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Activation and activities of the p53 tumour suppressor protein

É Bálint and KH Vousden

NCI at Frederick, Building 560, Room 22–96, 1050 Boyles Street, Frederick, MD 21702-1201, USA

Summary The p53 tumour suppressor protein inhibits malignant progression by mediating cell cycle arrest, apoptosis or repair following cellular stress. One of the major regulators of p53 function is the MDM2 protein, and multiple forms of cellular stress activate p53 by inhibiting the MDM2-mediated degradation of p53. Mutations in p53, or disruption of the pathways that allow activation of p53, seem to be a general feature of all cancers. Here we review recent advances in our understanding of the pathways that regulate p53 and the pathways that are induced by p53, as well as their implications for cancer therapy. © 2001 Cancer Research Campaign   http://www.bjcancer.com

The *p53* gene is frequently mutated in sporadic cancer (Hainaut and Hollstein, 2000) and germline mutations in p53 result in Li–Fraumeni syndrome, a hereditary cancer susceptibility syndrome predisposing individuals to sarcomas, lymphomas, breast, brain and other tumours (Malkin et al, 1990; Srivistava et al, 1990). These findings are paralleled by the observation that mice deficient for p53 are highly tumour susceptible, although p53 deficiency does not prevent normal development (Donehower, 1996). Malignancies that retain the wild-type *p53* gene have often acquired other mechanisms to compromise p53 function, and most cancer cells show a defect either in p53 or in the pathway that leads to activation of p53 in response to oncogenic stimuli (Vogelstein et al, 2000). Taken together, inactivation of the p53 pathway seems to be a general mechanism in tumour development and might be a common feature of all cancers. Thus understanding the mechanisms that regulate p53 function has great importance for cancer therapy.

CONTROL OF p53 FUNCTION

Since p53 is a powerful inhibitor of cell proliferation, control of its activity is essential during normal growth and development. Regulation of p53 has been described at the level of transcription, translation, conformational change, and various covalent and non-covalent modifications (Ashcroft and Vousden, 1999). However, at present it seems clear that one of the key mechanisms by which p53 function is regulated is through control of protein stability. Integral to this is the function of the MDM2 protein, and multiple forms of cellular stress activate p53 by countering the MDM2-mediated degradation of p53.

Regulation by MDM2

MDM2 has been shown to inhibit p53 activity in several ways: by binding to the transactivation domain of p53, by targeting p53 for ubiquitination, by inhibiting acetylation of p53 and by shuttling p53 to the cytoplasm. Since the *MDM2* gene is a transcriptional target of p53 (Barak et al, 1993), an autoregulatory feedback loop exists in which p53 activates expression of its own negative

regulator (Wu et al, 1993). The importance of MDM2 in the regulation of p53 activity is illustrated by the observation that MDM2 deficiency causes early embryonic lethality in mice which is rescued in the p53-null background (Jones et al, 1995; Montes de Oca Luna et al, 1995), indicating that in the absence of MDM2, unrestrained p53 activity blocks normal growth and development. Conversely, amplification of MDM2 is associated with the development of tumours that retain wild-type p53 (Oliner et al, 1992), suggesting that overexpression of MDM2 prevents the normal p53-mediated response to oncogenic stress.

MDM2 binds to p53 within the amino terminus of p53, (Figure 1) directly blocking the interaction of p53 with transcriptional coactivators (Momand et al, 1992; Wadgaonkar and Collins, 1999) and so inhibiting the ability of p53 to activate transcription of target genes. However, a more comprehensive inhibition of p53 function is achieved by the ability of MDM2 to promote proteasome-mediated degradation of p53 (Haupt et al, 1997; Kubbutat et al, 1997). MDM2 contains a RING finger domain (Figure 1) and, like many RING finger proteins, it can function in vitro as a ubiquitin protein ligase (E3) (Joazeiro and Weissman, 2000). MDM2 targets both itself and p53 for ubiquitination, and RING finger domain mutations lead to the stabilization of both proteins (Honda et al, 1997, Fang et al, 2000). Interestingly, the transcriptional cofactor, p300, that plays a role in acetylating and activating p53, also participates in the degradation of p53 by MDM2, possibly by functioning as a platform to allow efficient p53/MDM2 interaction (Grossman et al, 1998).

Besides direct ubiquitination of p53, MDM2 also plays a role in regulating the subcellular localization of p53. MDM2's ubiquitin ligase activity contributes to the efficient nuclear export of p53 (Boyd et al, 2000; Geyer et al, 2000), which depends on the nuclear export sequence (NES) identified in the C-terminus of p53 (Stommel et al, 1999). It is possible that ubiquitination of p53 reveals the NES, possibly by driving p53 into a monomeric form (Stommel et al, 1999), allowing access to the nuclear export machinery. Treatment of cells with leptomycin B, a drug that blocks nuclear export, results in stabilization and nuclear accumulation of p53 (Freedman and Levine, 1998; Lain et al, 1999; Tao and Levine, 1999) and mutation of the NES in p53 reduces, but does not abolish, the ability of MDM2 to target p53 for degradation (Yu et al,
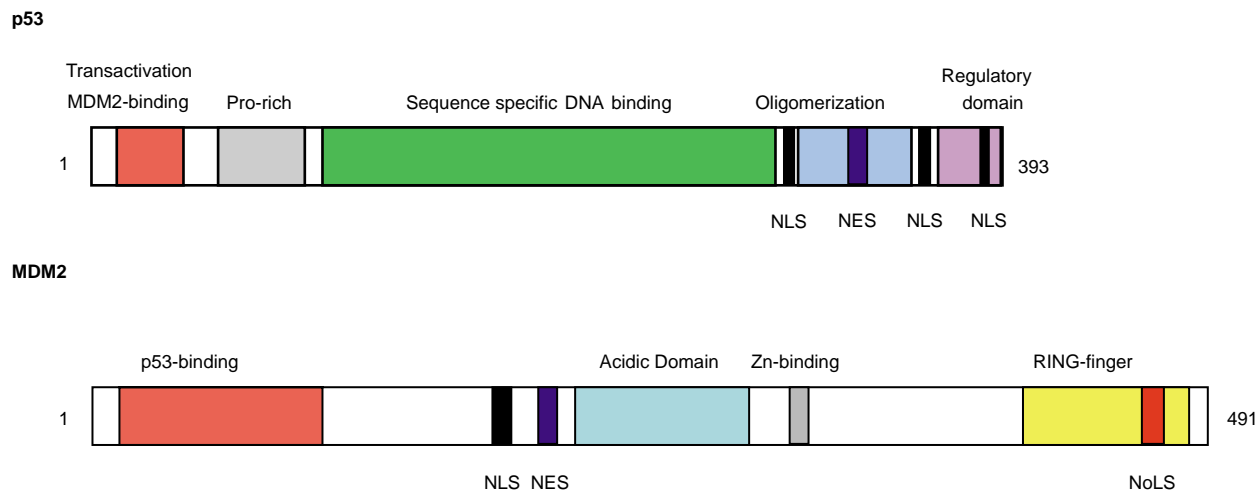
p53

Transactivation

MDM2-binding   Pro-rich   Sequence specific DNA binding   Oligomerization   Regulatory domain

1   393

NLS   NES   NLS   NLS

MDM2

p53-binding   Acidic Domain   Zn-binding   RING-finger

1   491

NLS NES   NoLS

Figure 1 Domain structure of the p53 and MDM2 proteins. NLS, nuclear localization signal; NES, nuclear export signal; NoLS, nucleolar localization signal

2000). Taken together, the results suggest that efficient degradation of p53 requires nuclear export, although some degradation can also occur in the nucleus, and indicate that ubiquitination of p53 by MDM2 may serve to both target p53 to the proteasome and allow export to the cytoplasm. In certain tumours, including neuroblastomas, breast and colon cancer, wild-type p53 is constitutively accumulated in the cytoplasm. Although this cytoplasmically sequestered p53 seems to be resistant to MDM2-mediated degradation because of post-translational modification (Zaika et al, 1999), recent evidence suggests that MDM2-mediated nuclear export might actually be responsible for the cytoplasmic accumulation of p53 (Lu et al, 2000). However, other studies indicate that in some tumours p53 may be sequestered in the cytoplasm through interaction with the glucocorticoid receptor (Sengupta et al, 2000).

In addition to its role in the regulation of p53, MDM2 has functions that are independent of p53 (Lundgren et al, 1997), with evidence that it can inhibit or promote cell growth depending on the cellular environment (Freedman et al, 1999). These activities of MDM2 are probably related to its interaction with other proteins, including regulators of the cell cycle and cell fate such as MTBP (Boyd et al, 2000), Numb (Juven-Gershon et al, 1998), the retinoblastoma tumour suppressor protein (pRB) (Hsieh et al, 1999), E2F1/DP1 (Loughran and La Thangue, 2000) and SMAD transcription factors (Yam et al, 1999). E2F-1 has been shown to be susceptible to proteasome-mediated degradation and, like p53, it can be stabilized by various forms of cellular stress (Blattner et al, 1999; O'Connor and Lu, 2000). However whether MDM2 participates in these processes remains unclear (Kubbutat et al, 1999; Loughran and La Thangue, 2000). MDM2 has been shown to bind ribosomal proteins and RNA (Marechal et al, 1994; Elenbaas et al, 1996), raising the question whether this contributes to the nucleolar localization of MDM2 seen in some circumstances (see below).

MDM2-independent regulation of p53 stability

While MDM2 has been well established as the key regulator of p53 abundance and activity, various additional mechanisms have been described to regulate stability of p53. In cervical cancer cells, p53 is degraded due to ubiquitination by the human papillomavirus (HPV) E6 oncoprotein in complex with the cellular E6AP protein (Scheffner et al, 1993). Although these HPV-associated tumours usually retain a wild-type *p53* gene (Crook et al, 1992),

the p53 response is severely compromised due to an inability to efficiently stabilize the p53 protein. However, E6AP does not appear to participate in the degradation of p53 in normal cells. Another cellular protein, JNK, was shown to bind p53 in normal, non-stressed cells. Interference with the p53-JNK association reduced p53 ubiquitination and increased p53 half-life, suggesting that JNK might target p53 to ubiquitination and degradation (Fuchs et al, 1998). In addition to degradation by the proteasome, p53 has been shown to be cleaved by another protease, calpain, which may also serve to regulate p53 (Kubbutat and Vousden, 1997; Pariat et al, 1997; Zhang et al, 1997; Atencio et al, 2000).

Mechanisms to stabilize p53 in response to stress

1. Phosphorylation

Many stress signals, including some DNA-damaging agents, modulate p53 and MDM2 activity through induction of kinases (Lakin and Jackson, 1999). Numerous phosphorylation sites within or near the N-terminal MDM2-binding region of p53 have been described (Meek, 1999; Ljungman, 2000) and phosphorylation at many of these sites can attenuate binding of p53 to MDM2 in vitro, potentially leading to stabilization of p53 in vivo (Unger et al, 1999; Chehab et al, 2000; Sakaguchi et al, 2000; Shieh et al, 1997, 2000). The kinases signalling to p53 include casein kinase 1 and 2, ATM (ataxia telangiectasia mutated), ATR (ATM/Rad3 related kinase) CHK1 and 2, JNK (jun N-terminal kinase) and DNA-PK (DNA-dependent protein kinase) (Jayaraman and Prives, 1999). Many of the same kinases also phosphorylate MDM2 in vitro, (Guerra et al, 1997; Mayo et al, 1997; Gotz et al, 1999; Khosravi et al, 1999) and MDM2 is heavily phosphorylated in vivo (Hay and Meek, 2000). Phosphorylation of MDM2 within the p53 binding domain, around the NLS, NES and in the acidic domain strongly suggests a regulatory role for these modifications (Hay and Meek, 2000; Maya and Oren, 2000).

Genetic evidence from both mice and humans suggests that ATM and CHK2 are key players in the pathway of response to ionizing radiation. The *ATM* gene is mutated in the genetic disorder ataxia telangiectasia, which is characterized by hypersensitivity to ionizing radiation and predisposition to cancer (Meyn, 1999), while Chk2 was found to be mutated in patients with Li–Fraumeni syndrome who do not carry mutations in p53 (Bell

et al, 1999). Cells deficient for ATM or Chk2 show a defect in their ability to stabilize p53 following exposure to IR (Kastan et al, 1992; Hirao et al, 2000), strongly supporting a role for these kinases in this damage response.

2. Regulation of MDM2 expression

Although phosphorylation probably plays an important role in some pathways leading to the stabilization of p53, other forms of stress can signal without a requirement for p53 phosphorylation (Ashcroft et al, 1999; Blattner et al, 1999). Several DNA-damaging agents including UV, topoisomerase inhibitors and non-genotoxic stress such as hypoxia, induce a p53 response by specific inhibition of MDM2 transcription (Wu and Levine, 1997; Arriola et al, 1999; Ashcroft et al, 2000; Ma et al, 2000; Zeng et al, 2000; Koumenis et al, 2001). Down-regulation of MDM2 was shown to be p53-independent, but the exact mechanisms are yet to be elucidated.

3. ARF

The alternative reading frame product of the INK4A locus, called p14[ARF] (mouse p19[ARF]) binds directly to MDM2, inhibiting the ubiquitin ligase activity of MDM2 and blocking the inhibition of p53 acetylation by MDM2 (Bates et al, 1998; Kamijo et al, 1998; Pomerantz et al, 1998; Stott et al, 1998; Zhang et al, 1998; Honda and Yasuda, 1999; Midgley et al, 2000; Ito et al, 2001). In some systems, ARF also leads to the relocalization of MDM2 from the nucleoplasm to the nucleolus (Weber et al, 1999) utilizing nucleolar localization signals in both ARF and MDM2 (Lohrum et al, 2000; Weber et al, 2000), and the consequence of ARF expression is the efficient stabilization and activation of p53. ARF plays an important role in the induction of p53 in response to oncogene activation, a critical fail-safe mechanism that eliminates cells with proliferative abnormalities. For example, deregulated E2F1 activity, which is seen in almost all cancers following disruption of the pRB tumour suppressor pathway, sends a strong apoptotic signal. Although part of this E2F1-induced apoptotic response is p53 independent (Phillips et al, 1999; Irwin et al, 2000), E2F1 transcriptionally activates ARF and the subsequent induction of p53 in response to deregulated E2F1 activity is an important component of the response. Similarly, the growth suppressive effects of activated Ras or Myc depend, in part, on the induction of p53 through ARF (Sherr and Weber, 2000). Other oncogenic events that induce a p53 response and might function through ARF include activation of the c-Abl protein-tyrosine kinase (Radfar et al, 1998; Sionov et al, 1999) and deregulation of beta-catenin, a frequent early event in colon carcinogenesis (Damalas et al, 1999). The importance of the ARF/p53 pathway is illustrated in mice, where deletion of ARF results in tumour development (Kamijo et al, 1997). Although mutations specific to ARF are rarely found in human tumours, loss of ARF expression resulting from methylation of the ARF promoter (Esteller, 2000), or overexpression of transcriptional repressors of ARF such as Twist (Maestro et al, 1999), Bmi-1 (Jacobs et al, 1999) or TBX2 (Jacobs et al, 2000) is associated with human cancer development.

4. Other regulators of p53 stability

MDMX, a protein related to MDM2, also possesses a p53-binding domain and a RING finger domain. Binding of MDMX inhibits p53 transactivation function (Shvarts et al, 1996), although MDMX does not appear to target p53 for degradation. It is possible that MDMX does not show ubiquitin ligase activity, and

hetero-oligomerization of MDMX with MDM2 through their RING finger domains results in the stabilization of MDM2 (Sharp et al, 1999; Tanimura et al, 1999). Furthermore, when overexpressed, MDMX protected p53 from MDM2-mediated degradation while still maintaining suppression of p53 transactivation (Jackson and Berberich, 2000). The role of MDMX in tumour development remains to be determined, although there is evidence that amplification of MDMX may substitute for p53 mutation or amplification of MDM2 in some tumours (Riemenschneider et al, 1999). Alternatively spliced forms of MDM2, lacking the N-terminal p53-binding domain, have also been described in human cancers and may play a role in regulating full-length MDM2 activity (Sigalas et al, 1996; Perry et al, 2000).

Several other proteins have been reported to interfere with the MDM2-mediated degradation of p53, although their mechanism of function is not well understood. pRB binds MDM2 and inhibits MDM2-dependent degradation of p53, with selective restoration of p53's apoptotic function (Hsieh et al, 1999). Other proteins that regulate p53 stability, and so potentially inhibit MDM2, include HIF1α (An et al, 1998) ING1 (Garkavtsev et al, 1998), WRN (Blander et al, 2000) and WT1 (Maheswaran et al, 1995).

Regulation of p53 activity

In addition to the regulation of protein stability, there are mechanisms that regulate the activity of p53. The extreme C terminus of the protein controls its sequence-specific DNA binding and transcriptional activity, and these functions can be influenced by a multitude of covalent and non-covalent modifications within the C terminus. Modifications suggested to be involved in activation of p53 include sumoylation (Gostissa et al, 1999; Rodriguez et al, 1999; Muller et al, 2000), phosphorylation, dephosphorylation, acetylation, glycosylation (Shaw et al, 1996), ribosylation (Vaziri et al, 1997; Wang et al, 1998; Simbulan-Rosenthal et al, 1999) and redox regulation.

Transcriptional coactivators p300, CBP and PCAF have been shown to enhance p53-mediated transcription, and are important for p53 growth arrest and apoptotic functions. These coactivators bind to the N terminus and acetylate p53 at C-terminal lysine residues, thereby enhancing its sequence-specific DNA binding (Gu and Roeder, 1997). Phosphorylation of the N terminus of p53 enhances acetylation of the C terminus (Sakaguchi et al, 1998), and these modifications are DNA damage inducible (Sakaguchi et al, 1998; Liu et al, 1999). MDM2 can prevent this acetylation of p53 (Kobet et al, 2000; Ito et al, 2001), and association of p53 with deacetylating complexes provides further levels of control on p53 function (Juan et al, 2000; Luo et al, 2000). Acetylation of p53 is regulated by interaction with the promyelocytic leukaemia protein (PML), a RING domain containing tumour suppressor protein. Overexpression of PML relocalizes p53 into nuclear bodies and induces phosphorylation and acetylation of p53, thereby stimulating its transcriptional activity (Ferbeyre et al, 2000; Fogal et al, 2000; Guo et al, 2000; Pearson et al, 2000). Both DNA damage-induced apoptosis and oncogenic ras-induced senescence are impaired in PML-deficient cells, indicating an important role for PML in various p53-mediated stress responses.

Phosphorylation has also been shown to regulate p53 transcriptional activity. For example, the rapid phosphorylation on the C terminus on serine 392 in response to UV (Kapoor and Lozano, 1998) may stimulate sequence-specific DNA-binding activity of p53 (Hupp et al, 1992). A role for phosphorylation is also

implicated in changing the oligomerization state of p53, or regulating its promoter specificity and the choice between apoptosis or cell cycle arrest (Lohrum and Scheidtmann, 1996; Sakaguchi et al, 1997; Oda et al, 2000). An ATM-dependent dephosphorylation of p53 at Ser376 has been described, creating a binding site for 14-3-3 proteins which, in turn, activate sequence-specific DNA binding of p53 (Waterman et al, 1998).

Non-covalent interaction with proteins such as Ref-1 and HMG-1 have also been shown to activate p53 DNA binding. Ref-1 is a multifunctional protein that participates in DNA repair through its abasic endonuclease activity and regulates the activity of several transcription factors by changing their redox state. Presumably by regulating the redox state of p53, it enhances transactivation of p53 target promoters and increases p53-induced apoptosis (Jayaraman et al, 1997; Gaiddon et al, 1999). HMG-1 (high mobility group protein-1), a chromatin-associated non-histone protein, also increases the transcription of p53-dependent promoters, probably by inducing bending of the DNA (Jayaraman et al, 1998).

THE p53 RESPONSE

The tumour suppressor function of p53 depends principally on its ability to prevent cellular proliferation in response to stress stimuli that are encountered during tumourigenic progression. Activated p53 leads to cell cycle arrest and apoptosis, and can play a role in the induction of differentiation and cellular senescence (Almog and Rotter, 1997; Lundberg et al, 2000). Wild-type p53 has been shown to inhibit angiogenesis in tumours, by activating or repressing genes that regulate new blood vessel formation (Dameron et al, 1994; Nishimori et al, 1997; Bouvet et al, 1998). p53 can also play a direct role in the repair of DNA damage, both through nucleotide excision repair and base excision repair (Ford and Hanawalt, 1995; Wani et al, 1999; Offer et al, 2001; Zhou et al, 2001).

Cell cycle arrest

The cell cycle arrest function of p53 correlates well with its ability to function as a transcription factor (Crook et al, 1994; Pietenpol et al, 1994). Of the myriad of *p53* target genes identified to date p21[Waf1/Cip1] stands out as playing a critical role in the induction of cell cycle arrest (El-Deiry et al, 1993; Brugarolas et al, 1995). p21[Waf1/Cip1] is a cyclin-dependent kinase inhibitor that can activate both G_1 and G_2 cell cycle arrests similar to those seen in response to p53 induction (Harper et al, 1993; Agarwal et al, 1995; Bates et al, 1998). Importantly, cells deleted for *p21[Waf1/Cip1]* are deficient in both G_1 and G_2 arrest, and in the coupling of DNA synthesis and mitosis. These defects are also described in p53-null cells (Waldman et al, 1995; Waldman et al, 1996). Another target of p53 that contributes to the p53-induced G_2 arrest is 14-3-3 sigma (Hermeking et al, 1997). The 14-3-3 family proteins play a role in signal transduction and cell cycle control, in part by binding and sequestering proteins (Muslin and Xing, 2000). Although 14-3-3sigma deficient cells could transiently arrest in G_2 phase after DNA damage, they were unable to maintain the cell cycle arrest (Chan et al, 1999). As mentioned above, 14-3-3 can bind p53 and activate its sequence-specific DNA binding after IR (Waterman et al, 1998), and so may represent a positive feedback loop to p53 to prevent cell cycle progression in damaged cells. Further potential mediators of the G2 arrest include GADD45 (Wang et al, 1999) and Reprimo (Ohki et al, 2000).

Apoptosis

While there is evidence that p53 can mediate apoptosis by transcription-independent mechanisms, p53 both activates and represses genes that participate in the apoptotic response. Cells in which the wild-type *p53* was replaced by a transcriptionally inactive mutant showed loss of both cell cycle arrest and apoptotic functions, supporting the importance of transcriptional regulation in these responses (Chao et al, 2000; Jimenez et al, 2000).

Numerous apoptotic genes that are transcriptionally activated by p53 have been identified, suggesting that the p53 apoptotic response is multifaceted (Vousden, 2000) (Figure 2). The first apoptotic target of p53 identified was the bax gene, a pro-apoptotic member of the BCL-2 family (Miyashita and Reed, 1995). Recently, other pro-apoptotic members of this family named Noxa (Oda et al, 2000) and PUMA (Nakano and Vousden, 2001; Yu et al, 2001) have been identified as p53 targets. These proteins, as well as another *p53* target gene product, p53AIP1 (Oda et al, 2000), localize to the mitochondria and promote loss of the mitochondrial membrane potential and cytochrome c release, thus activating the Apaf-1/caspase-9 apoptotic cascade (Bossy-Wetzel and Green, 1999). Significantly, p53-induced apoptosis was found to be inhibited by loss of Apaf-1 or caspase-9 (Soengas et al, 1999). Perturbation of mitochondrial integrity may also be mediated by several genes coding for redox-controlling enzymes, which were identified as *p53*-induced genes (PIGs) in a colon cell line undergoing p53-mediated apoptosis (Polyak et al, 1997). It has been proposed that reactive oxygen species (ROS) produced by these PIGs cause damage to mitochondria which in turn initiates apoptosis. This model is supported by the observations that antioxidants, which eliminate ROS, can inhibit p53-mediated apoptosis as well as concomitant changes in the mitochondrial membrane potential in some systems (Li et al, 1999). Recently a study revealed that the p53 protein itself can localize to the mitochondria presenting a potential additional transcription-independent way of mediating apoptosis (Marchenko et al, 2000).

p53 has also been implicated in the membrane death receptor-induced pathway of apoptosis in several ways. Expression of at least two of the death receptors, FAS/APO1 and DR5/KILLER, and one of the death receptor ligands, FASL, have been observed to be up-regulated by p53 (Owen-Schaub et al, 1995; Wu et al, 1997). The DR5 promoter was shown to be a direct target of p53 (Takimoto and El-Deiry, 2000), while cell surface expression of FAS was enhanced by p53 through promotion of its trafficking from the Golgi to the plasma membrane (Bennett et al, 1998). Activation of death receptors by their ligands (FAS by FASL and DR5 by TRAIL) results in trimerization and recruitment of intracellular adapter molecules which initiate the caspase cleavage cascade and apoptosis (Ashkenazi and Dixit, 1998). Activation of PIDD, a death domain containing protein, by p53 also induces apoptosis and is likely to function through the death receptor pathway (Lin et al, 2000).

Loss of survival signalling can augment p53-mediated apoptosis (Gottlieb et al, 1994; Abrahamson et al, 1995; Canman et al, 1995; Lin and Benchimol, 1995; Prisco et al, 1997), and the ability of p53 to negatively regulate the IGF pathway (Buckbinder et al, 1995) and inhibit intergrin-associated survival signalling may further sensitize cells to p53-induced death (Bachelder et al, 1999). The NF-κB transcription factor has lately been shown to play an important role in p53-mediated apoptosis (Ryan et al, 2000), in contrast to the anti-apoptotic effect of NF-κB induced in
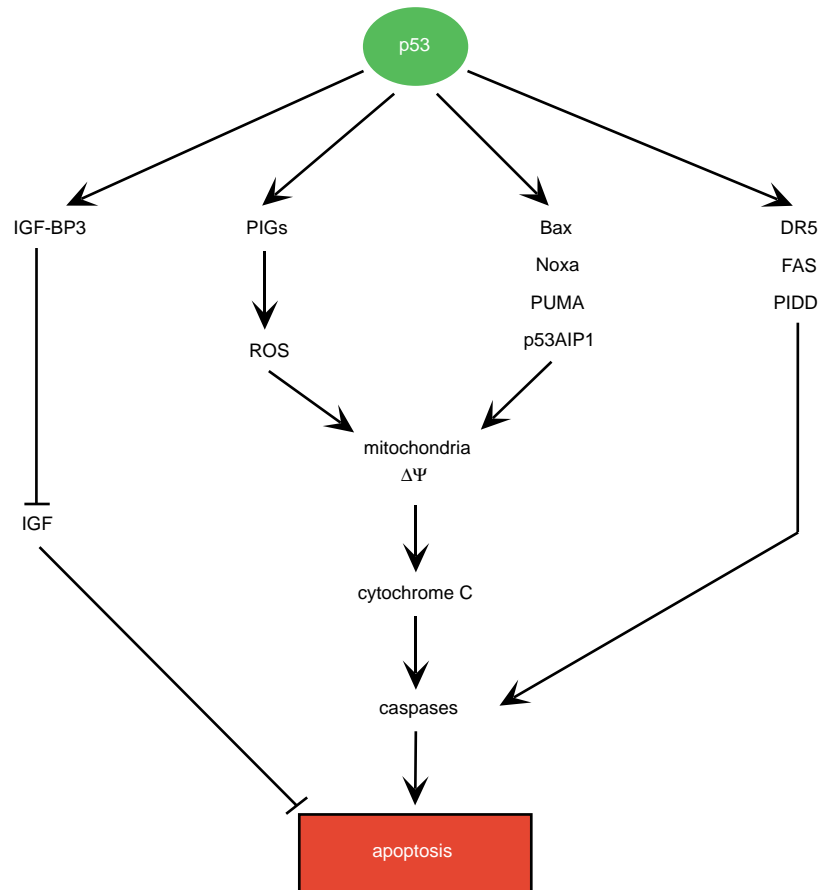
Figure 2 p53 induces apoptosis by activating target genes such as PIGs, Bax, Noxa, PUMA, p53AIP1 DR5, FAS PIDD and IGF-BP3. p53-induced apoptosis involves change in mitochondrial membrane potential ($\Delta\Psi$), cytochrome C release and caspase activation

response to TNF (Van Antwerp et al, 1996; Phillips et al, 1999). However, in other systems p53 expression has been shown to be dependent on NF-κB (Wu and Lozano, 1994; Kirch et al, 1999), and the contribution of NF-kB to the p53 apoptotic pathway remains unclear.

Choice of response

Whether a cell undergoes cell cycle arrest or apoptosis in response to p53 depends on several factors. Some of these may be independent of p53, such as the presence of extracellular survival factors, the presence of other oncogenic alterations and the availability of additional transcription factors or cofactors (Vousden, 2000). However, the activity of p53 can also contribute to the choice of response. The type and the magnitude of the cellular stress may control p53 function by affecting the level or activity of the p53 protein that is induced. Activation of apoptosis has been associated with higher levels of p53 than those required for cell cycle arrest (Chen et al, 1996), suggesting that the promoters regulating expression of apoptotic genes bind p53 with a lower affinity than the cell cycle arrest targets. Alternatively, affinity of p53 to target promoters might be regulated by conformational change (Thornborrow and Manfredi, 1999), and several mutants of p53 show selective loss of the ability to activate apoptotic target genes and to induce apoptosis (Ryan and Vousden, 1998). Covalent modification such as phosphorylation can also regulate conformation and/or promoter specificity of p53. Phosphorylation of p53 on

serine 46, for example, is required for the induction of the apoptotic target gene *p53AIP1* (Oda et al, 2000) and inhibition of the kinase responsible for serine 46 phosphorylation by the phosphatase WIP1, which is also p53-inducible, inhibits the ability of p53 to activate the apoptotic response (Takekawa et al, 2000).

DNA repair

Besides preventing cells with damaged genomes from replicating, via its apoptotic and cell cycle arrest function, p53 also participates in DNA damage repair. Cells lacking p53 function are deficient in nucleotide excision repair (NER), which repairs UV-induced DNA damage (Ford and Hanawalt, 1995; Wani et al, 1999) and base excision repair (BER), which removes bases damaged by alkylating agents, oxygen-free radicals or hydrolysis (Offer et al, 2001; Zhou et al, 2001). The C-terminus of p53 directly binds to different forms of damaged DNA: single-stranded DNA, ends of double-strand breaks and DNA 'bulges' resulting from insertion/deletion mismatches. Also, p53 can associate with several components of the repair machinery in vitro, including XPB/ERCC3, XPD/ERCC2, p62 subunit of TFIIH, CSB, replication protein A and Ref-1. Other biochemical activities of p53, such as DNA reannealing, DNA strand transfer and $3'–5'$ exonuclease activity might also play a role in its repair function (for review see Albrechtsen et al (1999) McKay et al (1999)).

Some of the *p53* target genes also participate in DNA damage repair. GADD45 binds proliferating cell nuclear antigen (PCNA),
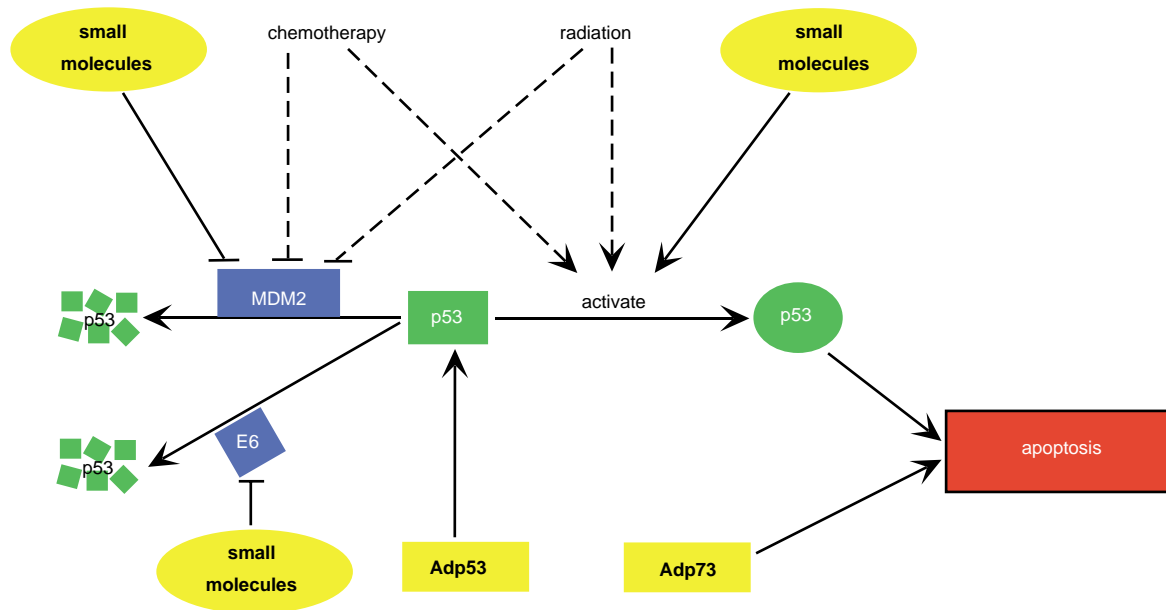
Figure 3   In tumour cells with p53, radiation and certain chemotherapeutic agents activate p53 by various mechanisms discussed in the text. Small molecules can be used to inhibit MDM2- or E6-mediated degradation of p53 or to stabilize p53 in the active conformation. Alternatively, p53 or its homologues can be introduced by adenoviral vectors (Adp53, Adp73). Gene therapy is used in combination with radiation or chemotherapy

and could inhibit replicative DNA synthesis, thus allowing DNA repair to proceed (Smith et al, 1994). Gadd45-null fibroblasts have defects in NER similar to those seen in p53-null fibroblasts (Smith et al, 2000) and Gadd45-deficient mice show increased radiation carcinogenesis and genomic instability comparable to that seen in p53-deficient mice (Hollander et al, 1999). Another transcriptional target of p53 that plays a role in DNA repair is p53R2, a ribonucleotide reductase gene (Nakano et al, 2000; Tanaka et al, 2000).

POTENTIAL OF p53 IN CANCER THERAPY

Since most cancers are defective in the p53 response, and tumour cells are generally more sensitive to p53-mediated death than many normal cells, reintroduction or reactivation of p53 in tumour cells may have profound therapeutic utility. Several approaches to restore p53 function in tumour cells are presently being pursued (Figure 3). Mutant p53 can be re-activated in cells by small peptides derived from the C-terminus of p53 (Selivanova et al, 1997). Even more promising, small compounds were identified that stabilize both wild-type and mutant *p53* in the active conformation and thus are able to slow tumour growth in mice (Foster et al, 1999). Inhibition of MDM2 may be effective in tumours that retain wild-type *p53*, but fail to properly activate it, due to MDM2 overexpression or loss of ARF. Small peptides or antisense oligonucleotides that target MDM2 have been shown to activate p53 successfully in p53-positive tumour cells (Böttger et al, 1997; Chen et al, 1999). Similarly, inhibition of the HPV E6 protein can induce p53 in cervical cancer cells (Butz et al, 2000; Hietanes et al, 2000). These approaches may be less effective, however, in those cancers where resistance to p53-mediated tumour suppression results from defects in downstream effectors, such as Bax (Rampino et al, 1997) or Apaf-1 (Soengas et al, 2001).

Adenoviral or retroviral vectors have been used to re-introduce wild-type *p53* into tumour cells with no or mutant p53, inducing apoptosis and promoting tumour regression in combination with radiation therapy in clinical trials (Roth et al, 1999; Zeimet et al,

2000). Adenoviral expression of the p53 family members p63 or p73 was also able to induce apoptosis in certain cancer cells (Ishida et al, 2000), and since p73 is resistant to degradation by MDM2 and E6 (Marin et al, 1998; Prabhu et al, 1998; Balint et al, 1999; Dobbelstein et al, 1999; Ongkeko et al, 1999; Zeng et al, 1999), its potential for therapeutic application may be promising. In another approach, an adenovirus lacking the p53-inactivating oncogene E1B (Onyx-015) was shown to be able to replicate only in tumour cells that are defective in the p53 pathway, but not in normal cells, thus causing selective tumour cell killing and tumour regression in many patients (McCormick, 2000).

Despite the enhanced sensitivity of many cancer cells to p53-mediated death, many normal cells also undergo apoptosis in response to radiation or chemotherapy, leading to the debilitating side effects that limit the extent of chemotherapy that can be tolerated. In a contrasting approach, an inhibitor of p53 was shown to protect mice from the lethal effects of radiation treatment by preventing damage of wild-type *p53*-containing normal tissues (Komarov et al, 1999). Although many questions remain unanswered, it is apparent that our improving insights into the regulation and function of the p53 tumour suppressor will yield exciting advances in cancer therapy.

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