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Regulation of the p53 Transcriptional Activity

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Abstract In response to various stresses, p53 is rapidly activated and transcriptionally regulates a number of target genes by which p53 modulates a variety of cellular activities. The transcriptional activity of p53 is delicately regulated by a plethora of cellular factors, independently or synergistically, in multiple ways in order to achieve a specific response. This article reviewed the role of the basal transcriptional machinery, co-activators, and co-repressors involved in p53-dependent transcription, and the underlying mechanism by which the p53 transcriptional activity is regulated. We also discussed some potentially interesting questions and future directions in the field. J. Cell. Biochem. 97: 448–458, 2006.

Key words: p53; transcription; basal transcriptional machinery; co-activator; co-repressor; post-translational modification

p53 is one of the most important tumor suppressors in the cell and often referred to as "the guardian of the genome" [Kastan et al., 1991; Lane, 1992]. In unstressed cells, p53 is maintained at very low levels. In response to various intracellular and extracellular stresses, such as damages to DNA integrity, hypoxia, and oncoprotein expression, p53 is rapidly stabilized and activated [Vousden, 2002]. The activated p53 mainly functions as a sequence-specific DNA-binding transcription factor to regulate a large number of target genes. These genes mediate cell-cycle arrest, apoptosis, senescence, differentiation, DNA repair, inhibition of angiogenesis and metastasis, and other p53-dependent activities [Harms et al., 2004]. For example, p53 induces G1 arrest by upregulating p21 [el-Deiry et al., 1993], and G2 arrest by upregulating 14-3-3σ, Gadd45, and p21 [Hermeking et al., 1997; Bunz et al., 1998; Wang et al., 1999; Zhan et al., 1999]. p53 induces apoptosis by upregulating several groups of pro-apoptotic genes, such as Bcl-2 family member proteins: Bax, Noxa, and Puma [Miyashita and Reed, 1995; Oda et al., 2000; Nakano and Vousden, 2001; Yu et al., 2001], and death receptors: Fas and DR5 [Owen-Schaub et al., 1995; Wu et al., 1997]. In addition to activate gene expression, p53 is able to repress gene expression. For example, p53 suppresses myc expression to promote G1 arrest [Ho et al., 2005]; cyclin B1 expression to promote G2 arrest [Innocente et al., 1999]; and RECQ4 expression to regulate DNA replication and recombination [Sengupta et al., 2005].

The transcriptional activity of p53 is critical to its function as a tumor suppressor [Vogelstein and Kinzler, 1992]. This is highlighted by the fact that approximately 50% of human cancers contain a mutation in the *p53* gene. Among them, more than 80% are located in the p53 DNA-binding domain (DBD), which abrogates the p53 transcriptional activity [Hainaut et al., 1998]. The p53 protein contains several functional domains: activation domain 1 (AD1) within residues 1–42; activation domain 2 (AD2) within residues 43–91, which includes the proline-rich domain (PRD) within residues 64–91; the sequence-specific DBD within residues 100–300; the nuclear localization signal (NLS) within residues 316–325; the tetramerization domain (TD) within residues 334–356; and the C-terminal basic domain (BD) within residues 364–393 [Harms et al., 2004]. Since p53 is a sequence-specific DNA-binding transcription factor, it has some features common to

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be a transcription factor. To activate downstream target genes, first of all, there must have sufficient p53 being present in the nucleus. p53 DBD then must bind to the specific DNA sequence (p53 responsive element) usually located in the promoters of target genes. Finally, p53 AD must be able to recruit the basal transcriptional machinery, and co-activators or co-repressors to regulate gene expression. If any of the process is affected, the intensity of p53 on the target genes' transcription will be altered, that is, the p53 transcription-dependent functions.

Genomic DNA in eukaryotic cells, when not used for transcription, exists in a highly organized chromatin, which is assembled with nucleosomes [Emerson, 2002]. Each unit of the nucleosome is composed of a histone core of octamer and double-strand DNA wound for approximately 1.7 rounds on the histone core. The octamer histone core consists of two H2A, two H2B, one H3, and one H4. Chromatin is a highly dense structure, in which gene promoters are embedded, being kept from access to the basal transcriptional machinery [Featherstone, 2002]. For transcriptional activation, the chromatin structure must be resolved to be accessible to the transcriptional machinery. The accessibility of promoters is largely controlled by histones, which are often covalently modified in their N-terminal tails. Histone modifications, such as phosphorylation, acetylation, methylation, and ubiquitination, alter the conformation of chromatin, thereby making promoters more or less accessible for transcription [Cheung et al., 2000]. Most histone modifications can be reversed. Thus, transcription undergoes another layer of regulation. Since histone modifications are so versatile, it has been dubbed as "histone code" for transcription [Cheung et al., 2000]. Enzymes that covalently modify the histones are co-activators or co-repressors.

In this article, we first reviewed the role of the basal transcriptional machinery, co-activators, and co-repressors that are involved in p53-dependent transcription. We then summarized how the p53 transcriptional activity is regulated, based on the mechanism by which the regulation works.

BASAL TRANSCRIPTIONAL MACHINERY

RNA polymerase II (Pol II)-dependent transcription starts with TFIID binding to TATA box. TFIIB then comes in, forming a ternary structure with TFIID, which recruits TFIIF, TFIIE, TFIIH, and Pol II to form a preinitiation complex (PIC) [Orphanides et al., 1996; Woychik and Hampsey, 2002]. p53 is able to recruit some components of the basal transcriptional machinery, including TBP, several TBP-associated factors (TAFs: TAFII31, TAFII40, TAFII60), and TFIIH to the promoters of p53 target genes [Ko and Prives, 1996]. Recent data suggest that PICs are composed of different sets of factors, which are recruited by various activators to distinct promoters [Muller and Tora, 2004]. Thus, does p53 recruit the same basal transcriptional machinery to all of the target genes? The answer is apparently No. But what are the specific components of the basal transcriptional machinery recruited by p53 to individual target gene? How this process is regulated? The study by Emerson and co-workers tried to answer these questions [Espinosa et al., 2003]. They found that the p53-dependent transcription appears to be stress and promoter specific. In contrast to the conventional opinion, they showed that some components of the transcription machinery are already loaded on the *p21* promoter before the stress, including TBP, TAFII250, TFIIB, TFIIH, and Pol II [Espinosa et al., 2003]. In unstressed cells, p53, which was assumed to be latent and incapable of binding DNA, bound to the p53 responsive element in the *p21* promoter. After UV irradiation, the level of TAFII250 on the promoter was significantly increased whereas TFIIB, TFIIH, and RNA Pol II level constantly decreased. After doxorubicin treatment, no increase of TAFII250 was detected. Moreover, although the total level of RNA Pol II was significantly dropped, accompanied by a conversion from S5P-CTD to S2P-CTD, the level of TFIIB was substantially increased, instead decreased. The composition and kinetics of the transcriptional machinery on the promoter of *Fas*, a pro-apoptotic target of p53, are quite different from those on the promoter of *p21*. RNA Pol II was not detectable on the *Fas* promoter before UV stress, but it was rapidly accumulated after UV irradiation. Furthermore, the level of TFIIB was not decreased after UV, in contrast to that on the *p21* promoter. All the evidence suggests that the recruitment of the transcriptional machinery by p53 is determined by specific core promoter architectures and specific stress signals [Espinosa et al., 2003].

p53 not only activates PolII-dependent transcription, it also represses PolI- and PolIII-dependent transcription. p53 binds to TAF(I)110 and interferes with the association of SL1 and UBF. Thus, p53 can suppress the formation of the PolI transcriptional machinery on rRNA promoter [Zhai and Comai, 2000]. p53 is able to suppress the expression of 5S RNA, tRNA, and U6 snRNA, which is mediated by p53 binding to TFIIIB, presumably through its known interaction with TBP, a component of TFIIIB [Chesnokov et al., 1996; Cairns and White, 1998; Crighton et al., 2003; Felton-Edkins et al., 2003]. As a result, p53 reduces the occupancy of TFIIIB on these promoters. Hence, interaction with TFIIIB extends p53′s transcriptional activity to Pol III-directed templates [Chesnokov et al., 1996].

CO-ACTIVATORS: HISTONE ACETYLTRANSFERASES

The dense chromatin is a barrier for the basal transcriptional machinery to access promoters. To activate a specific gene expression, p53 interacts with and recruits histone modification enzymes to the promoter, where they modify histones, forcing the promoter into an open and accessible configuration. p300/CBP are histone acetyl transferase (HAT)-containing proteins [Chan and La Thangue, 2001]. Initial evidence for p300 being a p53 co-activator is indirect, as suggested by the finding that the adenoviral protein E1A, a p300-binding protein, represses p53-activated promoters [Steegenga et al., 1996; Somasundaram and El-Deiry, 1997]. Later, it was found that overexpression of p300/CBP bolsters p53 transactivation and p53 directly interacts with p300/CBP [Avantaggiati et al., 1997; Gu and Roeder, 1997; Lill et al., 1997; Scolnick et al., 1997]. As a p53 co-activator, the major role of p300/CBP is to acetylate histones in the vicinity of p53 target promoters [Barlev et al., 2001; Liu et al., 2003]. In addition to p300/CBP, three other proteins hADA3, TRRAP, and Tip60 that are a part of HAT complex, play an important role in regulating the transcriptional activity of p53 through histone acetylation [Wang et al., 2001; Ard et al., 2002; Legube et al., 2004].

CO-ACTIVATORS: HISTONE METHYLTRANSFERASES

The evidence that the p53-dependent transcription is regulated by histone methylation has just emerged. A recent study showed that two methyltransferases, PRMT1 and CARM1, directly interact with p53 and that PRMT1, CARM1, and p300 can modify histones, independently and cooperatively [An et al., 2004]. Interestingly, p300 and PRMT1 increase their respective activities reciprocally. Consistent with their effects on histones, PRMT1 and p300 are able to increase the p53 transcriptional activity synergistically. However, p300 stimulates histone methylation by CARM1 and boosts the effect of CARM1 on p53 activity, but CARM1 is incapable of enhancing histone acetylation by p300. The synergistic and coordinated effects of PRMT1, CARM1, and p300 on p53-dependent transcription are demonstrated using the promoter of the *GADD45* gene as a model. However, we are still far away from understanding how the promoter of histone methylation regulates p53 activity in response to different stresses and whether p53-repressed genes are regulated by histone methylation. In addition, it is expected that other histone methyltransferases will be identified to interact with p53 and potentially regulate p53-dependent transcription.

CO-REPRESSORS: HISTONE DEACETYLASES

Histone acetylation can be reversed by histone deacetylases (HDACs) [de Ruijter et al., 2003]. Thus, HDACs act as p53 co-repressors. p53 recruits HDACs to promoters through interacting with mSin3a, which directly binds to HDACs [Murphy et al., 1999]. Recruitment of HDACs to promoters through mSin3a is one of the major mechanisms by which p53 transcriptionally represses target genes. Suppression of myc, Nanog, and HSP90 beta expression by p53 all requires recruitment of HDAC1 via interaction with mSin3A [Zhang et al., 2004; Ho et al., 2005; Lin et al., 2005]. Moreover, p53 suppresses the expression of genes that do not contain a p53 responsive element in their promoters, such as *Cdc2* and *cyclin B* [Imbriano et al., 2005]. The promoter in these genes contains multiple CCAAT boxes, which are activated by NF-Y. NF-Y associates with p53 in vitro and in vivo. p53 is present on the *cyclin B2* and *Cdc2* promoters in vivo before and after DNA damage, which requires DNA-bound NF-Y [Imbriano et al., 2005]. Following DNA damage, the release of pCAF and p300 from the promoters correlates with the recruitment of HDAC1, followed by HDAC4 and HDAC5,

and promoter repression. HDAC1 recruitment requires intact NF-Y binding sites [Imbriano et al., 2005]. Therefore, p53 recruits HDACs via interaction with other DNA-binding proteins, and thus represses gene expression. However, a tempting question is surfaced here: since histone acetyltransferases and HDACs are ubiquitous in the cell, what determines p53 to selectively recruit histone acetyltransferase or HDACs to a specific target promoter? A recent study may provide a trace of clue [Koumenis et al., 2001], which showed that DNA damage induces the interaction of p53 with the transcriptional co-activator p300, as well as with the transcriptional co-repressor mSin3A. In contrast, hypoxia primarily induces the interaction of p53 with mSin3A, but not with p300. These data suggest that different cellular pools of p53 induced by specific stress signals can modulate transcriptional activity through differential interactions with transcriptional co-activators or co-repressors.

CO-REPRESSORS: UBIQUITIN LIGASES

Histone ubiquitination is able to regulate transcription. Ubiquitination mainly occurs on histone H2A and H2B [Wang et al., 2004]. Earlier studies showed that Rad6 has an E2 ubiquitin conjugase activity, which is critical for H2B ubiquitination and subsequent H3 lysine 4 methylation [Robzyk et al., 2000]. Recently, Bre1, a ring domain-containing protein, was found to interact with Rad6 and functions as an E3 ligase for histone H2B [Wood et al., 2003]. Moreover, an E3 ubiquin ligase complex, termed human Polycomb repressive complex 1-like (hPRC1L), was identified as a H2A ubiquitination ligase, and the monoubiquitination of H2A is responsible for polycomb-mediated repression [Wang et al., 2004]. However, little is known about the regulation of p53-mediated transcription by histone ubiquitination. The pioneer study by Oren's group showed that Mdm2, a p53 E3 ubiquitin ligase, is able to bind to histones H2A and H2B, and promotes their monoubiquitination in vitro [Minsky and Oren, 2004]. In addition, endogenous Mdm2 is tethered, presumably via p53, to the chromatin-containing *p21* promoter in vivo, and Mdm2 overexpression enhances histone ubiquitination in the vicinity of the p53 binding site within the *p21* promoter. Furthermore, the Mdm2 RING domain is required for efficient p53-independent transcriptional repression. The above evidence suggests that ubiquitination of H2A and H2B by Mdm2 may represent another mechanism by which Mdm2 negatively regulates p53 activity [Minsky and Oren, 2004]. However, given that p53 may recruit other not-yet-identified ubiquitin ligases to the target gene promoter, it is likely that in addition to Mdm2, p53 may repress gene expression via these ubiquitin ligases to mono-ubiquitinate histones.

In sum, the ability of p53 to interact with and recruit the basal transcriptional machinery to the promoter is an indispensable step for transcription. Furthermore, p53-mediated histone modifications are a dynamic and cooperative process. It is clear that not all types of modifications are at the disposal of p53 at a given time. But what determines p53 to selectively exploit histone modifications in vivo on a specific promoter is largely unknown. We also have little knowledge about the mutual effects of different histone modifications on p53-dependent transcription. Furthermore, it is not clear whether histone modifications are temporally regulated for p53-dependent transcription. All these questions are definitely worth further investigation.

REGULATION OF THE p53 TRANSCRIPTIONAL ACTIVITY

The p53 activity is largely controlled by the cellular p53 level, its DNA-binding ability, its sub-cellular location, and its recruitment of transcriptional co-activators or co-repressors.

Regulation of the Cellular p53 Level

It has been known for a long time that turnover of p53 is mediated by 26S proteosome in an ubiquitination-dependent manner [Bond et al., 2005]. Mdm2 is one of the first two E3 ubiquitin ligases identified to mediate p53 degradation [Bond et al., 2005]. Mdm2 binds to the p53 N-terminus through a hydrophobic pocket domain in its N-terminus. The minimal binding site in p53 has been mapped within residues 18–26. Residues Leu14, Phe19, Leu22, Trp23, and Leu26 are important to the binding, of which residues Phe19, Trp23, and Leu26 are essential [Moll and Petrenko, 2003]. Once bound to p53, Mdm2 transfers monoubiquitin tags onto lysine residues mainly in the C-terminus of p53. The monoubiquitination is sufficient for p53 nuclear export, but not for p53 degradation by 26S proteosome [Li et al., 2003;

Yang et al., 2004]. Interestingly, p300 plays a critical role in the addition of polyubiquitin chain to p53. In addition to its HAT activity, p300 carries an intrinsic ubiquitin ligase activity [Grossman et al., 2003]. It is unexpected for one protein to have two exactly opposite functions. However, one could imagine that p300 promotes degradation of p53 in unstressed cells or in cells that damage has been repaired. Under these circumstances, cells must keep p53 in tight control or get rid of p53 quickly to restore the normal cell growth. But in response to stresses, cells need a prompt increase in p53 to either arrest cell cycle for DNA repair or induce cell death when damage is irreparable. However, how does p300 switch the function of HAT to the one of ubiquitin ligase is not clear.

Recently, a study showed that p53 ubiquitination is reversible. Herpes virus-associated ubiquitin-specific protease (HAUSP), identified as a novel p53-interacting protein, has an intrinsic enzymatic activity that specifically deubiquitinates p53 both in vitro and in vivo. Thus, HAUSP stabilizes p53 and induces p53-dependent growth suppression [Li et al., 2002]. HAUSP also deubiquitinates Mdm2, leading to Mdm2 stabilization [Li et al., 2004]. However, HAUSP is not induced upon DNA damage. Thus, the overall effect of HAUSP on p53 stabilization is complex and the functional significance of HAUSP-mediated p53 deubiquitination remains to be determined.

Mdm2 is thought to be the major p53 E3 ubiquitin ligase [Bond et al., 2005]. The picture has been changed by identification of several other E3 ligases, including Pirh2, constitutively photomorphogenic 1 (COP1), CHIP (chaperone-associated ubiquitin ligase), topors (human topoisomerase I- and p53-binding protein), and ARF-binding protein (ARF-BP1). These E3 ligases are all able to mediate p53 ubiquitination and degradation [Leng et al., 2003; Dornan et al., 2004; Chen et al., 2005; Esser et al., 2005]. Due to their recent discovery, what regulates the activity of these E3 ligases is largely unknown.

It is evident that more than one E3 ligases mediate p53 degradation, and the number is still counting. An intriguing question arises here: why do the cells employ so many ubiquitin ligases to degrade p53? The answer may lie in that different types of cells may preferentially use one ubiquitin ligase to keep p53 in control; the cell may need different sets of ubiquitin ligases to degrade p53 induced by specific stresses; or the cell simply need more than one set of ubiquitin ligase to be a backup.

The p53–Mdm2 interaction can be disrupted by phosphorylation of p53, especially of the N-terminal serine and threonine residues [Xu, 2003; Bode and Dong, 2004]. Phosphorylation of p53 is assumed to change its conformation, thereby preventing the binding with Mdm2, which consequently promotes p53 accumulation [Xu, 2003; Bode and Dong, 2004]. So far, 17 phosphorylation/dephosphorylation sites in p53 have been identified in human cells following DNA damage, including serines 6, 9, 15, 20, 33, 37, 46, 149, 315, and 392, and Threonines 18, 81, 150, and 155. In addition, Thr55, Ser376, and Ser378 seem to be constitutively phosphorylated in unstressed cells [Xu, 2003; Bode and Dong, 2004]. In addition, certain residues can be phosphorylated by several kinases and some kinases are able to phosphorylate several residues. Furthermore, most of stresses activate more than one kinase, leading to phosphorylation of multiple sites. This is significant since the cell can exploit different kinases in response to a variety of stimuli, which leads to specific responses [Xu, 2003; Bode and Dong, 2004]. The best example of p53 phosphorylation is the one on serines 15 and 20, and threonine 18. In response to DNA damage induced by ionizing radiation (IR) or UV irradiation, S15, S20, and T18 are rapidly phosphorylated by ATM, ATR, Chk1, and Chk2, independently or cooperatively [Canman et al., 1998; Tibbetts et al., 1999; Shieh et al., 2000]. Phosphorylation of S15 and S20 does not affect p53 binding to Mdm2, but phosphorylation of T18 significantly reduces their interaction. This does not mean that the role of S15 and S20 phosphorylation is minimal, since phosphorylation of T18 requires a sequential phosphorylation cascade, which starts from phosphorylation of S15 [Bode and Dong, 2004]. Given that each individual phosphorylation has specific effects on p53–Mdm2 interaction and on other p53 modifications, it is of great interest to see how cells integrate various phosphorylation events by a variety of kinases to tailor a delicate response to diverse stimuli. In addition to the well studied IR-ATM-Chk2-S20 and UV-ATR-Chk1-S15/S20 axes, there are a dozen of phosphorylation cascades catalyzed by specific kinases, which differentially regulates p53 [Bode and Dong, 2004].

Since p53 ubiquitination occurs at its C-terminal lysine residues, any other modifications at these residues could affect the p53–Mdm2 interaction, thereby promoting p53 accumulation. p300/CBP acetylate K372/373/381/382 in p53, which can also be ubiquitinated by Mdm2 [Moll and Petrenko, 2003; Xu, 2003]. Moreover, these lysine residues are acetylated in response to DNA damage in vivo [Sakaguchi et al., 1998; Liu et al., 1999]. Thus, p300/CBP acetylation of p53 contributes to p53 stabilization. Recently, an elegant study provided evidence that p53 is methylated both in vitro and in vivo by a methyl transferase (Set9) and the methylation site is mapped on K372 [Chuikov et al., 2004]. Moreover, endogenous p53 is methylated upon DNA damage and methylation of p53 by Set9 promotes p53 stabilization [Chuikov et al., 2004]. Thus, block of p53 ubiquitination by K372 methylation may also contribute to p53 accumulation. An interesting question here is whether methylation of K372 affects its acetylation upon DNA damage? Although it is suggested that methylation precedes acetylation [Chuikov et al., 2004], how the methyl moiety is removed from K372 before it is acetylated? Does demethylation exist? Since both acetylation and methylation positively regulate p53 activity, why do cells exploit two types of modifications on the same residue? Thus, future studies are needed to probe this. However, while the p53 C-terminus can be post-translationally modified and p53 can be stabilized by p300/CBP or Set9, the physiological effect of the C-terminal modifications on p53 stabilization has been questioned. The study from Xu's group clearly showed that mouse embryonic stem (ES) cells in which missense mutations (lysine to arginine) at the six lysine residues (K6R) in the C-terminus were introduced into the endogenous *p53* gene, have normal p53 stabilization both before and after DNA damage, indicating that ubiquitination of these lysine residues is not required for efficient p53 degradation [Feng et al., 2005]. Hence, the contribution of the C-terminal modifications to p53 stabilization is still a matter of debate.

Regulation of p53 DNA-Binding Ability by Post-translational Modifications

Acetylation. p300/CBP serve as a co-activator for numerous transcriptional factors, including p53, by mediating histone acetylation [Chan and La Thangue, 2001]. Interestingly, Gu and Roeder [1997] found that p300/CBP acetylate the C-terminus of p53, and that acetylated p53 has stronger ability to bind to short oligonuleotides containing p53 responsive elements [Gu and Roeder, 1997; Sakaguchi et al., 1998]. A recent study from Gu's group showed that highly purified acetylated p53 has an enhanced sequence-specific DNA-binding activity on both short oligonucleotide probes and long DNA fragments [Luo et al., 2004]. Moreover, acetylation of endogenous p53 significantly augments its ability to bind to the promoter of an endogenous target gene. These data suggest that p53 conformation is altered by the C-terminal acetylation, leading to the increased DNA-binding activity. However, using an artificial chromatin-containing longer DNA oligonucleotides as binding substrates for p53, Espinosa and Emerson [2001] showed that acetylation of the p53 C-terminus fails to enhance p53 DNA-binding activity. Additionally, an NMR study showed that wild-type p53 and the basic domain deletion mutant share the same overall structure [Ayed et al., 2001]. Furthermore, using ChIP assay, Barlev et al. [2001] showed that wild-type p53 and a mutant in which several acetylation sites were mutated (K320R, K373R, K381R, and K382R) bind similarly to the *p21* promoter. Thus, whether acetylation enhances p53 DNA-binding activity remains uncertain.

Deacetylation. The effect of p53 deacetylation on the p53 DNA-binding ability is indeed contingent on p53 acetylation. Histone deacetylase (HDAC)-1, -2, and -3 are all capable of downregulating p53 transcriptional activity. This effect is dependent on the deacetylase activity of HDACs and the acetylated region in p53 by p300/CBP [Juan et al., 2000]. Co-expression of HDAC1 greatly reduced the in vivo acetylation level of p53 [Juan et al., 2000], but p53 does not directly interact with HDAC1. A later study showed that p53 directly interacts with metastasis-associated protein 2 (MTA2)/PID both in vitro and in vivo, which likely recruits HDAC1 to p53 [Luo et al., 2000]. Indeed, overexpression of MTA2/PID significantly reduced the steady-state levels of acetylated p53. As a result, MTA2/PID overexpression markedly represseed p53-dependent transcriptional activation [Luo et al., 2000]. The NAD-dependent histone deacetylase of Sir2α physically interacts with p53 and

inhibition of Sir2α activity enhances the p53 acetylation levels in vivo [Luo et al., 2001]. Sir2α represses p53-dependent apoptosis in response to DNA damage and oxidative stress whereas expression of a mutant Sir2α increases the sensitivity of cells in the stress response [Luo et al., 2001; Vaziri et al., 2001]. The co-existence of p53 acetylation and deacetylation suggests that p53 is stabilized and activated at least in part by acetylation upon DNA damage and the acetylated p53 is inactivated by deacetylation once DNA damage is repaired. HDACs also mediate histone deacetylation to repress transcription (described above). However, MTA2/PID and Sir2α have not been shown to play a role in histone deacetylation.

Phosphorylation. The effect of p53 phosphorylation on its DNA-binding activity in vivo remains uncertain [Feng et al., 2005]. However, p53 phosphorylation promotes its interaction with Pin1, a member of peptidyl-prolyl isomerase. Once bound, Pin1 generates conformational changes in p53. Consequently, Pin1 stimulates the DNA-binding and transcriptional activity of p53. Stabilization of p53 is also impaired in UV-treated Pin1(−/−) cells owing to its inability to efficiently dissociate from Mdm2 [Zacchi et al., 2002]. These data suggest a novel mechanism by which phosphorylation indirectly regulates the DNA-binding activity of p53 in cellular response to genotoxic stresses.

Sumoylation. Small ubiquitin-like protein, SUMO-1, can be attached to many transcription factors, including p53 [Gostissa et al., 1999; Rodriguez et al., 1999]. This process is termed sumoylation which is similar to ubiquitination [Dohmen, 2004]. The sumoylation-specific E2 is Ubc9 and the sumoylation E3 ligase for p53 is protein inhibitor of activated STAT1 (PIAS-1) [Schmidt and Muller, 2003]. The sumoylation site in p53 has been demonstrated to be K386. Sumoylation stimulates p53 transcriptional activity. However, sumoylation is unable to affect p53 ubiquitination [Gostissa et al., 1999]. Thus, the mechanism by which sumoylation increases p53 activity remains to be determined. Since both sumoylation and acetylation target the p53 C-terminus, it is important to determine whether these two processes affect each other. Moreover, Mdm2 is subject to various regulations, it is reasonable to speculate that the SUMO E3 ligase, PIAS-1, may be regulated by other cellular factors.

Regulation of p53 DNA-Binding Ability by Non-Covalent Modifiers

p53 interacting proteins, which are incapable of covalently modify p53, can regulate the ability of p53 to bind to a specific DNA through various mechanisms. Ref-1, a dual function protein, can regulate the redox state of a number of proteins and function as a DNA repair (A/P) endonuclease [Gaiddon et al., 1999]. It has been shown that Ref-1 stimulates the DNA-binding ability of oxidized forms of full-length p53 and carboxy-terminally truncated p53ΔBD. Moreover, in the presence of a reducing agent, Ref-1 is an extremely potent stimulator of full-length p53 but not p53ΔBD [Gaiddon et al., 1999]. These data indicate that Ref-1 protein stimulates p53 by both redox-dependent and -independent means. This is the first example of non-covalent modifiers of p53. The architectural DNA-binding protein, high mobility group protein B-1 (HMGB-1), belongs to a family of highly conserved chromatin-associated nucleoproteins that bend DNA and facilitate the binding of various transcription factors to their cognate DNA sequences [Jayaraman et al., 1998]. HMGB-1 directly interacts with p53 and is a unique activator of p53. HMGB-1 is able to stimulate both wild-type p53 and p53ΔBD to bind DNA, suggesting that HMGB-1 regulates p53 DNA-binding activity independent of its C-terminus. Additionally, HMGB-1 promotes the assembly of higher order p53 nucleoprotein structures [Jayaraman et al., 1998]. Further evidence showed that HMGB-1 augments p53 binding to the linear DNA but not to the microcircle DNA, suggesting that HMGB-1 functions by providing prebent DNA to p53 [McKinney and Prives, 2002].

p53 can induce cell-cycle arrest and/or apoptosis in response to various stresses. However, what determines p53 to differentially activate downstream targets responsible for these responses is a puzzle [Vousden and Lu, 2002]. One of the theories is that co-factors for p53 determine the specificity of target genes' activation [Coutts and La Thangue, 2005]. For example, the apoptotic-stimulating proteins of p53 (ASPPs) interact with p53 DBD and increase p53 transcriptional activity [Samuels-Lev et al., 2001]. Further evidence showed that ASPP1 and ASPP2 increased the ability of p53 to bind to the promoters of pro-apoptotic genes, such as *bax* and *pig3*, but not to those of *p21* and

Mdm2 [Samuels-Lev et al., 2001]. Nevertheless, how ASPP proteins regulate the selectivity of p53 to these promoters remains to be determined.

Regulation of p53 Localization

The proper localization of p53 is essential for its activation and activity. In unstressed cells, p53 is diffusely distributed in the nucleus and it is believed that a majority of p53 is translocated to nucleus through NLS [Liang and Clarke, 2001]. The nuclear p53 binds to and is ubiquitinated by Mdm2. The ubiquitination of p53 promotes its nuclear export and degradation [Liang and Clarke, 2001]. The production, nuclear translocation and nuclear export, and degradation of p53 are a dynamic process, which is to keep p53 in a low, but not negligible level, in normal cells. Any disturbance of this process alters p53 accumulation. Recently, Parc, a Parkin-like ubiquitin ligase, has been identified to interact with p53 [Nikolaev et al., 2003]. Parc directly interacts with and forms a 1 MDa complex with p53 in the cytoplasm in unstressed cells and thus serves as a cytoplasmic anchor for p53. Additional evidence showed that even in unstressed cells, inactivation of Parc induces nuclear localization of endogenous p53, and activates p53-dependent apoptosis. Overexpression of Parc promotes cytoplasmic sequestration of ectopic p53. More significantly, the Parc protein is highly expressed in the neuroblastoma cell lines, wherein p53 is located in the cytoplasm and these cells are resistant to DNA damage-induced apoptosis [Nikolaev et al., 2003]. The glucocorticoid receptor (GR) is also shown to regulate p53 localization in neuroblastoma cells. Dexamethasone-activated endogenous and exogenous GR inhibit p53-dependent functions. GR forms a complex with p53 in vivo, resulting in cytoplasmic sequestration of both p53 and GR. GR antagonists result in nuclear accumulation of p53 and enhance p53 activity in neuroblastoma cells [Sengupta et al., 2000]. Another regulator of p53 localization is glycogen synthase kinase-3β (GSK-3β), which binds to p53 in the nucleus and enhances the cytoplasmic localization of p53 upon ER stress. This effect is induced by GSK-3β-mediated p53 phosphorylation at S315 and S376 [Qu et al., 2004].

In addition to the shuttle of p53 between nucleus and cytoplasm, p53 can be recruited to a specific nuclear substructure. The promyelocytic leukemia (PML) gene is a tumor suppressor originally identified in acute promyelocytic leukemia patients with a reciprocal t(15;17) chromosomal translocation [Bernardi and Pandolfi, 2003]. PML is an essential component of nuclear substructures, termed nuclear bodies (PML-NBs), which act as a "molecule depot" and regulate many nuclear processes [Coutts and La Thangue, 2005]. PML-NBs also serve as sites where nuclear proteins, including p53, are post-translationally modified [Bernardi and Pandolfi, 2003]. Indeed, upon DNA damage, PML recruits p53 and CBP to PML-NBs, where PML promotes p53 acetylation by CBP, and thus increases p53 transcriptional activity [Guo et al., 2000; Boisvert et al., 2001]. Within PML-NBs where HIPK2 phosphorylates S46 in p53, HIPK2 co-localizes and interacts with p53 and CBP. Moreover, S46 phosphorylation promotes K382 acetylation in p53 [D'Orazi et al., 2002; Hofmann et al., 2002]. Thus, PML promotes p53 acetylation in multiple ways. In addition to regulate p53 acetylation, PML stimulates phosphorylation of p53 S20 in PML-NBs and promotes p53 stabilization [Louria-Hayon et al., 2003]. Furthermore, PML is able to sequester Mdm2 into the nucleolus, leading to p53 accumulation [Bernardi et al., 2004].

CONCLUSION REMARKS

In response to various stresses, p53 differentially regulates target genes' expression; thereby p53 is able to regulate a variety of cellular activities. It has been well accepted that a specific stress activates a distinct pool of p53, which may regulate a subset of p53 target genes. Furthermore, every single stress could exploit multiple pathways to regulate the transcriptional activity of p53 to achieve a delicate functional outcome. However, it is the biggest challenge for us to face up with is to understand how these regulators of p53 are dynamically integrated.

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