JOURNAL OF CELLULAR PHYSIOLOGY 181:231–239 (1999)

The p53 Pathway and Apoptosis

TIMOTHY F. BURNS AND WAFIK S. EL-DEIRY*

Laboratory of Molecular Oncology and Cell Cycle Regulation, Howard Hughes Medical Institute, Departments of Medicine and Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

The p53 tumor suppressor plays a key role in the cell's response to genotoxic stress and loss of this "guardian of the genome" is an important step in carcinogenesis. Loss of the p53 gene has been observed in almost all tumor types and the gene is mutated in over 50% of tumors (Hollstein et al., 1991). It has been estimated that the vast majority of tumors have a disruption in the p53 pathway either by mutation of p53 or inhibition of its function through a variety of mechanisms (Vogelstein and Kinzler, 1992). Studies of the p53 -/- knockout mice established p53 as an important tumor suppressor. These mice develop normally but are prone to spontaneous tumors as 75% of the p53-null animals develop tumors by six months and 100% of the animals die from their tumors by 10 months (Donehower et al., 1992). The p53 tumor suppressor is mutated in the germline of individuals with Li-Fraumeni syndrome. These individuals are highly cancer prone as greater than 50% of Li-Fraumeni patients will develop tumors by age 30 (Malkin et al., 1990).

p53 acts as a tumor suppressor by inducing growth arrest, senescence, or apoptosis in response to a variety of cellular stresses including exposure to DNA damaging agents, hypoxia, nucleotide depletion, and oncogene activation. These responses protect a cell from uncontrolled proliferation and neoplastic transformation. The last two years have seen several major advances in our understanding of how p53 is activated in response to environmental insults and inappropriate oncogenic signals and there has been some progress in understanding p53 regulation of downstream target genes. This review will focus on the activation and stabilization of p53 and the role of p53 in inducing apoptosis.

STRUCTURE AND FUNCTION

p53 is a transcription factor consisting of a conserved N-terminal transactivation domain, a proline-rich domain, a sequence-specific DNA-binding domain, a tetramerization domain, and a basic C-terminal tail (Fig. 1). The N-terminal transactivation domain is a site of important regulation of the stability of p53 in the cell. Studies have shown that the binding of mdm2 to the N-terminal region inhibits p53 transactivation and leads to its degradation. As discussed below in greater detail, the cell has evolved multiple mechanisms to disrupt this interaction in response to genotoxic stress or oncogenic stimulation. The proline-rich region located between the transactivation domain and the sequence specific DNA binding domain appears to be required for p53 to suppress growth in some systems although its function remains unclear (Walker and Levine, 1996; Sakamuro et al., 1997). Although transcription independent growth suppression by p53 has been reported, the majority p53 mutations in human tumors cluster to the DNA-binding domain suggesting that p53 mediates most of its growth suppressive effects through transcriptional mechanisms (Cho et al., 1994). The basic C-terminal region of p53 is able to bind single stranded DNA and also appears to allosterically inhibit sequence-specific binding in the cell (Hupp et al., 1995; Jayaraman and Prives, 1995; Lee et al., 1995; Selivanova et al., 1997). Therefore post-translational modifications of this basic C-terminal tail are necessary for efficient sequence-specific DNA-binding by p53.

REGULATION OF p53 STABILITY AND ACTIVITY

Since activated p53 has the ability to either cause cell cycle arrest or apoptosis, the cell has evolved several mechanisms to keep the level of p53 protein low and inactive. In fact the half life of wildtype p53 is normally very short, being on the order of 20–30 min and is therefore barely detectable in the unstressed cell. In response to a variety of genotoxic stresses (DNA damaging agents, UV damage, nucleotide depletion, hypoxia, or hypoglycemia) or inappropriate proliferative signals (c-Myc, E2F-1, E1A, or Ras), the p53 protein becomes stabilized and its DNA binding activity increases allowing it to mediate cell cycle arrest or apoptosis (Fig. 2). Although it was known that the levels and activity of p53 are primarily regulated at the post-transcriptional level (Kastan et al., 1992; Kuerbitz et al., 1992), only in the last 2 years have the mechanisms underlying the stabilization and activation of p53 been elucidated.

The stability of the p53 protein primarily depends upon its physical interaction with the oncogene and p53 target gene mdm2. When mdm2 binds the N-terminal domain of p53 , the transactivation activity of p53 is inhibited (Momand et al., 1992; Oliner et al., 1993; Thut et al., 1997) and p53 is degraded (Haupt et al., 1997; Honda et al., 1997; Kubbutat et al., 1997; Midgley and Lane, 1997). The mdm2 gene was first

*Correspondence to: Wafik S. El-Deiry, Laboratory of Molecular Oncology and Cell Cycle Regulation, Howard Hughes Medical Institute, Departments of Medicine and Genetics, University of Pennsylvania School of Medicine, Philadelphia, PA 19104. E-mail: weldeir@hhmi.upenn.edu

Received 2 June 1999; Accepted 2 June 1999

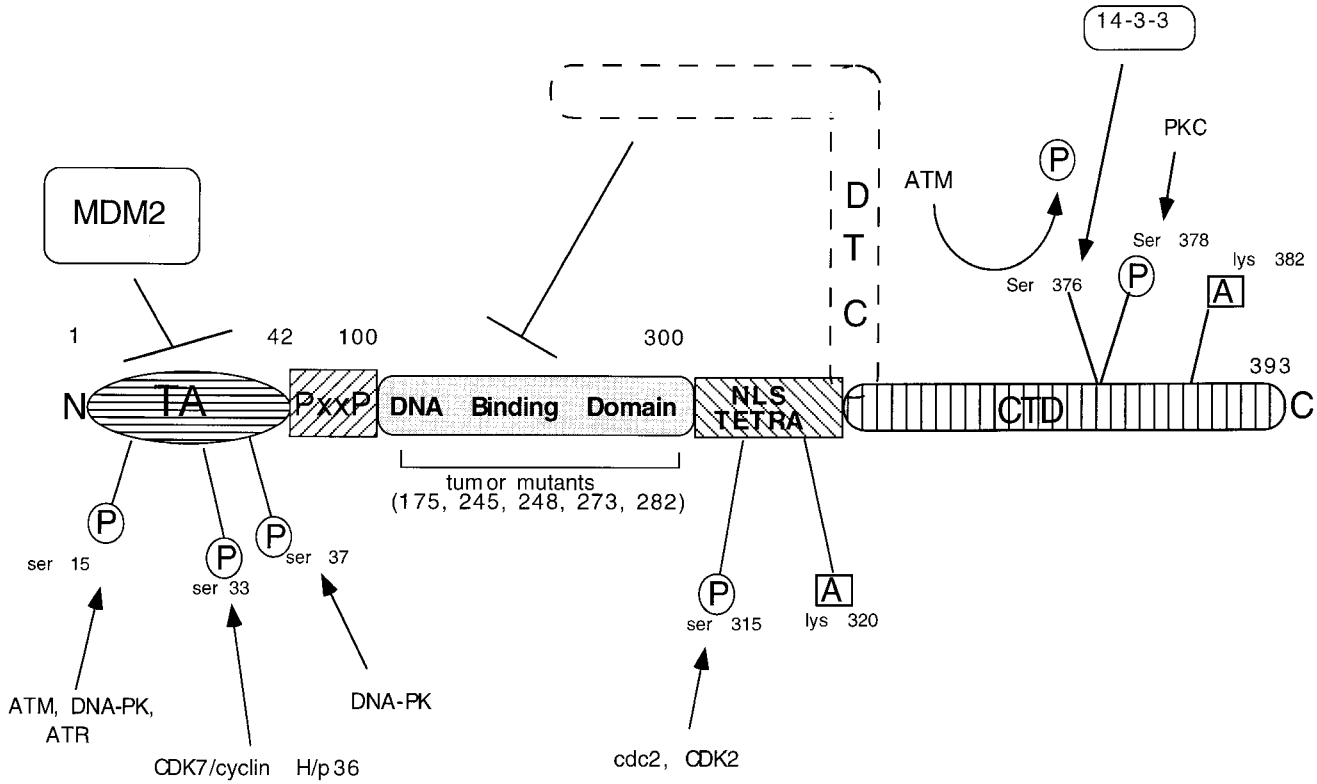

Fig. 1. Functional Domains of p53 and the post translational modifications which influence the stability and activity of p53. p53 is a 393 amino acid protein consisting of an N-terminal transactivation domain (TA), a proline rich region (PxxP), a DNA binding domain, a tetramerization domain (TETRA), a nuclear localization sequence (NLS), and a basic C-terminal domain. Binding of Mdm2 to the transactivation domain inhibits transactivation by p53 and leads to its degradation. Phosphorylation of N-terminal serines by ATM,DNA-PK, and ATR inhibit Mdm2 binding and lead to the stabilization of p53. Acetylation and dephosphorylation at the C-terminal region relieves the inhibition by the C-terminal tail of DNA binding.

discovered in a mouse tumor cell line as an amplified gene contained in a murine double minute (Fakharzadeh et al., 1991) and mdm2 has been shown to be amplified in 20–40% of human sarcomas (Oliner et al., 1992). Activated p53 induces mdm2 expression, which inhibits p53 stabilization and activation by binding the N-terminal region of p53. Therefore p53 and mdm2 participate in an autoregulatory loop that prevents the expression of p53 in the unstressed cell. Although mdm2 recently has been shown to inhibit the TGF-B pathway in a p53 independent manner (Sun et al., 1998), examination of the mdm2 -/- vs. Mdm2-/- p53 -/- knockout mice suggest that the inhibition of p53 is the primary *in vivo* function of mdm2. Several studies have shown that mdm2 -/- knockout mice are early embryonic lethals while the loss of p53 (mdm2-/-p53-/- double knockout) rescues this phenotype (Jones et al., 1995; Montes de Oca Luna et al., 1995). Study of DNA damage induced stabilization of p53 has revealed a key role for phosphorylation in regulating mdm2-p53 interactions.

Stabilization of p53 through phosphorylation

Previous studies suggested that serine 15 and 37 were important for p53 function as a serine to alanine substitution at these residues impaired the ability of p53 to inhibit cell cycle progression in human tumor lines or suppress E1A + Ras transformation of rat embryonic fibroblasts (Fiscella et al., 1993; Mayr et. al, 1995). More recent work demonstrated that both serine 15 and 37 become phosphorylated after DNA damage and that this phosphorylation reduces mdm2 binding to p53 (Shieh et al., 1997; Siliciano et al., 1997). Three members of the phosphoinositide-3-kinase-related (PIK) superfamily have been demonstrated to phosphorylate these residues in vitro and all may play a role in the regulation of p53 after DNA damage. Several lines of evidence support a role for the ataxia telangiectasia mutated (ATM) protein in the phosphorylation of p53. Cells derived from AT patients have an impaired ability to phosphorylate serine 15, stabilize p53 and induce p53 target genes in response to γ irradiation (Kastan et al., 1992; Canman et al., 1994; Siliciano et al., 1997). Furthermore studies of the atm -/- knockout animals have revealed that gamma irradiation induced G1 arrest in the atm-/- fibroblasts and gamma irradiation induced apoptosis in atm -/- thymocytes or in the developing CNS of atm -/- animals is impaired or absent (Xu and Baltimore, 1996; Westphal et al., 1997; Herzog et al., 1998). Finally, a series of recent studies have shown that ATM can phosphorylate p53 in vitro and in vivo (Banin et al., 1998; Canman et al., 1998; Khanna et al., 1998). Since the phosphorylation of serine 15 and the stabilization of p53 are

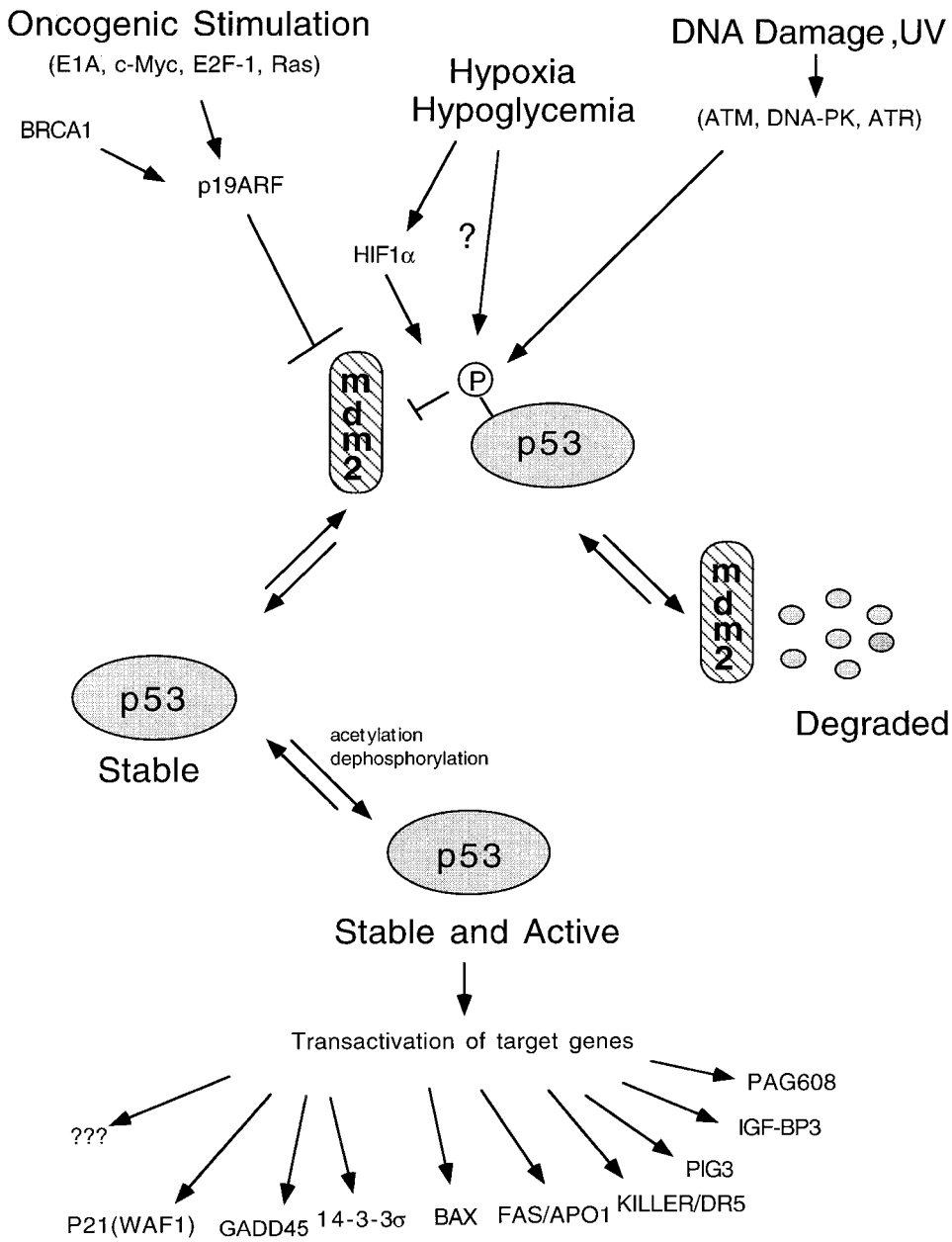

Fig. 2. A variety of stimuli lead to the activation and stabilization of p53. DNA damaging agents and UV irradiation stabilize p53 through phosphorylation of p53 at its N-terminal and activate its DNA binding through dephosphorylation and acetylation of its C-terminal region. Hypoxia and hypoglycemia stabilize p53 through both phosphorylation dependent and independent mechanisms. Inappropriate oncogene stimulation leads to p53 stabilization through the p19ARF pathway. Disruption of mdm2 and p53 interactions appears to be critical for the stabilization of p53. Stabilized and activated p53 can then transactivate its target genes

only delayed in gamma irradiated cells from AT patients and are normal in UV irradiated AT cells, this supports the existence of other kinases involved in the phosphorylation of serine 15. The DNA-PK kinase has also been shown to phosphorylate p53 on serine 15 and 37 in vitro and recent studies have shown that p53 activity is impaired in DNA-PK deficient cells (Lees-Miller et al., 1992; Shieh et al., 1997; Woo et al., 1998). Finally the ATM-Rad3 related protein ATR, has been shown to regulate the phosphorylation of serine 15 in response to DNA damage. Interestingly, ATR appears to be required for the phosphorylation of serine 15 in response to UV irradiation and for the late phase phosphorylation of serine 15 after gamma irradiation which suggests a complementary role of ATR for ATM (Tibbetts et al., 1999).

Stabilization of p53 by the p19ARF pathway

A variety of other stimuli besides DNA damaging agents and UV have been shown to stabilize p53 including hypoxia, hypoglycemia, nucleotide depletion, and inappropriate proliferative signals (for review, see

Giaccia and Kastan, 1998; Sherr, 1998). For the majority of these stimuli, the mechanisms by which they stabilize p53 are unclear. Several groups have reported that HIF-1alpha appears to mediate the stabilization of p53 in the response to hypoxic conditions and there has been some suggestion that phosphorylation of p53 may play a role (An et al., 1998; Giaccia and Kastan, 1998). A series of studies have shown that the INK4a locus which was previously shown to encode the CDK inhibitor, p16, encodes a second polypeptide derived from an alternative open reading frame known as p19ARF. P19ARF was shown to induce G1 arrest in a p16-independent p53-dependent manner (Quelle et al., 1995; Stott et al., 1998). Recent studies revealed that ARF overexpression leads to p53 stabilization by binding to Mdm2 and preventing the mdm2 mediated degradation of p53 (Kamijo et. al, 1998; Pomerantz et al., 1998; Stott et al., 1998; Zhang et al., 1998). Interestingly, p53 appears to negatively regulate the levels of p19ARF suggesting that p53 and ARF participate in a negative feedback loop (Zindy et al., 1998). Several groups have shown that p19ARF is required for the stabilization of p53 by the viral and cellular oncogenes E1A, c-Myc, E2F-1, and Ras as these oncogenes were unable to stabilize p53 in ARF null MEFs (Zindy et al., 1998, de Stanchina et al., 1998; Bates et al., 1998; Palmero et al., 1998). However, ARF may not be required for DNA damage induced stabilization of p53 (Kamijo et al., 1997, 1998). Therefore ARF appears to mediate a so-called "Oncogene Checkpoint" through p53, which allows the cell to check and prevent inappropriate proliferation. Surprisingly, evidence has emerged that hereditary breast and ovarian tumor suppressor BRCA1 may also stabilize p53 through a p19ARF-dependent mechanism (Somasundaram et al., data not shown). These findings suggest that ARF may also be responsible for sensing other stimuli beside oncogenic stimuli and suggest that much remains to be clarified concerning the signals that act through the p19ARF pathway to stabilize p53.

Activation of sequence specific DNA binding by p53: phosphorylation and acetylation

Several mechanisms have been shown to contribute to the activation of p53's DNA-binding activity. Post-translational modifications such as phosphorylation and acetylation at the C-terminal region of p53 increase DNA binding activity as recombinant p53 produced in bacteria appears to lack specific DNA-binding activity (Hupp et al., 1993). Evidence for the role of de-phosphorylation in activating p53 has come from studies which demonstrated that in addition to phosphorylating serine 15 and 37, ATM leads to the dephosphorylation of serine 376. This dephosphorylation creates a consensus binding site for 14-3-3, which increases the ability of p53 to bind DNA (Waterman et al., 1998). This result illustrates at least one instance in which changes in phosphorylation after DNA damage can both stabilize and activate p53. Recent evidence in the past year has shown that acetylation of the C-terminal region of p53 is also important for its activation after DNA damage. The transcriptional co-activators p300/CBP and PCAF have been shown to acetylate p53 in vitro on lysine residues 320 and 382 and lysine 382 has been shown to become acetylated after DNA damage. (Gu and Roeder., 1997; Sakaguchi et al., 1998). This data is consistent with findings showing that p300 can bind p53 and may be required for its transactivation and growth inhibitory responses after DNA damage (Avantaggiati et al., 1997; Yuan et al., 1998). Acetylation of p53 appears to disrupt interactions between the C-terminal domain and core DNA-binding domain, therefore allowing the core DNA-binding domain to assume an active conformation. Evidence now exists that phosphorylation of the N-terminal region of p53 after DNA damage may promote acetylation at the C-terminus suggesting that these post-translational modifications may be sequentially coordinated events after DNA damage (Sakaguchi et al., 1998). Therefore at least after DNA damage it has been demonstrated that phosphorylation and acetylation of p53 result in its stabilization and activation.

MEDIATORS OF P53 FUNCTION

p53 has been shown to be involved in several cellular processes including the induction of cell cycle arrest in G1 or G2, inhibition of growth factor signaling and angiogenesis, promotion of senescence, and induction of apoptosis. Although p53 has been demonstrated to induce apoptosis in the absence of transactivation (Haupt et al., 1995, 1996) and in the absence of de novo protein or RNA synthesis in some cell lines (Caelles et al., 1994), transcriptional activation of p53 downstream genes appears to be an important mechanism through which p53 mediates its biological effects (see El-Deiry, 1998 for recent review). The finding that most tumor-derived mutants of p53 are defective in DNA-binding and transactivation support the key role of transcriptional activation in the function of p53 (Hollstein et al., 1994).

P53 target genes involved in G1 and G2 cell cycle arrest

In response to DNA damage, mammalian cells generally undergo a G1 cell cycle arrest (Kastan et al., 1991) or apoptosis (Clarke et al., 1993; Lowe et al., 1993). p53 has been shown to required for the DNA damage induced G1 Arrest to occur as p53 -/- MEFs do not arrest in G1 after irradiation (Kastan et al., 1992). This G1 growth arrest in response to DNA damage is primarily mediated by the best characterized p53 target gene, p21WAF1 a cyclin-dependent kinase inhibitor (El-Deiry et al., 1993). However, other mechanisms may play a role in p53 mediated G1 Arrest as fibroblasts derived from p21 -/- mice are only partially defective in their irradiation induced G1 Arrest (Brugarolas et al., 1995; Deng et al., 1995). Although p53 is not required for DNA damage induced G2 arrest, several p53 target genes have been shown to induce a G2 arrest including GADD45 (Zhan et al., 1998), p21 (Bunz et al., 1998) and 14-3-3s (Hermeking et al., 1997) suggesting a role for p53 in G2 arrest.

P53 target genes involved in apoptosis

Although the ability of p53 to induce apoptosis after DNA damage in a variety of cell types (Clarke et al., 1993; Lowe et al., 1993) has been known for several years, only recently have some of the mechanisms by which p53's downstream targets mediate apoptosis been elucidated. The pro-apoptotic bcl-2 family mem-

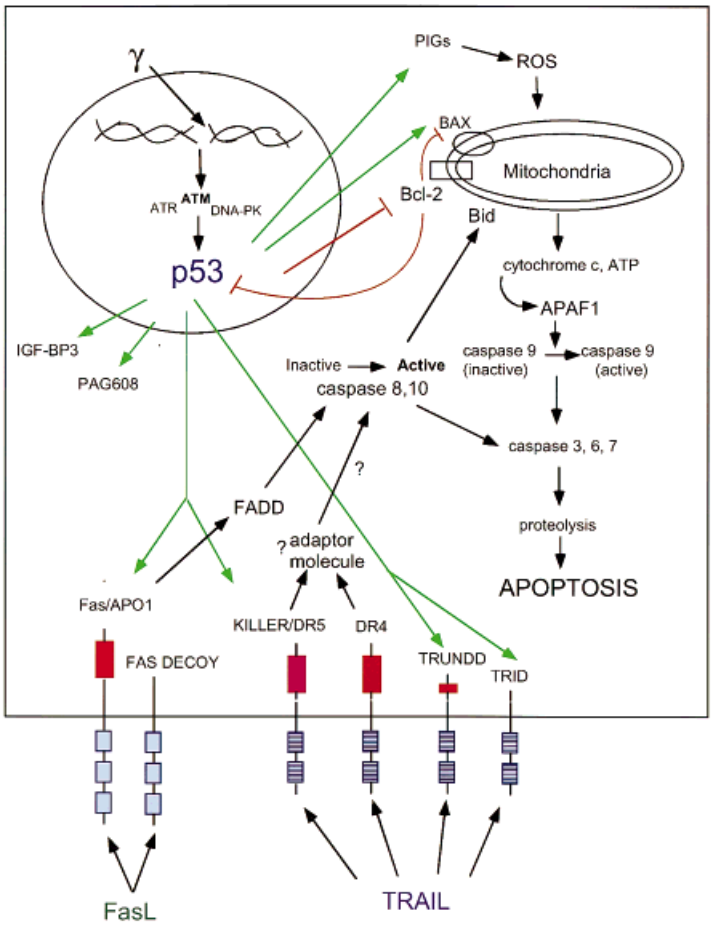

Fig. 3. p53 induces apoptosis in a caspase dependent manner through transactivation of its target genes. p53 induces Fas/APO1, KILLER/DR5, Bax, and PIGs and inhibits Bcl-2 allowing p53 to mediate apoptosis through several caspase dependent mechanisms. The death receptors Fas/APO1 and KILLER/DR5 form trimers upon binding their respective ligands and recruit adaptor molecules and initiator caspases to their cytoplasmic death domains. Activation of these initiator caspases results in the cleavage of the downstream effector caspases and cell death. Induction of Bax and inhibition of Bcl-2 leads to mitochondrial release of cytochrome c and ATP. APAF1 becomes activated upon binding cytochrome c and ATP and cleaves caspase 9. Activated caspase 9 cleaves the downstream effector caspases and apoptosis results. The PIG genes appear to induce apoptosis through the production of reactive oxygen species (ROS).

ber, bax, and the prototype death receptor, Fas/APO1, were the earliest discovered candidate mediators of p53-induced apoptosis (Miyashita et al., 1994; Owen-Scaub et al., 1995). These two targets illustrate two major pathways through which p53 activates the caspase cascade (Fig. 3; for review, see Thornberry and Lazebnik, 1998).

Bax is a pro-apoptotic member of the bcl-2 family of proteins. This family can be generally divided into pro-survival members such as Bcl-2, Bcl-X_L, Bcl-w, and CED 9 and pro-apoptotic members such as Bax, Bad, and Bid (for review, see Adams and Cory, 1998). These opposing family members can heterodimerize and it appears that the relative ratio of the pro-survival vs. pro-apoptotic members may determine whether the cell lives or dies. The anti-apoptotic members appear to function by inhibiting the release of cytochrome c from the mitochondria or by inhibiting Apaf-1 directly (reviewed in Nunez et al., 1998). Cytochrome c acts as a co-factor with ATP for the activation of Apaf-1, the mammalian homologue of CED4. Apaf-1 then activates caspase 9, an "initiator caspase" which can then in turn activate "effector caspases" such as caspase 3, 6, and 7 (Fig. 3). p53 not only induces Bax expression but also inhibits the expression of the pro-survival member, bcl-2 thereby shifting the balance toward cell death (Miyashita et al., 1994). Interestingly, bcl-2 has been shown to potently inhibit p53 induced apoptosis and to directly inhibit p53 transactivation of its target genes (Wang et al., 1993; Marin et al. 1994; Chiou et al, 1994; Froesch et al., 1999) Although Bax expression has been shown to be induced by p53, several lines of evidence suggest that Bax is neither sufficient nor required for p53-mediated apoptosis. Bax knockout thymocytes are not deficient in gamma-irradiation-induced apoptosis, while p53 -/- thymocytes are severely impaired (Knudson et al., 1995) and overexpression of Bax does not restore radiation induced apoptosis to p53 -/- cells (Brady et al., 1996). However, Bax may play a role in p53-dependent apoptosis in some tissues as Bax -/- fibroblasts are partially impaired in DNA damage-induced apoptosis (McCurrach et al., 1997).

Fas/APO1 belongs to the tumor necrosis factor (TNF) receptor superfamily which is characterized by the con-

served cysteine-rich extracellular domains and the presence of an intracellular "death domain" in a subset of its members (for review, see Ashkenazi and Dixit, 1998). Fas/APO1 has been shown to be important for peripheral deletion of T lymphocytes, mediating cytotoxic T-cell apoptosis and the destruction of inflammatory cells in immune-privileged sites (reviewed in Nagata, 1997). When the Fas/APO1 receptor is bound by its ligand FasL, the receptor trimerizes and its cytoplasmic death domain recruits the adaptor protein FADD (Fas-associated Death Domain). FADD contains a death effector domain (DED) which recruits the initiator caspase 8 to the receptor complex or death-inducing signaling complex (DISC). Recruitment of caspase 8 to the DISC results in auto-catalytic cleavage and activation which in turn activates downstream effector caspases (Fig. 3). Interestingly, a Fas/APO1 decoy receptor which is amplified and overexpressed in lung and colon cancer has recently been cloned and appears to bind FasL but does not result in the formation of the DISC (Pitti et al., 1998). It is possible that this Fas/APO1 decoy receptor may enable tumor cells to escape immune surveillance although further study is required to determine if this decoy receptor is immunoprotective. Although there is evidence that p53 increases Fas/APO1 levels by both transcriptional and transcription-independent mechanisms (Owen-Schaub et al., 1994; Bennett et al., 1998), Fas/APO1 does not appear to be required for p53 dependent apoptosis in response to DNA damage (Fuchs et al., 1997). A subtractive hybridization screen for p53 target genes recently led to the identification of KILLER/DR5, another member of the TNFR family, as a candidate mediator of p53-dependent apoptosis (Wu et al., 1997).

KILLER/DR5 is a pro-apoptotic member of the TRAIL (TNF-related apoptosis-inducing ligand) receptors. In humans, there are four TRAIL receptors, two pro-apoptotic receptors which contain death domains, KILLER/DR5 and DR4, and two anti-apoptotic or decoy receptors which lack or contain only a truncated death domain, TRID (Truncated Intracellular Domain) and TRUNDD (Truncated Death Domain). Like other TNFR family death receptors, both KILLER/DR5 and DR4 induce massive apoptosis when overexpressed by activating a downstream caspase cascade (For review see Ashkenazi and Dixit; 1998). KILLER/DR5 appears to be induced by p53 only under conditions in which p53 expression results in apoptosis and but not growth arrest (Wu et al., submitted). Furthermore, KILLER/DR5 has been connected to the ATM-p53 pathway as lymphoblastoid cells derived from patients with Ataxia-telangiectasia (AT) have an impaired induction of KILLER/DR5 compared to their heterozygous and wild type siblings (Wu et al., submitted). Recent work has revealed that p53 also induces the expression of the two decoy TRAIL receptors, TRID (Sheikh et al., in press) and TRUNDD (Meng et al., data not shown). This induction of decoy receptor expression may provide a mechanism by which p53 modulates its own apoptotic response. As with other p53 targets, it is possible that KILLER/DR5 may not be required for p53 mediated apoptosis.

In addition to the p53 target genes discussed above several other genes have been found which may also play a role in p53 mediated apoptosis. IGF-BP3 has been shown to be a p53 target gene and may block prosurvival signals by binding IGF-1. However overexpression studies with IGF-BP3 suggests that it may promote apoptosis independent of IGF-1 binding (Buckbinder et al., 1995; Rajah et al., 1997). A group of genes termed PIGs (p53-induced genes) have been identified through a SAGE (Serial Analysis of Gene Expression) screen for p53-induced genes (Polyak et al., 1997). Although the function of the majority of these PIGs is unknown, some appear to involved in the production of toxic reactive oxygen species which may contribute to p53-mediated apoptosis. Finally several other p53 target genes such as PAG608 (Israeli et al., 1997) and p85 (Yin et al., 1998) been implicated in p53-dependent apoptosis but their mechanisms of action remain to be elucidated.

TO BE OR NOT TO BE? GROWTH ARREST VS. APOPTOSIS

One of the major unanswered questions in the p53 field is what governs a cell's decision to undergo growth arrest vs. apoptosis in response to p53 expression. Several point mutation studies have demonstrated that the ability of p53 to induce growth arrest and apoptosis can be separated and p53 mutations have been isolated from tumors which selectively abrogate the ability of p53 to induce apoptosis (Delia et al., 1996; Rowan et al., 1996; Sakamuro et al., 1997; Ryan et al., 1998) Furthermore, these p53 mutants which are apoptosis-deficient can still induce Bax and IGF-BP3 in some cases which indicates that the induction of these two p53 targets may not necessarily correlate with apoptosis in some settings (Ryan et al., 1998). It appears that some p53 targets such as KILLER/DR5 may be specifically induced during p53-dependent apoptosis but not cell cycle arrest (Wu et al., data not shown). Although it has been well characterized that some cells or tissues undergo p53-mediated growth arrest in response to DNA damage while others undergo p53-induced apoptosis the factors which decide the cell's fate after DNA damage remain unclear.

Several factors have been proposed to play a role in shifting the balance between growth arrest or apoptosis including cell type differences, the presence of survival factors, and the overexpression of oncogenes (see Evan and Littlewood, 1998 for review). Cell type differences do appear to play a role in whether a cell undergoes apoptosis after DNA damage as normal diploid fibroblasts undergo cell cycle arrest (Kastan et al., 1992; Di Leonardo et al., 1994) while most lymphoid and myeloid derived cell lines undergo apoptosis after irradiation (Clarke et al., 1993; Lowe et al., 1993). However, even within a single cell type there appears to be other determinants of cell fate (Polyak et al., 1996). There are several examples where the presence of growth factors appears to protect against p53-induced apoptosis. In response to γ irradiation, Ba/F3 murine leukemia cells undergo a p53-dependent growth arrest in the presence of Il-3, and a p53-dependent apoptosis in the absence of Il-3 (Collins et al., 1992, El-Deiry et al., 1994; Canman et al., 1995). In DA-1, a murine lymphoma cell line the decision to undergo growth arrest vs. apoptosis also depends upon the presence or absence of Il-3 (Gottlieb et al., 1996). After Il-3 withdrawal in DA-1, the cleavage of Rb by

caspase activation suggests that the Rb protein may be inhibiting p53-mediated apoptosis (Gottlieb and Oren, 1998). A role for Rb in preventing p53-dependent apoptosis is supported by work performed using transgenic mice which overexpress the human papilloma virus E7 oncoprotein in the retina cells. HPV E7 inactivates Rb and results in massive apoptosis in the retina. However, if this transgenic mouse is crossed to a p53 null animal then the animals lack apoptosis in the retina and develop retinoblastoma (Howes et al., 1994). This p53 dependent apoptosis in the lens appears to require the unbound E2F-1 as apoptosis in the retina is abolished in Rb-/- E2F-1-/- double knockout mice (Tsai et al., 1998). This is consistent with the fact that E2F-1 overexpression can lead to the stabilization of p53 (Bates et al., 1998).

The overexpression of oncogenes can either increase the sensitivity or resistance of a particular cell line to p53 mediated apoptosis depending on the overexpressed oncogene. Overexpression of either cellular (c-Myc, E2F-1, Ras) or viral (E1A) oncogenes can lead to the stabilization of p53 (see Sherr, 1998 for review). Several studies have demonstrated that the overexpression of E1A in both mouse embryonic fibroblasts and normal human diploid fibroblasts leads to a p53-dependent apoptosis after DNA damage instead of the p53-dependent growth arrest which is normally observed after DNA damage in these cell types (Lowe et al., 1993; Samuelson and Lowe, 1997). Furthermore, this response does not depend on ARF-mediated stabilization of p53 as a similar p53-dependent apoptotic response is observed in ARF -/- MEFs expressing E1A (de Stanchina et al., 1998). Therefore the overexpression of some oncogenes can swing the balance toward apoptosis instead of growth arrest. Conversely, overexpression of activated c-Raf or v -Src have been demonstrated to result in a G1 arrest after irradiation in a cell line which would normally undergo apoptosis (Canman et al., 1995). Furthermore, overexpression of the cellular oncogene bcl-2 has been shown to potently inhibit p53-induced apoptosis (Wang et al., 1993; Marin et al. 1994; Chiou et al, 1994).

CONCLUSION

The p53 gene remains the most widely studied tumor suppressor and there are several major areas in which our knowledge is limited or incomplete. The mechanisms by which most environmental and cellular signals regulate p53 are unknown. Furthermore, the role of phosphorylation in regulating p53 is only beginning to be understood as p53 has been shown to be phosphorylated at numerous sites although the functional relevance of these modifications remains unclear (see Meek, 1998 for review). Likewise, we are only beginning to recognize the role of acetylation in regulating p53. Conversely we have only begun to understand the connection between p53 and the caspase cascade and identify the relevant target genes involved in p53-dependent apoptosis. Finally, the factors which decide whether a cell will undergo p53- mediated G1 arrest or apoptosis remain to be elucidated. The elucidation of the upstream regulators of p53 function and downstream mediators of p53-dependent apoptosis and growth suppression will allow for the development of clinical strategies to inhibit tumor growth.

LITERATURE CITED

Adams JM, Cory S. The Bcl-2 Protein Family: arbiters of Cell Survival. 1998. Science 281:322–325.

An WG, Kanekal M, Simon MC, Maltepe E, Blagosklonny MV, Neckers LM. 1998. Stabilization of wild-type p53 by hypoxia-inducible factor 1a. Nature 392:405–408.

Ashkenazi A Dixit VM. 1998. Death Receptors: signaling and modulation. Science, 281:1305–1308.

Avantaggiati, ML, Ogryzko, V, Gardner, K, Giordano, A, Levine, AS, Kelly, K. 1997. Recruitment of p300/CBP in p53-dependent signal pathways. Cell, 89:1175–1184.

Banin, S, Moyal, L, Khostravi, R, Shieh, S-Y, Taya, Y, Anderson, CW, Chessa, L, Smorodinsky, NI, Prives, C, Shiloh, Y, Ziv, Y. 1998. Enhanced phosphorylation of p53 by ATM in response to DNA damage. Science 281:1674–77.

Bates, S, Phillips, AC, Clark, PA, Stott, F, Peters, G, Ludwig, RL, Vousden KH. 1998. p14ARF links tumour suppressors RB and p53. Nature 395:124–125.

Bennett M, MacDonald K, Chan S-W, Luzio JP, Simari R, Weissberg P. 1998. Cell surface trafficking of Fas: a rapid mechanism of p53-mediated apoptosis. Science 282:290–293.

Brady HJ, Salomons GS, Bobeldijk RC, Berns AJ. 1996. T cells from baxalpha transgenic mice show accelerated apoptosis in response to stimuli but do not show restored DNA damage-induced cell death in the absence of p53. EMBO J 15:1221–1230.

Brugarolas J, Chandrasekaran C, Gordon JI, Beach D, Jacks T, Hannon GJ. 1995. Radiation-induced cell cycle arrest compromised by p21 deficiency. Nature 377:552–557.

Buckbinder L, Talbott R, Velasco-Miguel S, Takenaka I, Faha B, Seizinger BR, Kley N. 1995. Induction of the growth inhibitor IGF-binding protein 3 by p53. Nature 377:646–649.

Bunz F, Dutriaux A, Lengauer C, Waldman T, Zhou S, Brown JP, Sedivy JM, Kinzler KW, Vogelstein B. 1998. Requirement for p53 and p21 to sustain G2 arrest after DNA damage. Science 282:1497–1501.

Caelles C, Helmberg A, Karin M. 1994. p53-dependent apoptosis in the absence of transcriptional activation of p53-target genes. Nature 370:220–223.

Canman CE., Wolff AC, Chen CY, Fornace AJJ, Kastan MB. 1994. The p53-dependent G1 cell cycle checkpoint pathway and ataxia-telangiectasia. Cancer Res 54:5054–5058.

Canman CE, Gilmer TM, Coutts SB, Kastan MB. 1995. Growth factor modulation of p53-mediated growth arrest versus apoptosis. Genes Dev 9:600–611.

Canman CE, Lim DS, Cimprich KA, Taya Y, Tamai K, Sakaguchi K, Appella E, Kastan MB, Siliciano DD. 1998. Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. Science 281:1677–1679.

Chiou SK, Rao L, White E. 1994. Bcl-2 blocks p53-dependent apoptosis. Mol Cell Biol 4:2556–25563.

Cho Y, Gorina S, Jeffrey PD, Pavletich NP. 1994. Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. Science 265:346–355.

Clarke AR, Purdie CA, Harrison DJ, Morris RG, Bird CC, Hooper ML, Wyllie AH. 1993. Thymocyte apoptosis induced by p53-dependent and independent pathways. Nature 362:849–852.

Collins MK, Marvel J, Malde P, Lopez-Rivas A. 1992. Interleukin 3 protects murine bone marrow cells from apoptosis induced by DNA damaging agents. J Exp Med 176:1043–1051.

Delia D, Goi K, Mizutani S, Yamada T, Aiello A, Fontanella E, Lamorte G, Iwata S, Ishioka C, Krajewski S, Reed JC, Peirotti MA. 1997. Dissociation between cell cycle arrest and apoptosis can occur in Li-Fraumeni cells heterozygous for p53 gene mutations. Oncogene 14:2137–2147.

Deng C, Zhang P, Harper JW, Elledge SJ, and Leder P. 1995. Mice lacking p21CIP1/Waf1 undergo normal development, but are defective in G1 checkpoint control. Cell 82:675–684.

de Stanchina E, McCurrach ME, Zindy F, Shieh S-Y, Ferbeyte G, Samulsen AV, Prives C, Roussel MF, Sherr CJ, Lowe SW. 1998. E1A signaling to p53 involves the p19ARF tumor suppressor. Genes Dev 12:2434–2442.

Di Leonardo A, Linke SP, Clarkin K, Wahl GM. 1994. DNA damage triggers a prolonged p53-dependent G1 arrest and long-term induction of Cip1 in normal human fibroblasts. Genes Dev 8:2540–2551.

Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery Jr CA, Butel JS, Bradely A. 1992. Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature 356:215–221.

El-Deiry WS, Tokino T, Velculescu VE, Levy DB, Parsons R, Trent

JM, Lin D, Mercer E, Kinzler KW, Vogelstein B. 1993. WAF1, a potential mediator of p53 tumor suppression. Cell 75:817–825.
El-Deiry WS, Harper JW, O'Connor PM, Velculescu VE, Canman CE, Jackman J, Pietenpol JA, Burrell M, Hill DE, Wang Y, et al. 1994. WAF1/CIP1 is induced in p53-mediated G1 arrest and apoptosis. Cancer Res 54:1169–1174.
El-Deiry WS. 1998. Regulation of p53 downstream genes. Seminars in Cancer Biol 8:345–357.
Evan G, Littlewood T. 1998. A matter of life and cell death. Science 281:317–321
Fakharzadeh SS, Trusko SP, George DL. 1991. Tumorigenic potential associated with enhanced expression of a gene that is amplified in a mouse tumor cell line. EMBO J 10:1565–1569.
Fiscella M, Ullrich SJ, Zambrano N, Shields MT, Lin D, Lees-Miller SP, Anderson CW, Mercer WE, Appella E. 1993. Mutation of the serine 15 phosphorylation site of human p53 reduces the ability of p53 to inhibit cell cycle progression. Oncogene 8:1519–1528.
Froesch BA, Aime-Sempe C, Leber B, Andrews, D and Reed JC. 1999. Inhibition of p53 transcriptional activity by Bcl-2 requires its membrane-anchoring domain. JBC 274:6469–6475.
Fuchs EJ, McKenna KA, Bedi A. 1997. p53-dependent DNA damage-induced apoptosis requires Fas/APO-1-independent activation of CPP32 beta. Cancer Res 57:2550–2554.
Giaccia AJ, Kastan MB. 1998. The complexity of p53 modulation: emerging patterns from divergent signals. Genes Dev 12:2973–2983.
Gottlieb E, Lindner S, Oren M. 1996. Relationship of sequence-specific transactivation and p53-regulated apoptosis in interleukin 3-dependent hematopoietic cells. Cell Growth Diff 3:301–310.
Gottlieb E, Oren M. 1998. p53 facilitates pRb cleavage in IL-3-deprived cells: novel pro-apoptotic activity of p53. EMBO J 17:3587–3596.
Gu W, Shi X-L, Roeder RG. 1997. Synergistic activation of transcription by CBP and p53. Nature 387:819–822.
Haupt Y, Rowan S, Shaulian E, Vousden K, Oren M. 1995. Induction of apoptosis in HeLa cells by transactivation-deficient p53. Genes Dev 9:2170–2183.
Haupt T, Barak Y, Oren M. 1996. Cell type specific inhibition of p53-mediated apoptosis by mdm2. EMBO J 15:1596–1606.
Haupt Y, Maya R, Kazaz A, Oren M. 1997. Mdm2 promotes the rapid degradation of p53. Nature 387:296–299.
Hermeking H, Lengauer C, Polyak K, He TC, Zhang L, Thiagalingam S, Kinzler KW, Vogelstein B. 1997. 14-3-3sigma is a p53-regulated inhibitor of G2/M progression. Mol Cell 1:3–11.
Herzog K-H, Chong MJ Kapsetaki M, Morgan JI, Mckinnon PJ. 1998. Requirement for Atm in ionizing radiation-induced cell death in the developing central nervous system. Science 280:1089–1091.
Hollstein M, Sidransky D, Vogelstein B, Harris CC 1991. p53 mutations in human cancers. Science 253:49–53.
Hollstein M, Rice K, Greenblatt MS, Soussi T, Fuchs R, Sorlie T, Hovig E, Smith-Sorensen B, Montesano R, Harris CC. 1994. Database of p53 gene somatic mutations in human tumors and cell lines. Nucleic Acids Res 22:3551–3555.
Honda R, Tanaka H, Yasuda H. 1997. Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. FEBS Lett 420:25–27.
Howes KA, Ransom N, Papermaster DS, Lasudry JG, Albert DM, Windle JJ. 1994. Apoptosis or retinoblastoma: alternative fates of photoreceptors expressing the HPV-16 E7 gene in the presence or absence of p53. Genes Dev 8:1300–1310.
Hupp TR, Meek DW, Midgley CA, Lane DP. 1993. Activation of the cryptic DNA binding function of mutant forms of p53. Nucleic Acids Res 21:3167–3174.
Hupp TR, Sparks A, Lane DP. 1995. Small peptides activate the latent sequence-specific DNA binding function of p53. Cell 83:237–245.
Israeli D, Tessler E, Haupt Y, Elkeles A, Wilder S, Amson R, Telerman A, Oren M. 1997. A novel p53-inducible gene, PAG608, encodes a nuclear zinc finger protein whose overexpression promotes apoptosis. EMBO J 16:4384–4392.
Jayaraman L, Prives C. 1995. Activation of p53 sequence-specific DNA binding by short single strands of DNA requires the C-terminus. Cell 81:1021–1029.
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.
Kamijo T, Zindy F, Roussel MF, Quelle DE, Downing JR, Ashmun RA, Grosveld G, Sherr CJ. 1997. Tumor suppression at the mouse INK4a locus mediated by the alternative reading frame product p19ARF. Cell 91:649–659.
Kamijo T, Weber JD, Zambetti G, Zindy F, Roussel MF, Sherr CJ. 1998. Functional and physical interactions of the ARF tumor suppressor with p53 and Mdm2. Proc Natl Acad Sci USA 95:8292–8297.
Kastan MB, Onyekwere O, Sidransky D, Vogelstein B, Craig RW. 1991.
Participation of p53 in the cellular response to DNA damage. Cancer Res 51:6304–6311.
Kastan MB, Zhan Q, El-Diery W, Carrier F, Jacks T, Walsh WV, Plunkett BS, Vogelstein B, Fornace AJ. 1992. A mammalian cell-cycle checkpoint pathway utilizing p53 and gadd45 is defective in Ataxia-Telangiectasia. Cell 71:587–597.
Khanna KK, Keating KE, Kozlov S, Scott S, Gatei M, Hobson K, Taya Y Gabrielli B, Chan D Lees-Miller SP, Lavin MF. 1998. ATM associates with and phosphorylates p53: mapping the region of interaction. Nat Genet 20:398–400.
Knudson, CM Tung KSK, Tourtellotte WG, Brown GAJ, Korsmeyer SJ. 1995. Bax-deficient mice with lymphoid hyperplasia and male germ-cell death. Science 270:96–99.
Kubbutat MH, Jones SN, Vousden KH. 1997. Regulation of p53 stability by Mdm2. Nature 387:299–303.
Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB. 1992. Wild-type p53 is a cell cycle checkpoint determinant following irradiation. PNAS 89:7491–7495.
Lee S, Elenbass B, Levine A, Griffith J. 1995. p53 and its 14 kDa C-terminal domain recognize primary DNA damage in the form of insertion/deletion mismatches. Cell 81:1013–1020.
Lees-Miller, SP Sakaguchi K, Ullrich S, Appella E, Anderson CW. 1992. Human DNA-activated protein kinase phosphorylates serines 15 and 37 in the amino-terminal transactivation domain of human p53. Mol Cell Biol 12:5041–5049.
Lowe SW, Schmitt EM, Smith SW, Osborne BA, Jacks T. 1993. p53 is required for radiation-induced apoptosis in mouse thymocytes. Nature 362:847–852.
Malkin D, Li FP, Strong FC, Fraumeni JFJ, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA. 1990. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233–1238.
Marin MC, Hsu B, Meyn RE, Donehower LA, el-Naggar AK, McDonnel TJ. 1994.. Evidence that p53 and bcl-2 are regulators of a common cell death pathway important for in vivo lymphomagenesis. Oncogene 9:3107–3112.
Mayr GA, Reed M, Wang P, Wang Y, Schwedes JF, Tegtmeyer P. 1995. Serine phosphorylation in the NH2 terminus of p53 facilitates transactivation. Cancer Res 55:2410–2417.
McCurrach ME, Connor TMF, Knudson CM, Korsmeyer SJ, Lowe SW. 1997. Bas-deficiency promotes drug resistance and oncogenic transformation by attenuating p53-dependent apoptosis. PNAS 94: 2345–2349.
Meek DW. 1998. Multisite phosphorylation and the integration of stress signals at p53. Cell Signal 10(3):159–166.
Midgley CA, Lane DP. 1997. p53 protein stability in tumor cells is not determined by mutation but is dependent on Mdm2 binding. Oncogene 15:1179–1189.
Miyashita T, Reed JC. 1995. tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell 80:293–299.
Momand J, ZambettiGP, Olson DC, Geoge DL, Levine AJ. 1992. The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivaton. Cell 69:1237–1245.
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.
Nagata S. 1997. Apoptosis by death factor. Cell 88:355–365.
Nunez G, Benedict MA, Hu Y, Inohara N. 1998. Caspases: the proteases of the apoptotic pathway. Oncogene 17:3237–3245.
Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. 1992. Amplification of a gene encoding a p53-associated protein in human sarcomas. Nature 358:80–83.
Oliner JD, Pietenpol JA, Thiagalingam S, Gyuris J, Kinzler KW, Vogelstein B. 1993. Oncoprotein MDM2 conceals the activation domain of tumor suppressor p53. Nature 362:857–860.
Owen-Schaub LB, Zhang W, Cusack JC, Angel LS, Santee SM, Fujiwara T, Roth JA, Deisseroth AB, Zhang W-W, Kruzel E, Radinsky R. 1995. Wild-type human p53 and a temperature sensitive mutant induce fas/APO1 expression. Mol Cell Biol 15:3032–3040.
Palmero I, Pantoja C, Serrano M. 1998. p19ARF links the tumour suppressor p53 to Ras. Nature 395:125–126.
Pitti RM, Marsters SA, Lawrence DA, Roy M, Kischkel FC, Dowd P, Huang A, Donahue CJ, Sherwood SW, Baldwin DT, Godowski PJ, Wood WI, Gurney AL, Hillan KJ, Cohen RL, Goddard AD, Botstein D, Ashkenazi A. 1998. Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. Nature 396:699–703.
Polyak K, Waldman T, He T-C, Kinzler KW, Vogelstein B. 1996.

Genetic determinants of p53-induced apoptosis and growth arrest. Genes Dev 10:1945–1952.
Polyak K, Xia Y, Zweier JL, Kinzler KW, and Vogelstein B. 1997. A model for p53-induced apoptosis. Nature 389:300–305.
Pomerantz J, Schreiber-Agus N, Liegeois NJ, Silverman A, Alland L, Chin L, Potes J, Chen K Orlow I, Lee HW, Cordon-Cardo C, DePinho RA. 1998. The Ink4a tumor suppressor gene product, p19Arf, interacts with MDM2 and neutralizes MDM2's inhibition of p53. Cell 92:713–723.
Quelle DE, Zindy F, Ashmun RA, Sherr CJ. 1995. Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest. Cell 83:993–1000.
Rajah R, Valentinis B, Cohen P. 1997. Insulin like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-beta 1 on programmed cell death through a p53- and IGF-independent mechanism. JBC 272:12181–12188.
Rowan S, Ludwig RL, Haupt Y, Bates S, Lu X, Oren M, Vousden KH. 1996. Specific loss of apoptotic but not cell cycle arrest function in a human tumour derived p53 mutant. EMBO J. 15:827–838.
Ryan KM, Vousden KH. 1998. Characterization of structural p53 mutants which show selective defects in apoptosis but not cell cycle arrest. MCB 18:3692–3698.
Sakaguchi K, Herrera JE, Saito S, Miki T, Bustin M, Vassilev A, Anderson CW, Appella E. 1998. DNA damage activates p53 through a phosphorylation-acetylation cascade. Genes Dev 12:2831–2841.
Sakamuro D, Sabbatini P, White E, Prendergast GC. 1997. The polyproline region of p53 is required to activate apoptosis but not growth arrest. Oncogene 15: 887–898.
Samuelson AV, Lowe SW. 1997. Selective induction of p53 and chemosensitivity in RB-deficient cells by E1A mutants unable to bind the RB-related proteins. PNAS 22:12094–12099.
Selivanova G, Iotsova V, Okan I, Fritsche M, Storm M, Groner B, Crafstorm RC, Wilman KG. 1997. Restoration of the growth suppression function of mutant p53 by a synthetic peptide derived from p53 C-terminal domain. Nat Med 3:632–638.
Sheikh MS, Burns TF, Huang Y, Wu GS, Amundson S, Brooks KS, Fornace AJ Jr, El-Deiry WS. 1998. p53-dependent and -independent regulation of the death receptor KILLER/DR5 gene expression in response to genotoxic stress and tumor necrosis factor alpha. Cancer Res 58:1593–1598.
Sherr CJ. 1998. Tumor surveillance via the ARF-p53 pathway. Genes Dev 12:2984–2991.
Shieh S-Y, Ikeda M, Taya Y, Prives C. 1997. DNA damage-induced phosphorylation of p53 alleviates inhibition by MDM2. Cell 91:325–334.
Siliciano JD, Canman CE, Taya Y, Sakaguchi K, Appella E, Kastan MB. 1997. DNA damage induces phosphorylation of the amino terminus of p53. Genes Dev 11:3471–3481.
Stott F, Bates SA, James M, McConnell BB, Starborg M, Brookes S, Palmero I, Hara E, Vousden KH, Peters G. 1998.. The alternative product from the human CDKN2A locus, p14ARF, participates in a regulatory feedback loop with p53 and MDM2. EMBO J 17:5001–5014.
Sun P, Dong P, Dai K, Hannon GJ, Beach D. 1998. P53-Independent Role of MDM2 in TGF-B1 Resistance. Science 282:2270–2272.
Thornberry NA, Lazebnik Y. 1998. Caspases: enemies within. Science 281:312–316.
Thut CJ, Goodrich JA, Tjian R. 1997. Repression of p53-mediated transcription by MDM2: a dual mechanism. Genes Dev 11:1974–1986.
Tibbetts RS, Brumbaugh KM, Williams JM, Sarkaria JN, Cliby WA, Shieh S-Y, Taya Y, Prives C, Abraham RT. 1999. A role for ATR in the DNA damage-induced phosphorylation of p53. Genes Dev 13: 152–157.
Tsai KY, Hu Y, Macleod KF, Crowley D, Yamasaki L, Jacks T. 1998. Mutation of E2f-1 suppresses apoptosis and inappropriate S phase entry and extends survival of Rb-deficient mouse embryos. Mol Cell 3:293–304.
Vogelstein B, Kinzler KW. 1992. p53 function and dysfunction. Cell 70:523–526.
Walker KK, Levine AJ. 1996. Identification of a novel p53 functional domain that is necessary for efficient growth suppression. Proc Natl Acad Sci USA 93:15335–15340.
Wang Y, Szekely L, Okan I, Klein G, Wiman KG. 1993. Wild-type p53-triggered apoptosis is inhibited by bcl-2 in a v-myc-induced T-cell lymphoma cell line. Oncogene 12:3427–3431
Waterman MJF, Stavridi ES, Waterman JLF, HalazonetisTD. 1998. ATM-dependent activation of p53 involves dephosphorylation and association with 14-3-3 proteins. Nature Genet 19:175–178.
Westphal CH, Rowan S, Schmaltz C, Elson A, Fisher DE, Leder P. 1997. atm and p53 cooperate in apoptosis and suppression of tumorigenesis, but not in resistance to acute radiation toxicity. Nat Genet 16:397–401.
Woo RA, McLure KG, Lees-Miller SP, Rancourt DE, Lee PWK. 1998. DNA-dependent protein kinase acts upstream of p53 in response to DNA damage. Nature 394:700–704.
Wu GS, Burns TF, McDonald ER III, Jiang W, Meng R, Krantz ID, Kao G, Gan D-D, Zhou J-Y, Muschel R, Hamilton SR, Spinner NB, Markowitz S, Wu G, El-Deiry WS. 1997. KILLER/DR5 is a DNA damage-inducible p53-regulated death receptor gene. Nature Genet 17:141–143.
Xu Y, Baltimore D. 1996. Dual roles of ATM in the cellular response to radiation and in cell growth control. Genes Dev, 10:2401–2410.
Yin Y, Terauchi Y, Solomon GG, Aizawa S, Rangarajan PN, Yazaki Y, Kadowaki T, Barrett JC. 1998. Involvement of p85 in p53-dependent apoptotic response to oxidative stress. Nature 391:707–710.
Yuan Z-M, Huang Y, Ishiko T, Nakada S, Utsugisawa T, Shioya H, Utsugisawa Y, Yokoyama K, Weichselbaum R, Shi Y, Kufe D. 1999. Role for p300 in Stabilization of p53 in the Response to DNA Damage. JBC 274:1883–1886.
Zhang Y, Xiong Y, Yarbrough WG. 1998. ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. Cell 92:725–734.
Zhan Q, Antinore MJ, Wang XW, Carrier F, Smith ML, Harris CC, Fornace AJ, Jr. 1999. Association with Cdc2 and inhibition of Cdc2/Cyclin B1 kinase activity by the p53-regulated protein Gadd45. Oncogene 18:2892–2900.
Zindy F, Eischen CM, d Randle Kamijo T, Cleveland JL, Sherr CJ,
Roussel MF. 1998. Myc signaling via the ARF tumor suppressor regulates p53-dependent apoptosis and immortalization. Genes Dev 12:2424–2433.