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p53 Modulation of the DNA Damage Response

E. Scott Helton and Xinbin Chen*

Department of Cell Biology, The University of Alabama at Birmingham, Birmingham, Alabama 35294

Abstract The tumor suppressor p53 plays a central role in the DNA damage response. After exposure to genotoxic stress, p53 can both positively and negatively regulate cell fate. Initially, p53 promotes cell survival by inducing cell cycle arrest, DNA repair, and other pro-survival pathways. However, when cells accumulate DNA damage or demonstrate aberrant growth, p53 can direct the elimination of damaged cells. In this review, we will discuss the transcriptional-dependent and -independent roles of p53 in regulating the DNA damage response. J. Cell. Biochem. 100: 883–896, 2007. © 2006 Wiley-Liss, Inc.

Key words: p53; DNA damage response; DNA repair; pro-survival; cell cycle

p53 is a sequence-specific transcription factor that serves as a potent tumor suppressor. Inactivating mutations in the p53 gene (*TP53*) are found in over 50% of cancers, suggesting that loss of p53 function provides a selective advantage to tumor cells. Similarly, germline mutations in *TP53* cause Li-Fraumeni syndrome (LFS), a genetic disorder characterized by spontaneous tumor formation. Studies utilizing fibroblasts from LFS patients demonstrate that loss of p53 function results in abnormal karyotypes with altered chromosome structure and number [Boyle et al., 1998]. Likewise, p53-null mice develop spontaneous tumors, gene amplifications, and polyploidy [reviewed in Attardi and Donehower, 2005]. In addition, reciprocal studies in transgenic mice carrying supernumerary copies of the p53 gene demonstrate an increased DNA damage response [Garcia-Cao et al., 2002]. All together, these studies establish p53 as a critical tumor suppressor that functions at least in part by promoting genomic integrity.

Under normal cell growth conditions, p53 protein levels are kept low through regulation of its protein stability. HDM2, the human homolog of mouse double-minute-2, binds to p53, blocks interaction with transcriptional co-activators, and ubiquitinates p53, thus targeting p53 for proteosomal degradation [reviewed in Brooks and Gu, 2006]. DNA damage, oncogene activation, hypoxia, nutrient deprivation, and other stress-related signals activate and stabilize p53 primarily through post-translational modifications. Specifically, following genotoxic stress, p53 is activated and stabilized by the DNA damage kinases [reviewed in Lukas et al., 2004]. Phosphorylation of p53 at N-terminal sites stabilizes the p53 protein by disrupting MDM2 binding and promoting acetylation and phosphorylation of the C-terminus. Ataxia telangiectasia mutated kinase (ATM) and ataxia telangiectasia RAD3-related kinase (ATR) phosphorylate p53 on Serine-15, while their downstream kinases checkpoint kinase-2 (Chk2) and checkpoint kinase-1 (Chk1), respectively, phosphorylate p53 on Serine-20. Although p53 levels are primarily regulated at the post-translational level, several RNA-binding proteins including HuR (Hu antigen R), ribosomal protein L26 (RPL26), and nucleolin have recently been shown to increase p53 levels after DNA damage through promotion of p53 translation [reviewed in Takagi et al., 2005].

Following activation by DNA damage kinases, p53 accumulates in the nucleus and regulates transcription of target genes involved in the DNA damage response. In addition, recent evidence suggests that p53 modulates the DNA damage response through transcriptional-independent mechanisms. Whether p53

*Correspondence to: Xinbin Chen, MCLM 660, 1918, University Blvd., Birmingham, AL 35294-0005.
E-mail: xchen@uab.edu

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promotes cell survival or cell death likely depends upon the extent of DNA damage. Early in the DNA damage response, p53 promotes cell survival by regulating cell cycle arrest, DNA repair, and other cell survival pathways. However, upon accumulation of excessive DNA damage, p53 eliminates the threat of tumorigenesis by promoting apoptosis and potentially by inducing senescence and differentiation (Fig. 1). Because the ability of p53 to negatively regulate cell fate has been extensively reviewed elsewhere [reviewed in Harms et al., 2004; Jin and El-Deiry, 2005; Chipuk and Green, 2006], in this review, we will only highlight several key components. Instead, we will direct the focus of this review on the pro-survival pathways activated by p53 that promote recovery following DNA damage.

p53 AND THE ELIMINATION OF TUMORIGENIC CELLS

Apoptosis

Apoptosis is a form of programmed cell death that is dependent upon serial activation of cysteine proteases called caspases. Depending upon the initiating signal, apoptosis can be triggered through either an intrinsic or extrinsic apoptotic pathway [reviewed in Jin and El-Deiry, 2005]. The extrinsic apoptotic pathway, also called the death receptor pathway, requires ligand-dependent activation of cell surface receptors to initiate an apoptotic response. In brief, ligand binding stimulates assembly of the death-inducing signaling complex (DISC), consisting of adaptor molecules and pro-caspase-8, on the cytoplasmic tail of the activated receptor.

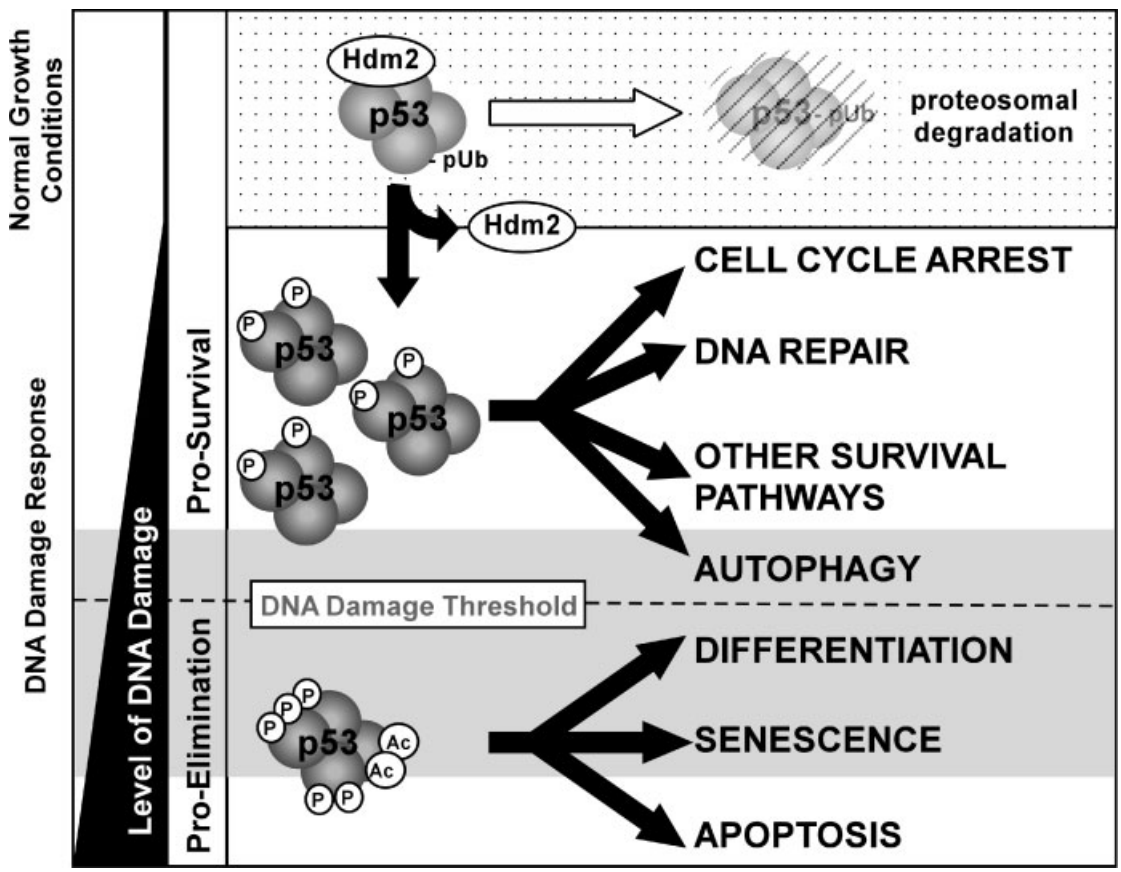

Fig. 1. p53 modulates the DNA damage response. Under normal cell growth conditions p53 protein levels are kept low by ubiquitin-mediated protein degradation. Phosphorylation of p53 following DNA damage stabilizes and activates p53. At low levels of DNA damage, p53 promotes cell survival by initiating cell cycle arrest, regulating DNA repair, and inducing other pro-survival pathways, including autophagy. At high levels of DNA damage, p53 pro-apoptotic function is enabled leading to programmed cell death. Autophagy, differentiation, and senescence may also serve as alternative mechanisms to eliminate damaged cells.

DISC formation promotes oligomerization and activation of the initiator caspase, caspase-8. Caspase-8 cleaves and activates downstream effector caspases which in turn cleave substrate proteins to cause cell death. The intrinsic apoptotic pathway induces cell death by disrupting mitochondrial function. In brief, pro-apoptotic Bcl-2 family members accumulate in response to apoptotic stimuli, disrupt the mitochondrial membrane, and promote cytochrome *c* release. Cytoplasmic cytochrome *c* permits formation of the apoptosome, which consists of cytochrome *c*, pro-caspase-9, and apoptotic protease activating factor-1 (APAF1). Formation of the apoptosome activates caspase-9, the initiator caspase. Caspase-9 cleaves and activates the effector caspases which cleave substrate proteins to effect apoptosis.

Under situations of extreme DNA damage, p53-dependent transcription is well known to stimulate apoptosis. p53 promotes the extrinsic pathway through upregulation of the TRAIL receptors, death receptor-4 (DR4) and death receptor-5 (DR5, KILLER) [reviewed in Jin and El-Deiry, 2005], as well as the FAS receptor (CD95) [Owen-Schaub et al., 1995] and the FAS/APO-1 ligand [Owen-Schaub et al., 1995]. p53 activates the intrinsic apoptotic pathway through multiple mechanisms [reviewed in Harms et al., 2004]. For example, p53 induces pro-apoptotic Bcl-2 family members, Bax, PUMA, and NOXA. p53 also upregulates expression of APAF1 and p53AIP1, which promote cell death through the intrinsic pathway. In addition to those mentioned above, p53 regulates numerous other genes that induce apoptosis [reviewed in Harms et al., 2004]. Besides the transcriptional-dependent function, it has recently been found that p53 may play a direct role in activating the intrinsic apoptotic pathway. Through translocation to the mitochondria, p53 may promote apoptosis by provoking cytochrome *c* release [Mihara et al., 2003].

Senescence

Senescence can be triggered by DNA damage or oncogene activation. Cells entering senescence are characterized by a permanent cell cycle arrest, an altered transcriptional program, a large flattened morphology, and a failure to replicate their DNA. p53 regulates both replicative senescence and premature senescence. Replicative senescence is activated by telomeric signals and is maintained by the p53-p21-Rb pathway. Interestingly, Serine-15 phosphorylated p53 and p21 accumulate during replicative senescence suggesting that telomere shortening may trigger a DNA damage signal similar to that seen with DNA double-strand breaks (DSBs) [d'Adda di Fagagna et al., 2003]. In contrast, premature senescence is activated in response to non-telomeric signals, such as DNA damage, oncogene activation, or reactive oxygen species (ROS). Non-telomeric signals activate both the p53-p21-Rb pathway and the p16-Rb pathway to induce senescence [reviewed in Dimri, 2005]. In support of the important role of p53 and p21 in the senescent program, $p53^{-/-}$ and $p21^{-/-}$ HCT116 cells are less able to undergo senescence following DNA damage treatment [Chang et al., 1999]. In addition, Eμ-myc lymphomas, which are induced by c-myc and Bcl-2 over-expression, undergo senescence in a p53-dependent manner following DNA damage treatment [Schmitt et al., 2002]. Altogether, these studies directly link p53 to cellular senescence and implicate senescence as a potential tumor suppression pathway following DNA damage.

Differentiation

Differentiation may be another way in which p53 eliminates damaged cells. Stem cells possess the ability to self-renew and are often resistant to cell cycle arrest and apoptosis, making them prime targets for tumorigenesis. Thus, p53 may promote differentiation of stem cells into a less malignant cell type competent to undergo cell cycle arrest and apoptosis. It has been found that following DNA damage, p53 represses transcription of nanog, a protein required for stem cell self-renewal [Lin et al., 2005]. In addition, p53 induces differentiation in L12 cells, a murine B cell line [Shaulsky et al., 1991]. Since cells must exit the cell cycle to undergo differentiation, p53-mediated cell cycle arrest may allow p53 to promote differentiation. p21 likely plays a role in differentiation and may contribute to this initial cell cycle arrest. p21 is expressed at the onset of keratinocyte differentiation but must be downregulated during terminal differentiation [Di Cunto et al., 1998]. Thus, following DNA damage, upregulation of p21 by p53 may have the potential to promote differentiation. Although p53 may upregulate p21 and downregulate nanog, the role of p53 in

differentiation remains controversial and needs further investigation.

p53 AND CELL SURVIVAL PATHWAYS

To ensure survival of a multicellular organism, eukaryotic cells have developed pro-survival mechanisms to block cell death. Interestingly, recent studies have identified a number of p53 activities that promote cell survival after DNA damage.

Cell Cycle Arrest

Progression through the cell cycle is mediated by the G1, S, and G2/M cell cycle checkpoints. During the early response to DNA damage, the ATM and ATR pathways initiate a transient cell cycle arrest [reviewed in Lukas et al., 2004]. During this initial delay in cell cycle progression, p53 is activated by DNA damage kinases and induces genes required for a sustained cell cycle arrest. The block of cell cycle progression mediated by p53 is critical to the DNA damage response because it allows time for DNA repair and prevents propagation of DNA errors.

G1 checkpoint. Arrest in the G1 phase of the cell cycle is critical for genomic integrity because it blocks entry into S phase and prevents replication of damaged DNA. Under normal growth conditions, progression through G1 is promoted by D-type and E-type cyclins and their associated cyclin-dependent kinases (cdk2, cdk4, and cdk6). Upon DNA damage, p53 is activated and induces $p21^{WAF1/CIP1}$, a cyclin-dependent kinase inhibitor [reviewed in Weinberg and Denning, 2002]. p21 sustains G1 arrest by inhibiting cdk2 and cdk4 activities. While p21 is the primary regulator of p53-mediated G1 arrest, other p53 target genes are also involved in maintaining G1 arrest, such as BTG2, GADD45, and MCG10 (referenced in Table I).

S checkpoint. DNA is most susceptible to DNA damage during S phase when chromosomes are being replicated. At least two checkpoints protect the cell during this vulnerable time: the intra-S checkpoint and the replication checkpoint. The intra-S phase checkpoint is activated when DNA damage occurs during S phase. Although it has yet to be confirmed, a newly identified p53 isoform called Δp53 may participate in the intra-S checkpoint. Δp53 is generated by alternative splicing of exons 7–9 which results in deletion of part of the DNA-binding domain. Δp53 may promote the intra-S arrest by inducing p21 and 14-3-3σ [Rohaly et al., 2005]. The replication checkpoint inhibits replication fork collapse when the DNA polymerase stalls at DNA lesions. If DNA repair is not completed in a timely manner, the replication fork collapses leading to DNA DSBs. In brief, the ATR-ATRIP heterodimer and RAD17 localize to the site of DNA damage. ATR activates Chk1, and these kinases induce a halt in DNA replication [referenced in Lukas et al., 2004]. Although p53 is phosphorylated and stabilized by ATR and Chk1, full-length p53 does not appear to contribute to S phase arrest. Instead, p53 protects genomic integrity during S phase by promoting DNA repair (as discussed later in this review).

G2/M checkpoint. The G2/M checkpoint plays a role in genomic maintenance by preventing segregation of damaged chromosomes. In order to sustain a G2/M arrest, Cdc2-cyclinB activity must be inhibited. p53 regulates many target genes that play critical roles during G2/M arrest (Table I). For example, p53 regulates p21 which blocks G2/M progression by binding the Cdc2–cyclinB complex and preventing the activating phosphorylation of Cdc2 at Thr161 by CAK [Smits et al., 2000]. p53 also induces 14-3-3σ which blocks entry into mitosis by promoting Wee1 kinase activity and by sequestering Cdc25C phosphatase in the cytoplasm [reviewed in Hermeking and Benzinger, 2006]. Moreover, other p53 targets, such as GADD45, BTG2, REPRIMO, B99 (*GTSE-1*), hematopoietic zinc finger protein (*HZF*), and MCG10 have been implicated in the maintenance of the G2/M checkpoint (summarized and referenced in Table I).

p53 AND DNA REPAIR

Various insults including chemotherapeutic drugs, chemical carcinogens, gamma-irradiation, ultraviolet-irradiation (UV), ROS, and endogenous stressors lead to DNA damage. Failure to repair damaged DNA results in cell death or oncogenic transformation, neither of which is a desired outcome for a biological system. Depending upon the type of DNA lesion, eukaryotic cells utilize multiple DNA repair pathways to mend damaged DNA including nucleotide excision repair (NER), mismatch repair (MMR), base excision repair (BER), translesion synthesis (TLS), homologous recombination

TABLE I. p53 Target Genes Modulating the DNA Damage Response

Protein (*Gene*)	Mechanism	References
	Cell cycle arrest	
G1 checkpoint		
p21 (*CDKN1A*)	• Inhibits Cdk2 and Cdk4 activity	Reviewed by Weinberg and Denning [2002]
BTG2	• Inhibits cyclin D1 (Rb-dependent) • Inhibits cyclin E1	Rouault et al. [1996]; Lim et al. [1998]; Guardavaccaro et al. [2000]
hCDC4b (*FBXW7*)	• Targets cyclin E for ubiquitin-mediated degradation	Reviewed by Harms et al. [2004]
GADD45A	• Binds to PCNA, inhibits S phase entry	Kastan et al. [1992]; Smith et al. [1994]
G2/M checkpoint		
p21 (*CDKN1A*)	• Inhibits Cdc2-cyclin B activation by CAK	Smits et al. [2000]
14-3-3σ (*STRATIFIN*)	• Sequesters cyclin B and CDC2 from nucleus	Reviewed by Hermeking and Benzinger [2006]
BTG2	• Inhibits cyclin B1-Cdc2	Rouault et al. [1996]; Ryu et al. [2004]
GADD45A	• Inhibits Cdc2/Cyclin B1 activity	Kastan et al. [1992]; Zhan et al. [1999]
B99 (*GTSE-1*)	• Overexpression results in G2-M arrest • Inhibits p53 in G2 and S phases and promotes cytoplasmic p53 localization	Reviewed by Harms et al. [2004]
HZF	• Required for G2 checkpoint maintenance and p21 protein stability	Sugimoto et al. [2006]
MCG10 (*PCBP4*)	• RNA binding protein	Zhu and Chen [2000]
Reprimo (*RPRM*)	• Inhibits Cdc2-cyclin B1 activity	Ohki et al. [2000]
	Other pro-survival pathways	
Antioxidants		
GPX1	• Reduces oxidized glutathione	Hussain et al. [2004]
GPX2	• Reduces oxidized glutathione	Yan and Chen [2006]
Hi95 (*SESN2*)	• Reduces over-oxidized peroxiredoxins	Budanov et al. [2004]
ALDH4A1	• Protects cells from oxidative stress	Yoon et al. [2004]
MnSOD (*SOD2*)	• Mitochondria superoxide dismutase	Hussain et al. [2004]
Other pathways		
cFLIP	• Inhibits caspase-8 activity	Reviewed by Harms et al. [2004]
COX2	• Promotes inflammation, cell survival, and cell proliferation • Inhibits DNA damage-induced apoptosis by direct binding to p53	Han et al. [2002]; Choi et al. [2005]; Corcoran et al. [2005]
Cyclin G	• Promotes p53 binding to HDM2	Okamoto et al. [2002]
DDR1	• Collagen-activated tyrosine kinase receptor • Inhibits p53-mediated apoptosis	Ongusaha et al. [2003]
HB-EGF	• Activates MAPK cascade; inhibits p53-mediated apoptosis	Fang et al. [2001]
Wip1 (*PPM1D*)	• Blocks p38 phosphorylation of p53 (Ser33,Ser46) • Dephosphorylates p53 (Ser15) and Chk1 (Ser345)	Fiscella et al. [1997]; Takekawa et al. [2000]; Lu et al. [2005]
Myosin VI (*MYO6*)	• Regulates protein trafficking for normal cell growth and Golgi integrity after DNA damage	Jung et al. [2006]
TRIDD	• TRAIL decoy receptor	Reviewed by Harms et al. [2004]
TRUNDD	• TRAIL decoy receptor	Reviewed by Harms et al. [2004]

(HR), and non-homologous end joining (NHEJ) pathways. Not surprisingly, studies show that p53 promotes genomic integrity by regulating the DNA repair pathways. In addition, many p53 target genes participate in the DNA repair process, as summarized in Table II. Furthermore, p53 directly modulates DNA repair through transcriptional-independent mechanisms.

p53 and NER

Nucleotide excision repair is responsible for repairing pyrimidine dimers formed by exposure to UV irradiation and other bulky DNA lesions induced by cross-linking agents and base-damaging chemical carcinogens. The genetic disorder xeroderma pigmentosum (XP) is directly linked to deficiencies in NER-assisted DNA repair, as mutations in XP complementation groups A, B, C, D, E, F, and G lead to a deficiency in DNA repair. Depending upon the complexes that initiate repair, NER is subdivided into two repair pathways: transcription-coupled repair (TCR) and global genome repair (GGR) [reviewed in Costa et al., 2003]. TCR is activated when RNA polymerase II stalls at sites of DNA damage. In TCR, RNA Pol II and the Cockayne syndrome proteins, CSA and CSB, recruit NER repair proteins to sites of DNA damage. In contrast, GGR is initiated by the DNA damage-binding protein complex (DDB1-DDB2) and the XPC-HR23B (homolog of RAD23B) complex (Fig. 2). Following the recognition step, both TCR and GGR utilize the same proteins to repair the DNA lesion. First,

TABLE II. p53 Regulates Expression of DNA Repair Genes

Protein (*Gene*)	Mechanism	References
Global genome repair (GGR)		
XPC	• Part of the initiation complex for GGR	Adimoolam and Ford [2002]
DDB2 (*XPE*)	• Required for DNA binding of DDB1 • Translocates XPC to UV-induced lesions	Hwang et al. [1999]; Fitch et al. [2003]; Wang et al. [2004]
Mismatch repair (MMR)		
MLH1	• Recruits additional repair enzymes	Chen and Sadowski [2005]
MSH2	• Mismatch recognition	Scherer et al. [2000]
PCNA	• Facilitate repair of mismatched bases by MSH2	Xu and Morris [1999]
PMS2	• Sensor of DNA damage • Stabilizes p73 and activates apoptotic function	Shimodaira et al. [2003]; Chen and Sadowski [2005]
Translesion synthesis (TLS)		
DNA Pol η (*XPV*)	• Replication bypass of T-T dimmers • Functions in p53 activation	Johnson et al. [1999]; Masutani et al. [1999]; Liu and Chen [2006a]
Homologous recombination (HR)		
RAD51	• Transcription is repressed by p53 • Promotes strand invasion	Arias-Lopez et al. [2006]
DNA Pol η (*XPV*)	• Binds RAD51, extends invading strand, restarts replication after HR	Kawamoto et al. [2005]; McIlwraith et al. [2005]; Liu and Chen [2006a]
RECQ4	• Transcription is repressed by p53	Sengupta et al. [2005]
WRN	• Transcription is repressed by p53-SP1	Yamabe et al. [1998]
Miscellaneous DNA repair mechanisms		
GADD45A	• Binds and promotes access to DNA lesions • Contributes to genomic stability in mouse	Kastan et al. [1992]; Carrier et al. [1999]; Hollander et al. [1999]
P53R2	• Provides dNTPs for DNA synthesis and repair • Protects against radiation-induced mutagenesis	Tanaka et al. [2000]; Tsai et al. [2006]

the transcription factor IIH (TFIIH) complex is recruited to the site of DNA damage. Next, two TFIIH subunits with helicase activity, XPD and XPB, unwind the DNA strand on either side of the DNA lesion creating a "DNA bubble" around the lesion. Subsequently, XPA and RPA (replication protein A) stabilize the exposed single-strand DNA and ensure proper NER complex assembly. Then, approximately 30-nucleotide long stretch of DNA including the DNA lesion is excised by XPG and XPF, which cleave the damaged strand upstream and downstream of the DNA lesion, respectively. Using the undamaged strand as a template, DNA Polymerases δ and ε synthesize a new strand of DNA to replace the excised damaged DNA. The repair is completed when DNA ligase covalently joins newly synthesized DNA.

The differences in the two NER pathways may have a dramatic effect on cell survival and genomic integrity. Because RNA Pol II senses DNA lesions and initiates rapid repair, TCR quickly relieves transcriptional stress and promotes cell survival. Unfortunately, TCR only initiates repair of the template strand, thus errors accumulate on the non-template strand. In contrast, GGR corrects damage on both strands of DNA and is more critical for the maintenance of genomic integrity. Supporting a role for p53 in DNA repair, LFS fibroblasts demonstrate defects in GGR [Ford and Hanawalt, 1995]. p53 contributes to GGR by transactivating the genes encoding both DDB2 (p48/XPE) [Hwang et al., 1999] and XPC [Adimoolam and Ford, 2002]. As a result, loss of p53 and subsequent deficiencies in the GGR proteins DDB2 and XPC shift the burden of DNA repair to the TCR pathway. Significantly, the contribution of GGR to p53-mediated genomic stability has been effectively demonstrated in knockout mouse studies where 100% of $XPC^{-/-}$ mice develop lung cancer [Hollander et al., 2005] and $DDB2^{-/-}$ mice develop skin tumors and are more resistant to p53-mediated apoptosis [Itoh et al., 2004]. p53 also directly regulates NER-mediated DNA repair by interacting with the TFIIH complex and by regulating XPB and XPD helicase activities [Leveillard et al., 1996].

p53 and MMR

Despite the proof-reading capabilities of DNA polymerase, DNA replication errors occur, resulting in mismatches that fail to maintain normal Watson-Crick base pairing (A-T, C-G). The process of MMR is responsible for repairing DNA replication errors and increases the fidelity of DNA replication [reviewed in Kunkel and Erie, 2005]. The MMR pathway requires

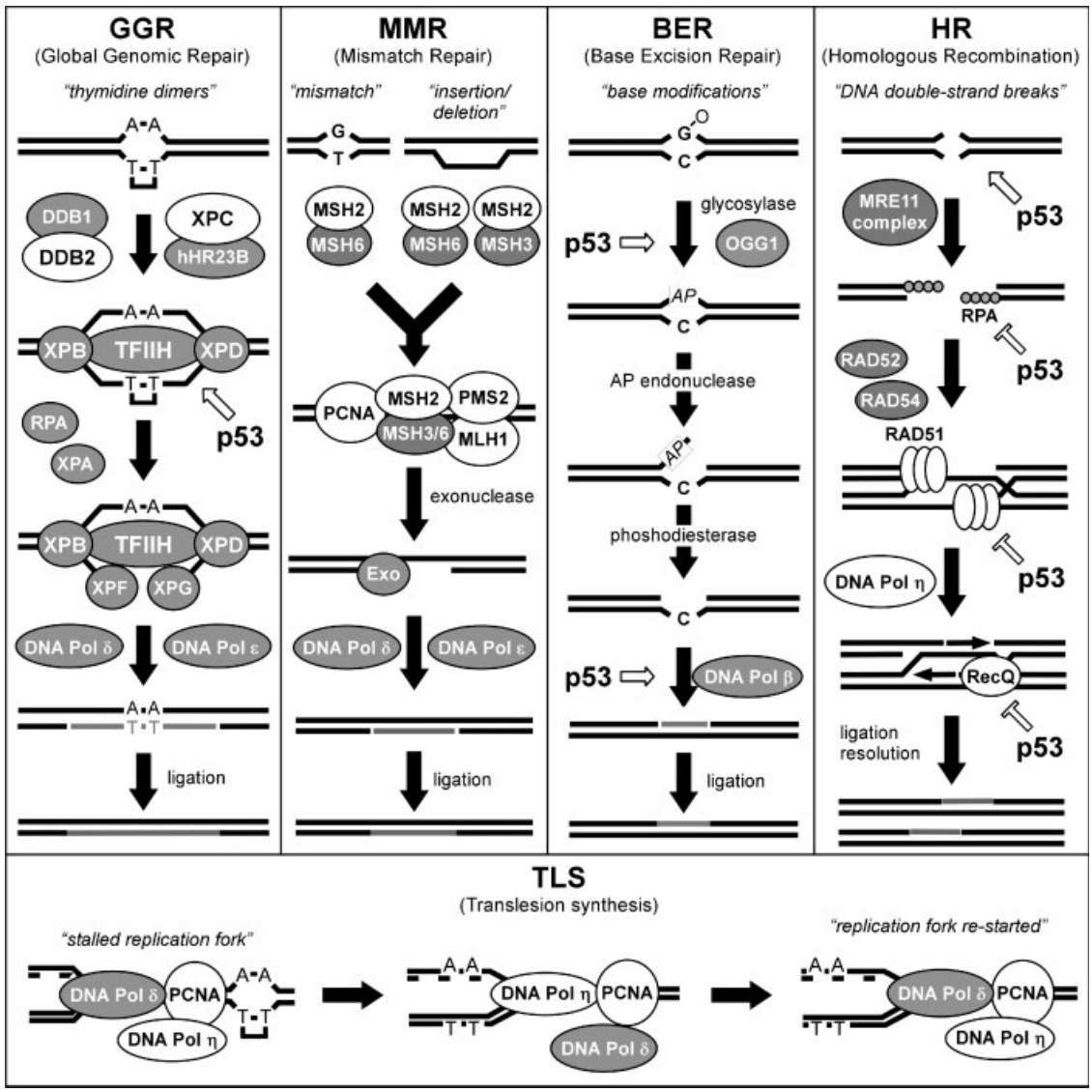

Fig. 2. p53 regulates the DNA repair pathways. p53 regulates DNA repair through both transcriptional-dependent and -independent mechanisms (DNA repair pathways are described in text). p53 target genes are in bold with a white background (Note: p53 represses RAD51 transcription; all other target genes are transcriptionally activated by p53). White pointed arrows indicate promotion of activity by p53, while white blocked arrows indicate an inhibitory role for p53.

the coordinated effort of several heterodimeric complexes including the human homologues of yeast MutS (MSH) and MutL (MLH) proteins (Fig. 2). MutS homolog heterodimers form a sliding clamp which moves along the DNA strand. While the MSH2-MSH6 heterodimer recognizes both insertion-deletion mispairs and single-base mismatches, MSH2-MSH3 heterodimers only recognize insertion-deletion mispairs. After sensing DNA replication errors, MSH proteins recruit MLH1 along with its binding partners, post-meiotic-segregation increased-1 (PMS1) and PMS2. Then, an exonuclease removes the DNA lesion, a DNA polymerase synthesizes a new strand, and finally a DNA ligase completes the repair.

As with GGR, p53 plays a critical role in MMR through the transcriptional regulation of several key components, including MSH2, PCNA, MLH1, and PMS2 (summarized and referenced in Table II). Interestingly, following treatment with the DNA damage agent cisplatin, PMS2 binds, stabilizes, and stimulates the pro-apoptotic function of p73, a p53 family member

[Shimodaira et al., 2003]. Thus, PMS2 might serve as a sensor for excessive DNA damage and promote the switch from DNA repair to apoptosis.

p53 and BER

While the major substrate for NER is UV-damaged DNA, the major substrate for BER is a DNA base damaged by ROS. BER is initiated by highly specialized DNA glycosylases which cleave the DNA base creating an apurinic or apyrimidinic (AP) site (Fig. 2). Next, AP endonuclease activity processes the AP site by generating nicked DNA with a 3′-hydroxyl end. Then, an exonuclease activity excises the lesion and DNA polymerase and ligase activities complete the repair. To date no transcriptional role for p53 has been found in promoting BER. Instead, p53 appears to directly interact with several key proteins to promote BER-associated DNA repair. First, p53 promotes 8-oxoguanine glycosylase (OGG1) and AP endonuclease (APE/Ref-1) activities and stimulates removal of the 8-oxoguanine base modification [Achanta and Huang, 2004]. In addition, p53 enhances BER by stabilizing DNA polymerases β, a critical BER component possessing both DNA polymerase and AP endonuclease activities [Zhou et al., 2001]. Interestingly, modulation of BER by p53 is context specific. Specifically, γ-irradiation has been shown to promote BER-associated activity in G0-G1 phases of the cell cycle, but inhibit BER function during G2/M phases [Offer et al., 2001]. Furthermore, p53 inhibits BER through transcriptional repression of 3-Methyladenine (3-MeAde) DNA glycosylase following exposure to nitric oxide, but not γ-irradiation [Zurer et al., 2004]. Interestingly, a recent study suggests that mitochondrial p53 may promote BER of damaged mitochondrial DNA [Chen et al., 2006].

p53 and TLS

Failure to repair ultraviolet light-induced DNA damage before entry into S phase may result in a stalled replication fork at the site of DNA damage. To avoid the detrimental collapse of replication forks, eukaryotes have developed a process known as DNA TLS to bypass DNA damage during replication (Fig. 2). In TLS, a stalled replication fork promotes polymerase switching from polymerase δ or ε to the lower fidelity Y family of polymerases (DNA polymerase κ, ι, η, and Rev1) that bypass the DNA lesion [McCulloch et al., 2004]. Unlike patients in other XP complementation groups, XPV carriers possess a functional NER pathway, but are deficient in replication of UV-damaged DNA. Interestingly, the mutation in XPV patients was mapped to the *POLH* gene encoding the DNA polymerase eta (DNA Pol η) which plays a prominent role in TLS-assisted replication of UV-damaged DNA [Johnson et al., 1999; Masutani et al., 1999].

Recent work in our laboratory has linked p53 and TLS by identifying POLH as a p53 target gene [Liu and Chen, 2006a]. Interestingly, knock-down of Pol η impaired camptothecin- and ionizing irradiation-induced apoptosis and reduced p53 activation, suggesting the presence of a positive feedback loop between p53 and Pol η. In further support of the notion that Pol η contributes to p53 tumor suppressor function, it has recently been shown that $POLH^{-/-}$ mice are more susceptible to UV-induced tumorigenesis [Lin et al., 2006].

p53 and DNA DSBs

DNA DSBs may be caused by IR, chemotherapeutic drugs, cleavage during V(D)J-recombination, meiotic recombination, or the collapse of replication forks. DSBs are the most severe form of DNA damage and threaten genomic stability by facilitating deletion and/or translocation of chromosomal DNA. Because of the deleterious nature of DSBs, it is not surprising that p53 plays an important role in the repair of DSBs through the regulation of both DSB repair pathways, HR and NHEJ.

p53 and HR

An overview of the HR pathway is shown in Figure 2 [reviewed in Jackson, 2002]. Briefly, HR is initiated when the MRN complex (Mre11, Nbs1, and RAD50) senses a DSB and directs the processing of the damaged DNA to yield single-stranded DNA (ssDNA) ends. Meanwhile, RPA binds to and stabilizes the ssDNA ends. Next, the HR components RAD51, RAD52, and RAD54 direct pairing of the processed DNA with a homologous region on the sister chromatid and initiate strand exchange by forming a Holliday junction. Finally, DNA Polymerases extend the 3′-end of the invading strand using the intact homologous strand as a template and the Holliday junctions are resolved.

Homologous recombination is active in S, G2, and M phases of the cell cycle where homologous

chromosomes serve as templates for damaged DNA. HR is essential for maintenance of genomic stability through the promotion of error-free DSB repair. In addition, HR is also required for generation of genomic variability through the promotion of meiotic recombination and V(D)J-recombination. Given that either a deficit or an excess in HR may lead to chromosomal instability, it is essential that HR is highly regulated. Because increased levels of HR have been observed in mice lacking wild-type p53 [Bishop et al., 2003; Lu et al., 2003], it is thought that p53 plays a critical role in the negative regulation of HR. Recently, several studies have described potential mechanisms whereby p53 regulates HR. First, p53 directly interacts with several essential HR-related proteins. Specifically, p53 represses HR through direct interaction with RPA, a single-strand DNA interacting protein required for stabilizing processed DNA ends [Romanova et al., 2004]. Additionally, p53 directly interacts with RAD51 to inhibit strand exchange between sister chromatids [Sturzbecher et al., 1996] and prevents excess recombination by promoting the clearance of RAD51 foci [Orre et al., 2006]. Moreover, p53 prevents HR by inhibiting the activity of RecQ helicases, BLM and WRN, which assist in restarting the replication fork [Yang et al., 2002]. Interestingly, p53 may monitor DNA repair by interacting with damaged DNA and DNA repair intermediates. For example, p53 has been shown to bind to Holliday junctions and to prevent recombination [Lee et al., 1997; Janz et al., 2002].

Although the role of p53 in HR is primarily thought to be transcriptionally independent, recent discoveries demonstrate roles for p53 target genes in regulation of HR. For example, it has been demonstrated that TLS-associated DNA Pol η is also involved in HR. Pol η was shown to interact with RAD51 and restarts DNA synthesis following HR by extending the 3′-end of the invading strand [McIlwraith et al., 2005]. p53 may also inhibit HR through the transcriptional repression of RAD51 [Arias-Lopez et al., 2006]. Finally, p53 also represses transcription of the recombination promoting RecQ4 helicases, WRN [Yamabe et al., 1998] and RecQ4 [Sengupta et al., 2005].

p53 and NHEJ

Non-homologous end joining repairs DSBs in the absence of a sister chromatid. The process of NHEJ is dependent upon the DNA-dependent protein kinase (DNA-PK), which consists of a catalytic subunit (DNA-PK_{cs}) and the regulatory Ku70-Ku80 heterodimer, DNA ligase 4, and XRCC4 (Fig. 2) [reviewed in Jackson, 2002]. NHEJ is the major form of DSB repair when a homologous template is not available during G0, G1, and S phases of the cell cycle. NHEJ-associated DNA repair is often error prone since genetic material is lost during DNA end processing. It is thought that p53 negatively regulates NHEJ since DNA end joining is elevated in cellular extracts obtained from p53-null MEFs compared to MEFs from wild-type littermates [Okorokov et al., 2002]. p53 may inhibit error-prone NHEJ by preventing annealing of mismatched DNA [Dahm-Daphi et al., 2005]. Conversely, p53 may promote error-free end joining by binding to and stabilizing broken DNA ends [Tang et al., 1999].

p53 AND OTHER SURVIVAL PATHWAYS

Negative Feedback Loops for p53

Perhaps the most critical pro-survival mechanism for p53 is the upregulation of proteins involved in the negative regulation of p53 function. In this manner, p53 accumulation is limited by its own transcriptional activity. The main negative feedback loop for p53 involves the E3 ubiquitin ligase HDM2 that promotes the degradation of p53 [reviewed in Brooks and Gu, 2006]. Cyclin G, one of the first p53 target genes identified, negatively regulates p53 function by stimulating the p53-HDM2 interaction [Okamoto et al., 2002]. Specifically, cyclin G promotes PP2A-mediated dephosphorylation of an inhibitory phosphate on Threonine-216 of HDM2. p53 also limits its activity as well as DNA damage signaling by inducing WIP-1, a serine/threonine phophatase. For example, WIP-1 dephosphorylates p38 at Threonine-180, which prevents phosphorylation of p53 at Serine-33 and Serine-46 by p38 [Takekawa et al., 2000]. WIP1 also dephosphorylates p53 directly at Serine-15 as well as inhibits Chk1 activity by removing the activating phosphate at Serine-345 [Lu et al., 2005].

Although p53 is clearly a potent inducer of apoptosis, p53 also plays an important role in limiting apoptosis. p53 attenuates the extrinsic apoptotic pathway by upregulating the decoy TRAIL receptors TRID, TRAIL receptor

without an intracellular domain, and TRUNDD, TRAIL receptor with a truncated death domain. Furthermore, p53 limits activation of the extrinsic pathway by inducing c-FLIP, an inhibitor of caspase-8 [reviewed in Harms et al., 2004].

Several other p53 target genes promote cell survival and inhibit p53-mediated apoptosis. For example, heparin-binding epidermal growth factor-like growth factor (HB-EGF) is upregulated by p53 and subsequently promotes activation of the pro-survival Ras/Raf/ERK cascade [Fang et al., 2001]. Likewise, cyclooxygenase 2 (COX2), which regulates prostaglandin synthesis and promotes cell survival and proliferation, is induced by p53 and inhibits p53-mediated apoptosis [Han et al., 2002], at least in part through a direct interaction with p53 [Choi et al., 2005; Corcoran et al., 2005]. In addition, the discoidin domain receptor 1 (DDR1), another p53 target, has been shown to inhibit p53-mediated apoptosis following exposure to genotoxic stress [Ongusaha et al., 2003]. Furthermore, we have recently shown that p53 may limit Golgi stress through the induction of the MYO6 gene [Jung et al., 2006].

p53 and Antioxidants

Reactive oxygen species are highly reactive molecules that modify proteins, DNA, and lipids. ROS can be generated by damaged mitochondria and by cellular enzymes as part of the apoptotic response. In order to prevent ROS-mediated damage, cells utilize an antioxidant defense. p53 promotes cellular survival by inducing target genes associated with the antioxidant defense (Table I). For example, the ROS hydrogen peroxide (H_2O_2) is reduced to water and oxygen by the glutathione (GSH) antioxidant system. In order to maintain the defense against H_2O_2, glutathione peroxidases restore GSH levels by reducing oxidized glutathione (GSSG). Recently, our laboratory has demonstrated that p53 and other p53 family members, specifically ΔNp63γ, induce expression of glutathione peroxidase-2 (GPX2) [Yan and Chen, 2006]. p53 also has been shown to upregulate glutathione peroxidase-1 (GPX1) [Hussain et al., 2004]. Peroxiredoxin is also an important hydrogen peroxide scavenger. p53 induces sestrin 2 (Hi95), which reduces oxidized peroxiredoxin [Budanov et al., 2004]. In addition, p53 transactivates the superoxide dismutase 2 (SOD2) gene, whose gene product, MnSOD, is the main defense against mitochondrial-generated superoxide [Hussain et al., 2004]. Finally, p53 also upregulates aldehyde dehydrogenase 4 (ALDH4A1), a mitochondrial-matrix enzyme that serves the dual function of catalyzing proline degradation and protecting cells from oxidative stress [Yoon et al., 2004]. Thus, antioxidant genes regulated by p53 may limit the amount of cellular stress and DNA damage caused by ROS. It is important to note that p53 also induces oxidoreductases, such as ferredoxin reductase, that produce ROS and may promote apoptosis [Hwang et al., 2001; Liu and Chen, 2002]. Therefore, p53 regulation of ROS could provide another means through which p53 can modulate cell survival or cell death following DNA damage.

Autophagy

Autophagy is an intracellular process in which cytoplasm and organelles are sequestered into a double membrane structure called the "autophagosome" and then degraded by the lysosome. Previously categorized as a form of programmed cell death, autophagy may actually be competent to promote both cell death and cell survival. It has been suggested that autophagy may be a tumor suppressor pathway since mice heterozygous for beclin-1, a major mediator of autophagy, display attenuated autophagy and enhanced cellular proliferation [Qu et al., 2003]. However, other studies support a role for autophagy in cell survival. Under normal cell growth conditions, autophagy is inhibited by mTOR (mammalian target of rapamycin), a downstream kinase in the PI3K/Akt pro-survival pathway. However, following DNA damage, p53 blocks mTOR repression of autophagy through p53-mediated induction of PTEN and TSC2 and p53-mediated activation of AMPK [Feng et al., 2005b].

Whether the promotion of autophagy by p53 directs cell survival or cell death is likely to depend upon the extent of cellular damage. For instance, p53-mediated autophagy could serve a protective function by removing damaged mitochondria capable of generating ROS and by recycling cytoplasm into useful components during times of nutrient deprivation. Conversely, severely damaged mitochondria fail to maintain energy levels and generate ROS, thus leading to p53 activation. Significantly, as apoptosis requires ATP-mediated caspase activation, promotion of autophagy by p53 may

provide an alternative form of programmed cell death when cellular energy levels are depleted following DNA damage.

CONCLUDING REMARKS

Paramount to its role as "guardian of the genome," p53 is positioned at the center of the DNA damage response and is a critical mediator of cell fate. Through its role as a sequence-specific transcription factor, p53 is able to regulate expression of proteins that promote both cell survival and cell death. In addition, p53 can regulate DNA repair and promote apoptosis through transcriptional-independent mechanisms. Altogether, the diverse and sometimes opposing functions attributed to p53 have made achieving a consensus on p53 function difficult. Nevertheless, a model has emerged in which p53 promotes cell survival at low levels of DNA damage, but induces apoptosis once a threshold of DNA damage has been surpassed (Fig. 1). In addition, the ability of p53 to regulate autophagy, senescence, or differentiation may provide an alternative means through which p53 directs cell fate. Still, for this model to be complete, the mechanisms that differentially regulate p53 function must be determined.

Currently, the mechanisms that regulate p53 pro-survival versus pro-apoptotic functions are not well defined. For instance, treatment of cells with the HDM2 inhibitor nutlin activates p53 function without inducing phosphorylation at key serine residues [Thompson et al., 2004]. In addition, acetylation of p53 C-terminal lysines was previously predicted to block HDM2-mediated p53 degradation; however, mutation of six C-terminal lysines, p53(K6R), failed to alter p53 protein stability before or after DNA damage treatment [Feng et al., 2005a]. While these studies can be seen as controversial, we believe they underscore the complexity of p53 regulation. It is thought that p53 function can be modulated by p53 protein accumulation, post-translational modifications, protein–protein interactions, and p53 localization [Lavin and Gueven, 2006; Liu and Chen, 2006b]. Clearly, even in the absence of specific residues, other mechanisms are still intact that can direct p53 function. Given that p53 function is impacted by diverse cellular pathways, it is important to recognize that p53 function is likely context specific. Thus, future studies must consider the activities of other pathways impacting p53 when attempting to come to a consensus on p53 function.

In process of compiling this manuscript, several questions arose that need to be addressed in future studies. p53 is mutated in greater than 50% of tumors. What pro-survival functions are maintained by mutant p53 that could promote tumorigenesis following DNA damage? Also, in what ways do the other p53 family members, p63 and p73, and the newly identified p53 isoforms regulate the DNA damage response?

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