell cycle arrest at the G1/S and G2/M restriction points through induction of p21, which supports the repair of the DNA damage and avoids mitosis of cells with genetically unstable DNA as a pathogenic element of cancerogenesis (Bunz et al., 1998; Vogelstein et al., 2000; Taylor and Stark, 2001; Foijer and te Riele, 2006). When the DNA damage is

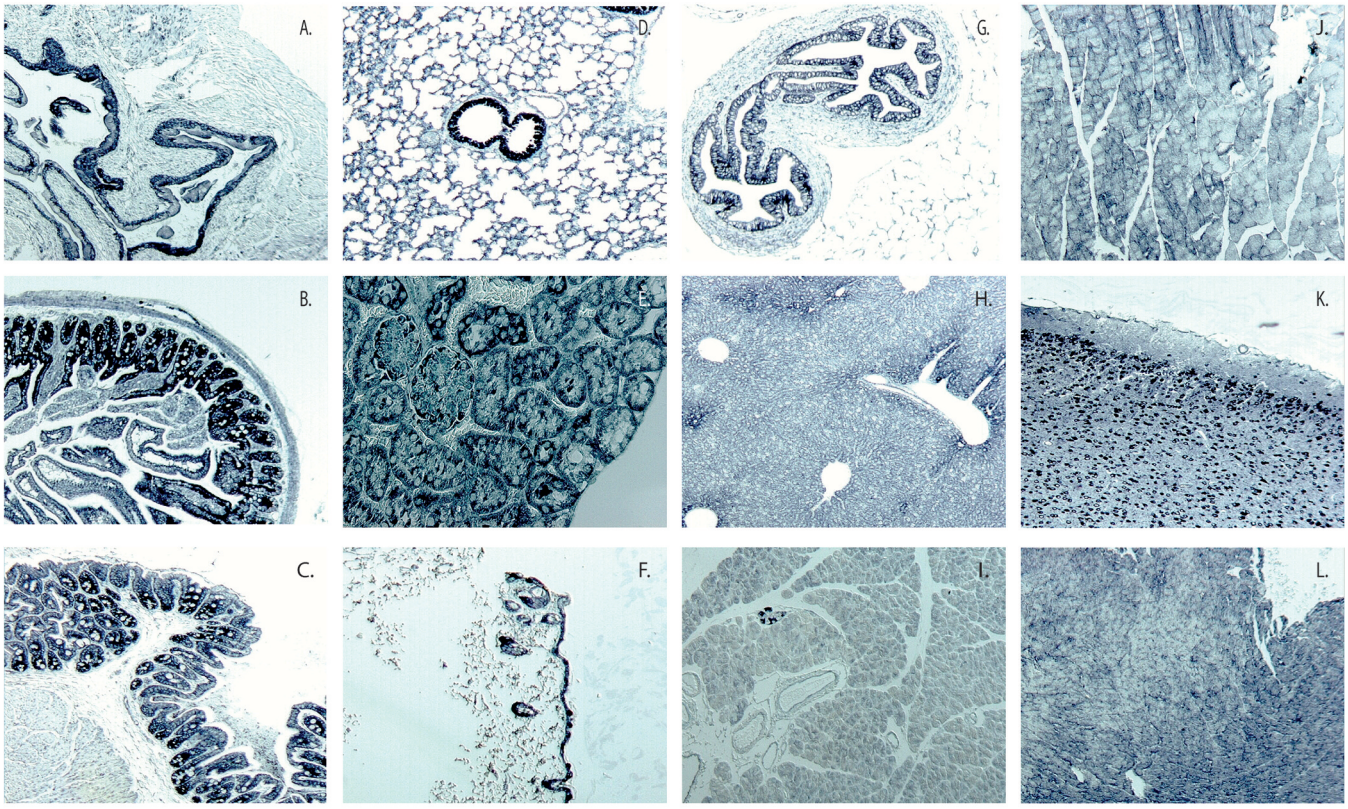

Fig. 1. MDM2 expression in different organs. MDM2 immunostaining was performed on paraffin-embedded tissue samples of adult C57BL/6 mice. **A.** Urinary bladder. **B.** Small intestine. **C.** Large intestine. **D.** Lung. **E.** Kidney. **F.** Skin. **G.** Oviduct. **H.** Liver. **I.** Pancreas. **J.** Skeletal muscle. **K.** Brain. **L.** Heart. A-D, F-L, x 50; E, x 100

irreparable, p53 overexpression can direct the cells into senescence or cell death, representing thus another mechanism to avoid malignant transformation (Zhang et al., 2007, 2009; Mirzayans et al., 2012). MDM2 can suppress these functions of p53 which results in abrogation of cell cycle arrest, which promotes cell proliferation or cell death by mitotic catastrophe in the case of severely damaged cells (Castedo et al., 2004; Mulay et al., 2013).

MDM2 and p53 regulate cell death

Inactivation of MDM2 leads to cell death, a process that depends on uncoupled activity of p53. For example, MDM2 suppression in zebrafish with morpholino oligonucleotides causes severe cell death-related developmental abnormalities, which can be completely reversed by co-deletion of p53 (Langheinrich et al., 2002). Lack of MDM2 in liver is associated with p53-dependent hepatocytes atrophy, cell death and liver fibrosis (Kodama et al., 2011). The genetic deletion of MDM2 in the cells of low turnover tissues such as heart, cerebrum or retina, resulted in p53-mediated permanent exit from the cell cycle or senescence (Zhang et al., 2014). Similarly, selective MDM2 deletion in intestinal epithelial cells in mice leads to loss of these cells via p53 overexpression and increased p53 target gene expression (Fig. 2) (Valentin-Vega et al., 2008). This implies that MDM2 prevents a p53 overexpression-dependent cell death, a process we recently named "podoptosis" (Thomasova et al., 2015). The vast majority of articles describing p53 overexpression-dependent cell death/podoptosis in the tumor literature assume apoptosis to be the involved mode of cell death, mainly because p53 induces numerous apoptosis-related genes (Aylon and Oren, 2007; Valentin-Vega et al., 2008). Apoptosis is a caspase-dependent form of cell death and surprisingly few studies document that caspase inhibitors can actually prevent podoptosis in malignant cells (Saha et al., 2010). Studying glomerular epithelial cells of the kidney we found that MDM2 inhibition-induced podoptosis was p53-dependent but caspase-independent, which excludes apoptosis as a routine of programmed cell death, despite induction of numerous pro-apoptotic genes (Thomasova et al., 2015). Other forms of programmed cell death such as necroptosis, ferroptosis, or mitochondrial membrane potential disruption could be excluded, so the precise form of regulated cell death remains unclear at this point. Morphologically, these cells revealed prominent vacuolization, signs of ER stress and dysregulated autophagy *in vitro* and *in vivo*, a phenotype that has been named 'paraptosis' by some authors (Sperandio et al., 2000; Schneider et al., 2004; Broker et al., 2005). As MDM2 inhibitors are being tested in clinical trials for cancer therapy it is important to ultimately identify the molecular pathways that can lead to podoptosis (Fig. 3).

MDM2 andp53 regulate stem cell function and organ development. Mice that lack the Mdm2 gene do not breed because of embryonic death before implantation in association with p53 overactivation in the blastocyst. Co-deletion of p53 rescues this phenotype (Jones et al., 1995; Montes de Oca Luna et al., 1995; Chavez-Reyes et al., 2003). Also at later developmental stages of the embryo MDM2-mediated inhibition of p53 is critical for organogenesis. For example, during kidney development MDM2 and p53 are strongly expressed in the Wolffian duct, the mesonephric tubules, the ureteric bud, the metanephritic mesenchyme, the nephron progenitors, and the cortical and medullary stroma (Hilliard et al., 2011). Selective deletion of Mdm2 from the ureteric bud epithelium causes renal hypoplasia due to defective ureteric bud branching and underdeveloped nephrogenic zone (Hilliard et al., 2011). Godley, et al. created mice that overexpress wild type p53 within the ureteric bud and observed acute kidney degeneration at E17.5 reaching half the size of normal kidneys (Godley et al., 1996). After birth, MDM2 and p53 expression gradually declines with time. The metanephric mesenchyme differentiates into stromal mesenchyme and cap mesenchyme, which is the main site of the nephron progenitor cells between E11.0 and E11.5 (Kobayashi et al., 2008). When such progenitor cells lack MDM2, neonates display hypo- or dysplastic kidneys, patchy depletion of the nephrogenic zone, and pockets of ectopic proximal tubules (Hilliard et al., 2014).

MDM2 has an important role in the development of other organs

Selective deletion of MDM2 in cardiomyocytes causes heart failure at E13.5, while MDM4 deletion had no effect (Grier et al., 2006). MDM2 is also important for osteoblast differentiation (Lengner et al., 2006). Mice with a selective deletion of MDM2 in osteoblast progenitor cells show defects of the developing tail bud region at E10.5 with complete absence of tissues around the somites and invagination in the dorsal region opposing the lumbar vertebrae (Lengner et al., 2006). Such mice die at birth with multiple skeletal defects due to activated p53 and decreased osteoblast proliferation and differentiation. Lens development is proceeding rapidly at p7 and is completed at p14. MDM is needed for normal development of the lens. MDM2 is expressed in nuclei of lens epithelium and lens fibre cells from E14.5 and disappears in the mature lens (Geatrell et al., 2009). The intestinal epithelium begins to develop as a single layered epithelium at E14.5 (Sancho et al., 2004), which invaginates to form intervillus pockets that contain stem and progenitor cells, while cell differentiation occurs along the villi (Crosnier et al., 2006). Lack of MDM2 in intestinal epithelial cells causes hypertrophy and hyperplasia of intervillus pockets, villi atrophy, and enterocyte vacuolization (Valentin-Vega et al., 2008). Interestingly, by the age of 8 weeks all these abnormalities disappear, probably due to insufficient Cre recombinase activity in all the cells

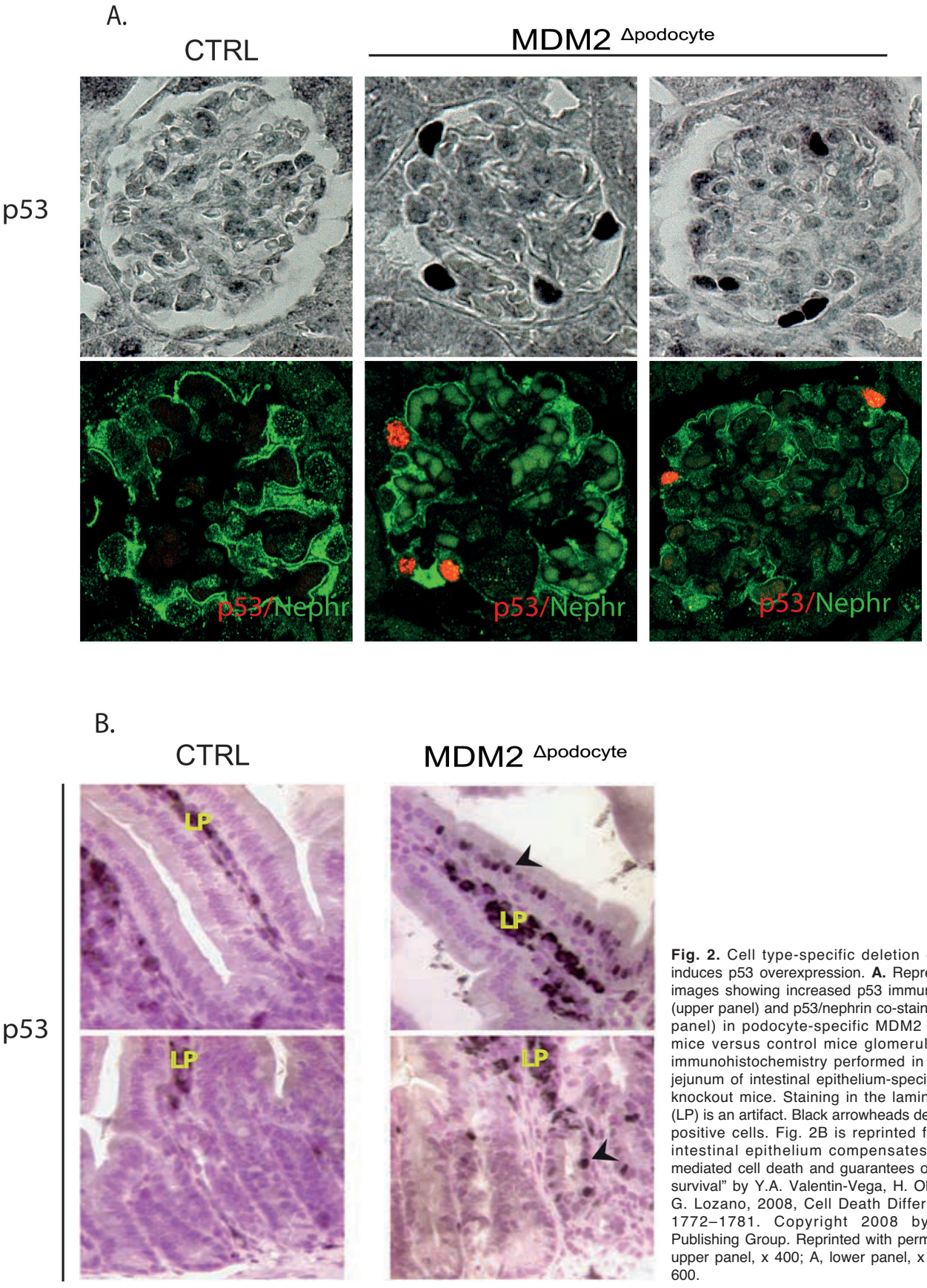

Fig. 2. Cell type-specific deletion of MDM2 induces p53 overexpression. **A.** Representative images showing increased p53 immunostaining (upper panel) and p53/nephrin co-staining (lower panel) in podocyte-specific MDM2 knockout mice versus control mice glomeruli. **B.** p53 immunohistochemistry performed in intestinal jejunum of intestinal epithelium-specific MDM2 knockout mice. Staining in the lamina propria (LP) is an artifact. Black arrowheads denote p53-positive cells. Fig. 2B is reprinted from "The intestinal epithelium compensates for p53-mediated cell death and guarantees organismal survival" by Y.A. Valentin-Vega, H. Okano, and G. Lozano, 2008, Cell Death Differ.; 15(11): 1772–1781. Copyright 2008 by Nature Publishing Group. Reprinted with permission. A, upper panel, x 400; A, lower panel, x 640; B, x 600.

and a positive selection of those cells that did not lose MDM2 expression. Altogether, MDM2 is needed to prevent podoptosis in progenitor cells or differentiated cells of the tissue. MDM2 loss leads to organ hypoplasia and dysfunction.

MDM2/p53 mutations and cancer

Tissues require a balance of MDM2 and p53. A disrupted balance that favors p53 inactivation can cause uncontrolled cell proliferation and cancer (Momand et al., 1998). This can occur when 1. Gain-of-function mutations amplify MDM2 along with normal p53, or 2. Normal MDM2 is expressed but p53 contains loss-of-function mutations, or 3. MDM2 with gain-of-function mutations is coupled with loss-of-function mutations in p53 (Giaccia and Kastan, 1998; Bossi et al., 2006; Hu et al., 2012; Bieging et al., 2014). Therefore MDM2 is considered an oncogene (Zhao et al., 2014). MDM2 over-expression occurs in multiple human tumors including sarcoma, breast cancer, melanoma, glioblastoma or leukemia (Momand et al., 1998). Studies in mice and cultured cells have shown that MDM2 also has p53-independent oncogenic functions, which control proliferation, apoptosis, tumor invasion, and metastasis (Jones et al., 1998). MDM2 also causes ubiquitination and proteasomal degradation of Foxo3A, another negative cell cycle regulator (Yang et al., 2008; Fu et al., 2009). In addition, MDM2 targets E-cadherin, which plays a crucial role in cancer metastasis (Yang et al., 2006). E2F-1 is another target of MDM2, which plays an important role in the cell cycle (Huart et al., 2009). Another target is XIAP, which is an anti-apoptotic protein (Gu et al., 2009). Restoration of wild-type p53 expression in Mdm2-overexpressing tumors results in tumor stasis and regression in some cases , which could be a clinical strategy to treat tumors that overexpress MDM2 (Li et al., 2014). These data provide a rationale for the development of MDM2 antagonists for tumor therapy, for example Nutlin-3a, MI-219, RITA, RO-5963, stapled peptides SAH-p53s. Another group of potential therapeutic agents, such as HLI98, MPD compounds, MEL23 and MEL24, target MDM2 E3 ubiquitin ligase function to restore p53 activity and thus promote tumor cell death (Issaeva et al., 2004; Vassilev et al., 2004; Yang et al., 2005; Bernal et al., 2007; Shangary et al., 2008; Herman et al., 2011; Graves et al., 2012).

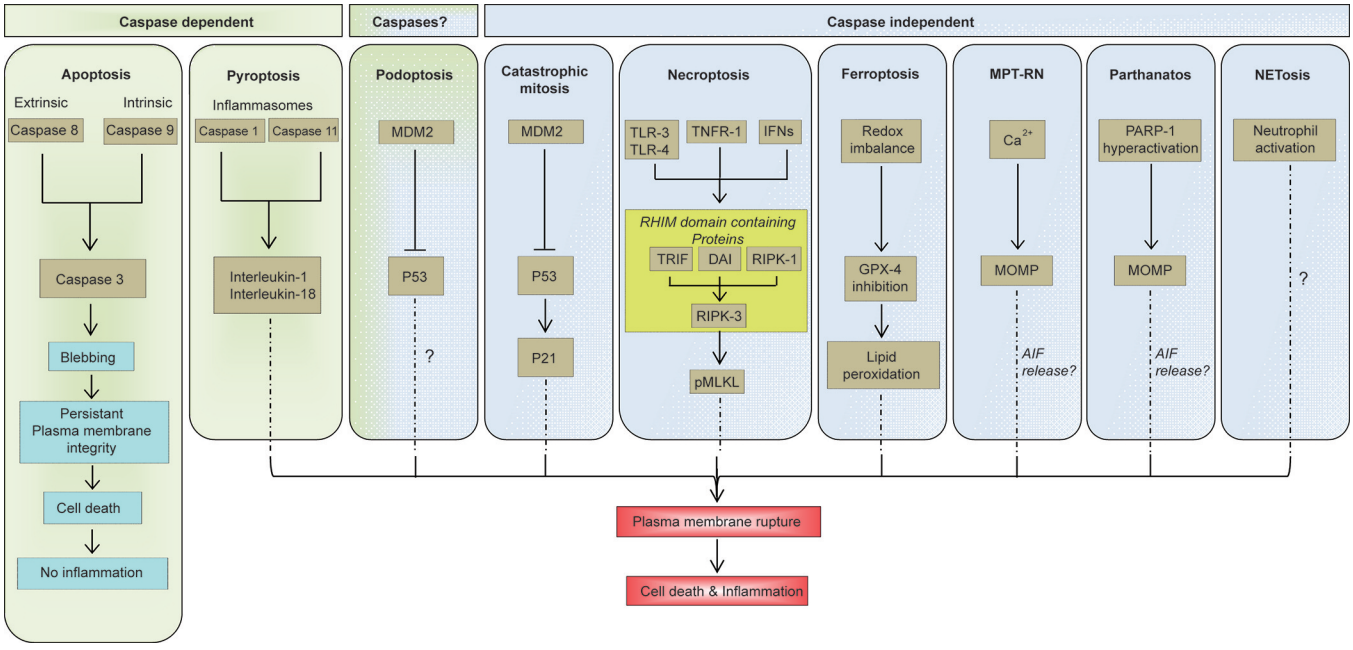

Fig. 3. MDM2/p53 and regulated cell death. Regulated cell death pathways are classified on the basis of their dependency on caspases. Apoptosis, either extrinsic or intrinsic is dependent on caspase 3 and associated with persistent plasma membrane integrity. Apoptosis is non-immunogenic whereas pyrroptosis is a highly immunogenic type of cell death. Necroptosis, ferroptosis, mitochondrial permeability transition related regulated necrosis (MPT-RT), parthenatos, NETosis, p53-Overactivation-Related Cell Death (Podoptosis) and catastrophic mitosis are associated with plasma membrane rupture and are highly immunogenic types of cell death. Podoptosis and catastrophic mitosis are regulated by MDM2/p53 balance within the cell. TLR- Toll like receptor; TNFR-α Tumor necrosis factor receptor; IFN- Interferon, TRIF-α TIR domain-containing adaptor protein inducing IFNβ; DAI- DNA-dependent activator of IFN-regulatory factors; RIPK- receptor-interacting serine/threonine-protein kinase; pMLKL- phosphorylated mixed lineage kinase domain-like protein; GPX-4- glutathione peroxidase 4; MOMP- mitochondrial outer membrane permeabilization; AIF- apoptosis-inducing factor; PAR- poly(ADP-ribose); PARP1- PAR polymerase 1.

MDMX/MDM4

MDMX is also known as MDM4, and it is a homologue of MDM2, which also negatively regulates the tumor-suppressor function of p53 by binding and masking the amino terminal transcriptional activation domain of p53 which is proved by the early embryonic lethality of MDMX-null mice which can be rescued by the loss of p53 (Shvarts et al., 1996; Parant et al., 2001) . Unlike MDM2, MDMX has no E3 ubiquitin activity and is not under transcriptional regulation of p53 (Linke et al., 2008). MDMX is overexpressed in many human cancers together with MDM2 (Riemenschneider et al., 1999; Ramos et al., 2001; Danovi et al., 2004; Han et al., 2007; Valentin-Vega et al., 2007; Gembarska et al., 2012; Leventaki et al., 2012, Wade et al., 2013). MDMX expression is increased in 65% of human retinoblastoma cases, a tumor of the eye resulting from inherited mutations in the RB1 gene (Laurie et al., 2006). In addition, approximately 65% of maliganant melanomas overexpress MDMX (Gembarska et al., 2012). These findings suggest a functional contribution of MDM4 to tumorigenesis (Eischen and Lozano, 2014) .

MDM2/p53 in wound healing

Wound healing is a complex but highly organized process comprising four different phases: clotting, inflammation, re-epithelialization (epithelial healing) and tissue remodeling (mesenchymal healing) (Martin, 1997; Anders, 2012). Various types of cell stress or DNA damage activate p53 transcription factor and induce the expression of genes that control cell growth and suppress tumor formation. While p53 activity is necessary for the suppression of carcinogenesis, the MDM2 negative regulation of p53 is crucial for tissue turnover, regeneration and healing. The mouse models which lack the MDM2-p53 interaction domain, such as transgenic mice overexpressing the short isoform of p53 (p44) (Maier et al., 2004) or mice heterozygous for a mutated p53 allele encoding an amino-terminal truncated p53 (Tyner et al., 2002) exhibit blocked cell proliferation, decreased cell turnover and accelerated aging. However, mouse models with increased levels of wild type p53 but sustained MDM2 regulation, such as the "super-p53" transgenic mice (Garcia-Cao et al., 2002) or mice with the hypomorphic *Mdm2* allele (Aylon and Oren, 2007) exhibit no characteristics of accelerated aging. Thus, the activation of endogenous p53 without Mdm2 regulation induces accelerated aging phenotypes, reduced wound healing and altered tissue homeostasis (Gannon et al., 2011).

MDM2-p53 balance is also crucial for maintenance of the epidermal stem cell compartment (Gannon et al., 2011). Mouse skin epithelium specific MDM2 deletion results in a p53-mediated increase in cellular senescence and a reduction in skin epidermal stem cell numbers and function (Gannon et al., 2011). Cellular senescence, promoted by scaffolding proteins such as caveolin-1, largely contributes to impaired chronic wound healing (Vande Berg and Robson, 2003; Zou et al., 2011). In diabetes, oxidative stress-induced caveolin-1 sequesters MDM2 away from p53, leading to p53 dependent cellular senescence and defective wound healing (Bitar et al., 2013).

The expression of p53 is up-regulated in renal parenchymal cells during acute kidney injury (Kelly et al., 2003; Molitoris et al., 2009). Stabilization and activation of p53 by MDM2 blockade impairs the tubular cell healing after injury (McNicholas and Griffin, 2012; Mulay et al., 2012). Furthermore, Nrf2 signaling promotes survival and regeneration of primary tubular epithelial cells via up-regulation of MDM2 in an *ex vivo* model of tubular cell injury and regeneration (Fledderus and Goldschmeding, 2013; Hagemann et al., 2013). Together, while MDM2 activation-related cell proliferation can promote cancer growth, the same process is needed for cell proliferation in wound healing and tissue repair. This should be kept in mind when considering MDM2 inhibitors for tumor therapy.

Beyond: P53-independent function of MDM2

MDM2 drives NFkB-dependent tissue inflammation

The main inflammation regulator NFκB and p53 engage in reciprocal negative regulation. Chronic NFκB activation was implicated in carcinogenesis through the inhibition of p53 function (Gurova et al., 2005; O'Prey et al., 2010), while p53 is a general inhibitor of inflammation that acts as an antagonist of NF-κB (Tergaonkar et al., 2002; Komarova et al., 2005). MDM2 is a transcriptional target of both NF-κB as well as p53 signaling, and as such links inflammation and tumorigenesis (Gu et al., 2002; Ponnuswamy et al., 2012). In contrast, MDM2 is also a regulator of both NF-Kb and p53 pathways and can push the balance in both directions i.e. proinflammatory and pro-proliferative or anti-inflammatory and anti-survival (Gu et al., 2002; Thomasova et al., 2012; Heyne et al., 2013). MDM2 also has a p53-independent function in NF-κB signaling, which facilitates post-ischemic inflammation and increases extent of acute tubular injury (Mulay et al., 2012). In the same manner MDM2 inhibition prevents glomerular inflammation and podocyte loss in early adriamycin nephropathy (Mulay et al., 2013). In a lupus nephritis model, Mdm2 blockade by nutlin-3a leads to inhibition of most autoreactive T-cells and plasma cells, and consequently to suppression of autoantibody production and lymphoproliferation as well as intrarenal and systemic inflammation (Allam et al., 2011). MDM2 blockade with nutlin also abrogates LPS-induced lung inflammation due to impaired NF-κB DNA binding in neutrophils and macrophages (Liu et al., 2009). Furthermore, nutlin treatment inhibits M2 macrophages polarization via MDM2 blockade and p53 stabilisation

(Li et al., 2015).

Complexity : regulaton of MDM2

Several pathways regulate MDM2 expression and function (Table 1).

Transcription

Two distinct promoters, P1 and P2, regulate the activation of the MDM2 gene (Mendrysa and Perry, 2000). The P1 promoter controls the basal constitutive expression of MDM2, and the P2 promoter, activated by p53, is responsible for the inducible expression of MDM2 (Barak et al., 1993). MDM2 homolog MDMX, is considered an inhibitor of transactivation by p53, through binding to the p53 activation domain. MDM2 and MDMX affect p53 target gene specificity and influence the activity of other transcription factors (Biderman et al. 2012a). Interestingly, upon DNA damage or ribosomal stress, MDMX enhances p53-mediated activation of the MDM2 gene, but not of numerous other p53 target genes including p21 (Biderman et al., 2012a,b). MDM2 is also negatively regulated by orphan receptor TR3 which directly interacts with p53 and suppresses p53-mediated transcriptional induction of MDM2 (Zhao et al., 2006) . In addition, both oncogenic as well as tumour suppressive pathways regulate MDM2 transcription (Zhao et al., 2014). For example, MDM2 is a transcriptional target of the MYCN oncogene in neuroblastoma cells (Slack et al., 2005), of Nuclear Factor of Activated T cells (NFAT1) in human hepatocellular carcinoma (Zhang et al., 2012) or of IFN regulatory factor 8 (IRF8) in germinal center B-cells (Zhou et al., 2009). On the other hand, tumour suppressor PTEN down-regulates MDM2 P1 promoter activity through its lipid phosphatase activity (Chang et al., 2004).

Translation

MDM2 transcripts from P1 or P2 promoter have different translation efficiency due to their differences in the 5'-UTR. p53 binds to MDM2 P2 promoter and induces the transcripts with increased translational efficiency (Trotta et al., 2003). Also, microRNAs regulate MDM2 translation. Several microRNAs targeting MDM2 have been identified, including miR-143/145, miR-605, miR-25, miR-32, miR-18b, and miR-661 (Xiao et al., 2011; Suh et al., 2012; Dar et al., 2013; Zhang et al., 2013; Hoffman et al., 2014). P53-regulated miR-143/145, miR-605, and miR-32 inhibit MDM2 translation, which in turn increases p53 protein and suppresses carcinogenesis. miR-661 targets both MDM2 and MDMX to activate p53 in a cell-type-dependent manner (Hoffman et al., 2014). These microRNAs contribute to the MDM2-p53 feedback loop regulation.

MDM2 protein activity

Genotoxic stress, such as ionizing radiation and ultraviolet irradiation cause DNA damage that activates protein kinases, which phosphorylate MDM2 (Tibbetts et al., 1999; Maya et al., 2001; Shinozaki et al., 2003). This process impairs the ability of MDM2 to negatively regulate p53 through multiple mechanisms and is essential for tumor suppression (Lohrum et al., 2000; Maya et al., 2001; Cheng et al., 2009; Gajjar et al., 2012). Oncogenes, such as E2F-1, beta-catenin, Myc, and Ras increase ARF (Alternative Reading Frame tumour suppressor protein), which in turn suppresses MDM2 function and activates p53 (Eischen et al., 1999; Manfredi, 2010; Hu et al., 2012). Similarly, ribosomal stress induced ribosomal proteins activate p53 in a MDM2 dependent manner. (Deisenroth and Zhang, 2010). On the contrary, glucocorticoids and catecholamines activate MDM2 to down-regulate p53 and thus contribute to tumorigenesis (Hara et al., 2011; Feng et al., 2012).

Ubiquitination targets proteins for degradation or modulates their function in regulation of immune processes and oncogenesis (Liu et al., 2005; Lipkowitz and Weissman, 2011). Deubiquitinase USP15 stabilizes MDM2, which in turn negatively regulates T cell activation by marking the T call transcription factor NFATc2 for degradation (Zou et al., 2014). USP15 also stabilizes MDM2 in cancer cells and promotes cancer-cell survival. The inhibition of USP15 in melanoma and colorectal carcinoma induces tumor cell death and stimulates antitumor T cell responses via spontaneous ubiquitination and degradation of MDM2. On the contrary, deubiquitinase HAUSP stabilizes p53 by removing ubiquitin chains from p53 molecule and thus regulates MDM2 (Li et al., 2002; Kon et al., 2010; Zou et al., 2014). Together, ubiquitination and deubiquitination of MDM2 and p53 represent potential therapeutic targets for cancer treatment.

Summary and perspective

MDM2 is present probably in all cell types but is strongly expressed especially in epithelial cells. MDM2 is a regulator of p53 and NF-κB signaling with additive effects on the survival and growth of malignant cells but potentially also on tumor stroma and vasculature. However, MDM2 inhibition in cancer will require a careful assessment of its potential suppressive effects on wound healing, tissue repair upon toxic or ischemic injury, as well as host defense. The anti-inflammatory and anti-mitotic effects of MDM2 blockade can also generate additive therapeutic efficacy in inflammatory and hyperproliferative disorders outside the oncology domain. Animal models of lymphoproliferative autoimmunity such as systemic lupus erythematosus or of crescentic glomerulonephritis with hyperplastic epithelial lesions respond very well to MDM2 blockade.

Thus, MDM is not only an important factor during organ development and tissue homeostasis but also represents an attractive therapeutic target for disorders with a central pathogenic role of NF-κB-dependent inflammation and MDM2-driven hyperproliferation.

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