available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Wild-type p53 in cancer cells: When a guardian turns into a blackguard

Ella Kim [a,*], *Alf Giese* [a], *Wolfgang Deppert* [b,**]

[a] *The Translational Neurooncology Research Group, Department of Neurosurgery, Georg-August-University of Göttingen, Robert-Koch-Strasse 40, 37074 Göttingen, Germany*

[b] *Heinrich-Pette-Institute for Experimental Virology and Immunology, Martinistrasse 52, 20251 Hamburg, Germany*

ARTICLE INFO

Keywords:
Wild-type p53
Cancer
Growth arrest
Apoptosis
Repair

ABSTRACT

The tumor suppressor p53 controls a broad range of cellular responses. Induction of a transient (cell cycle arrest) or a permanent (senescence) block of cell proliferation, or the activation of cell death pathways in response to genotoxic stress comprise the major arms of the survival-death axis governed by p53. Due to these biological properties, inactivation of p53 is a crucial step in tumor development and progression, reflected by the high incidence of *TP53* mutations in different types of human cancers. The remarkable potency of p53 in suppressing tumorigenic outgrowth has promoted the expectation that tumor cells expressing wild-type p53 (wtp53) should be more prone to elimination by cytotoxic treatments than tumor cells expressing mutant p53 (mutp53) with defunct wtp53 activities. However, recent findings yielded somewhat unexpected insights concerning the preponderance of the survival-promoting effects of wtp53 in cancer cells, a rather undesired property from the therapeutic point of view. In this commentary we will discuss the possibility that the developmentally established distinct patterns of wtp53 mediated responses in different tissues are an important factor in determining the ultimate outcome of cellular responses mediated by wtp53 in different types of tumor cells, with a particular focus on the divergent impact of wtp53 in malignant tumors of the central nervous system. We infer that a selective gain of pro-survival functions of wtp53 in cancer cells will confer a survival advantage that counteracts tumor therapy.

1. Functional diversification of wtp53 and cell specification

The remarkable functional dichotomy of wtp53, which can either promote cell survival or commit cells to a suicidal path, has been recognized since a long time and is manifested both during normal development and in the response of different types of embryonic and homeostatic tissues to DNA damage [1–3]. The palette of survival-promoting activities of wtp53 is much broader than previously thought, covering a broad range

* *Corresponding author*. Tel.: +49 551 39 22804; fax: +49 551 39 8794.
** *Corresponding author*. Tel.: +49 40 48051 261; fax: +49 40 48051 117.
E-mail addresses: ella.kim@med.uni-goettingen.de (E. Kim), alf.giese@med.uni-goettingen.de (A. Giese), wolfgang.deppert@hpi.uni-hamburg.de (W. Deppert).

Abbreviations: wtp53, wild-type p53; mutp53, mutant p53; CNS, central nervous system; BTISC, brain tumor initiating stem-like cells; GBM, glioblastoma multiforme; ClQ, chloroquine.

0006-2952/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2008.08.030

of cellular responses including regulation of the cell cycle, facilitation of DNA repair pathways by both transcriptional and non-transcriptional mechanisms, maintenance of low levels of reactive oxygen species, and a direct activation of genes with anti-apoptotic activities. A schematic diagram of p53's diverse roles as "guardian of the genome" is shown in Fig. 1. An overview of the complex network of pro-survival and apoptotic responses mediated by wtp53, and of their underlying mechanisms can be found in recent reviews [4–6]. In this commentary we will discuss the possibility that pro-survival functions of wtp53 in some types of cancer cells may contribute to their overall survival potential and thus counteract cytotoxic effects of tumor therapies targeting DNA damage pathways.

The spatio-temporal diversification of wtp53 functions during development is determined both at the level of p53 expression [7,8,1] and of modulation of p53 transcriptional activity, primarily through the Mdm2 inhibitory feedback loop [9,10]. Studies with mice carrying a hypomorphic allele of *mdm2* have been instrumental in revealing that p53 responses undergo a diversification during development, resulting in distinct effects in different tissues expressing comparable levels of wtp53: while triggering a strong apoptotic response in epithelial cells of the small intestine and in cells of the hematopoietic lineage even in the absence of DNA damage, a merely elevated wtp53 level does not lead to apoptosis in other tissues [11,12]. Studies with $p53^{515C/515C}Mdm^{-/-}$ mice expressing the transcriptionally active mutant $p53^{R172P}$ in an *mdm2*-null background revealed that the proliferation inhibiting function of p53 is also influenced by the cellular context [13]. The $p53^{R172P}$ protein is deficient for apoptosis-inducing functions, but has retained the ability to inhibit proliferation [13]. A tissue-comparative assessment of the expression of p21, a canonical transcriptional target of p53 that induces cell cycle arrest, revealed that responsiveness of the *p21* promoter to $p53^{R172P}$ varies among different tissues: whereas $p53^{R172P}$ activated *p21* in the bone marrow and in the proliferating compartment of the developing brain, *p21* was not induced in proliferating epithelial cells of the skin and dental epithelium [13]. Assuming that the tissue-specific transcriptional pattern of the $p53^{R172P}$ mutant reflects that of wtp53, these findings indicate that in different tissues the transcriptional potential of p53 might not be implemented uniformly, thereby establishing a framework for the functional diversification of p53 responses.

The inherent functional dichotomy of wtp53 is also manifested in distinct cell types within a given tissue. The different impact of p53 on different cell types of the central nervous system (CNS) constitutes a prominent example. p53 is a major regulator of developmental and DNA damage-induced apoptosis during embryogenesis [14,15,1,2]. In the developing CNS, p53-dependent apoptosis plays an essential role in the death response to genotoxic and non-genotoxic insults in neural precursor cells [16,17]. In the adult brain, p53 expression is confined to the neurogenic niche in the lateral ventricle, where p53 controls self-renewal of adult neural stem cells

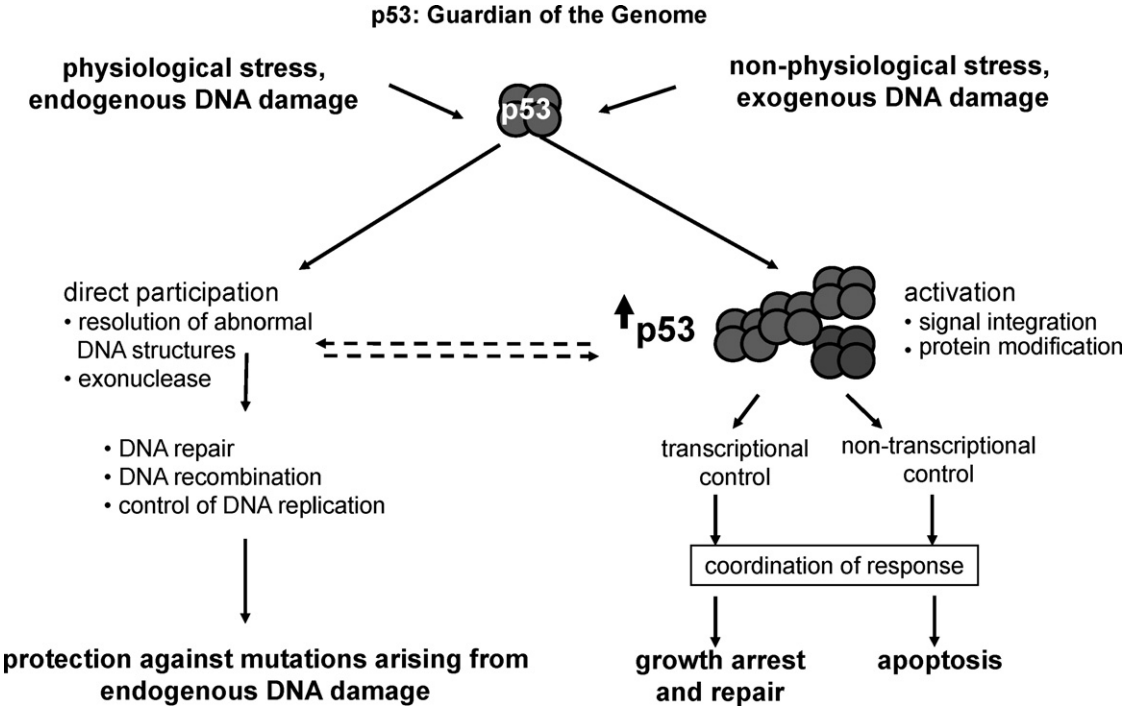

Fig. 1 – Diverse roles of p53 in its function as "guardian of the genome". p53 protects the genome under physiological and non-physiological stress conditions. Depending on stress levels, p53 will accumulate to different levels. p53 can directly participate in repair processes by binding to DNA and resolving abnormal DNA structures, by its exonuclease activity, or induce a transcriptional response by activating p53 target gene expression. In addition, p53 is able to mediate non-transcriptional responses, e.g. apoptosis induction via direct activation of the mitochondrial apoptosis pathway. Various activities of p53 might be performed simultaneously, as p53 exists in various subpopulations, which might perform different functions.

[18,19]. Loss of p53 leads to the expansion of the stem cell/progenitor compartment and, interestingly, an increase of compensatory apoptosis by p53-independent mechanisms [19]. The findings suggest that in the absence of DNA damage, suppression of proliferation is the prevailing function of p53 in the neurogenic compartment of the adult brain. Concordant with such an interpretation, constitutive expression of the transcriptionally active mutp53^{R172P} prevents expansion of the progenitor pool [13]. Whereas the role of p53 as a major mediator of DNA damage-induced apoptosis in embryonic neural progenitor cells has been well characterized, the precise impact of p53 in the DNA damage response of adult neural precursors is largely unknown. Further prompting the necessity to clarify the role of wtp53 in adult neural progenitors, recent findings indicate that adult neural stem cells or precursors may be the cells of origin of brain neoplasias, and the major determinants of radio- and chemo-resistance in malignant brain tumors [20–23]. A subpopulation of cancer cells possessing fundamental properties of neural stem cells, generally termed brain tumor initiating stem-like cells (BTISC), has been identified in different types of malignant brain tumors. In contrast to the cells comprising the bulk of the tumor, BTISC proliferate slowly, but possess a virtually unlimited self-renewal potential, an ability to divide both symmetrically and asymmetrically, and a high migratory potential. Intriguingly, DNA repair response is extraordinarily effective in BTISC, explaining their ability to survive radio- and chemotherapeutic treatments that cause physical damage in DNA [23].

The importance of DNA repair for the survival of BTISC necessitates a proper or augmented function of cellular pathways involved in the regulation of DNA repair. Owing to its functions in DNA repair and cell cycle regulation, wtp53 would be an ideal candidate for such a ''guardian'' function in cancer cells, provided that its apoptotic activities were ablated. Such an ablation could be achieved more easily or might even be unnecessary in cancer cells in which the apoptotic arm of the p53 pathway already became inhibited during the process of cell specification. In contrast, a global inactivation of p53 by mutation would be required in cancer cells originating from cell types in which, according to their specification program, the apoptotic arm of the p53 pathway is constitutively operational. Thus, a preponderance of functions related to DNA repair and cell cycle regulation might provide a survival advantage to some types of cancer cells with wtp53. This would explain why re-introduction of exogenous wtp53 leads to distinctly different outcomes in different types of cancer cells, and how the presence of wtp53 may confer, paradoxically, radio- and chemo-resistance in some types of cancer cells (discussed below).

2. Wtp53 in cancer cells: a guardian of the cancer genome?

The realization that survival-promoting activities mediated by wtp53 are abundant and under certain circumstances even dominant over the apoptosis-inducing potency of wtp53 calls for a reconsideration of the notion that a wtp53 status is a decisive or predictive factor for the potential of tumor cells to die after radio- or chemotherapy [4–6]. Furthermore, *TP53* mutations are rare in certain human cancer entities, supporting the notion that wtp53 activity may not always be a beneficial factor in preventing tumor progression. In this regard, the etiology of glioblastoma multiforme (GBM), the most frequently occurring and the most malignant form of brain cancers in adults, is an interesting example. Two major types of GBMs can be distinguished by clinical, histopathologic, molecular and etiological criteria [24]. Primary GBMs are the most frequently occurring and most aggressive form of GBMs. They arise without preceding lesions and are characterized by the least favorable clinical prognosis. Secondary GBMs exhibit growth patterns consistent with the gradual transition from low to higher malignant forms and have better survival prognoses. Primary and secondary GBMs represent distinct tumor entities and show distinct molecular signatures. Most importantly for this discussion, *TP53* mutations show different representation patterns: *TP53* mutations are often found in secondary GBM (65%), but are considerably less frequent in primary GBM, comprising less than 30% of the cases [25,26]. The relatively low percentage of *TP53* mutations has been explained by alternative mechanisms operating in primary GBM to ablate p53 function. Indeed, *mdm2* amplifications and mutations in genes encoding p53 regulators such as PTEN and p16^{INK4a} are frequently found in primary GBM. Intriguingly, glioma cells with an intact *TP53* gene show a selective impairment of the apoptotic functions of wtp53, while retaining the potential to mediate p53 responses relevant for DNA repair and control of cell cycle [27]. Though the molecular mechanism utilized in glioma cells to diminish the apoptosis-promoting activities of wtp53 remain to be elucidated, the poor responsiveness of apoptotic genes to p53 in conjunction with an elevated expression of anti-apoptotic members of the BCL-2 family seem to constitute some of the underlying principles (rev. in [28]). The data suggest that an at least partial maintenance of the pro-survival activities of wtp53 might be an important factor contributing to the overall survival potential of these cells. Concordant with this notion, glioma cells with wtp53 exhibit a higher resistance to cytotoxic treatments used in clinical practice compared to glioma cells with transcriptionally inactive mutp53 [29–31]. An adverse outcome mediated by wtp53 has also been noticed comparing the effects exerted by recombinant wtp53 exogenously introduced into glioma cells expressing endogenous wtp53 or mutp53, respectively. Surprisingly, induction of apoptosis by exogenously introduced wtp53 is more efficient in glioma cells expressing mutp53 than in glioma cells expressing wtp53 [32–34]. Furthermore, inhibition of endogenous wtp53 augmented apoptosis in glioma cells in response to temozolomide and the chloroethylating nitrosoureas ACNU and BCNU [31], indicating that wtp53 exerts cytoprotective effects and may thus contribute to the notorious chemo-resistance of gliomas. Both, temozolomide and chloroethylating agents induce double-strand breaks (DSB). It has been shown that DSB, while being efficiently removed in glioma cells with wtp53, continuously accumulate in glioma cells with transcriptionally inactive mutp53, eventually leading to the activation of p53-independent intrinsic apoptotic pathways [31]. It thus appears that wtp53 activities associated with DNA repair contribute to the overall survival potential and drug resistance

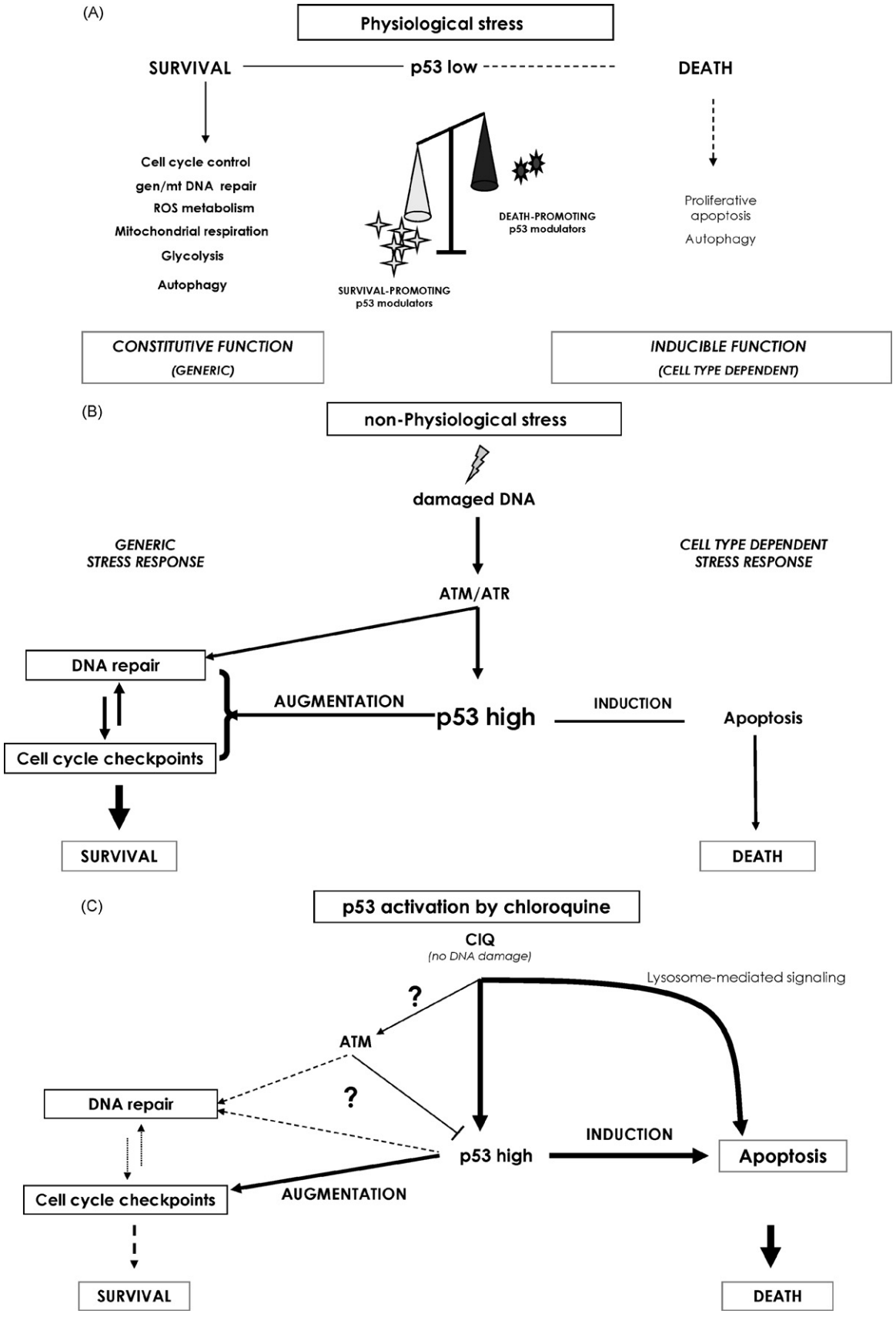

Fig. 2 – Functional dichotomy of wt p53 in normal and cancer cells. Low levels of p53 are sufficient to support the "housekeeping" functions of wt p53 in monitoring DNA and cellular metabolism under physiological conditions (depicted in A). The apoptosis-inducing potential of wt p53 is not implemented ubiquitously and requires a higher dose of the p53 protein

of glioma cells. Supporting the notion, there is evidence that chemo-resistance mediated by wtp53 in gliomas relies at least in part on the ability of wtp53 to activate transcription of DNA repair genes [31], and of genes whose products directly contribute to drug resistance of gliomas such as *MGMT* (O^6-methylguanine-DNA methyltransferase), an enzyme, which removes methyl and chloroethyl groups from the O^6-position of guanine [35,36]. By keeping in mind that temozolomide and the chloroethylating agents comprise the first line adjuvant chemotherapy currently used for glioma treatment, the somewhat paradoxical roles of wtp53 as a survival-promoting factor in malignant brain cells warrant further investigations of the relationship between wtp53 activities and the effects of genotoxic treatments in different types of cancer cells. Underscoring the importance of this notion, a contribution of wtp53 to the survival of tumor cells after radiation, the most common treatment for different kinds of cancer, has also been reported [37–39]. In this regard, the impact of pro-survival activities of wtp53 in progression of hematological malignancies presenting a relatively low frequency of *TP53* mutations (rev. in [40]) may provide further important insights. Interestingly, we found that radio-resistance and recurrence of secondary and tertiary lymphatic tumors do not correlate with a strongly increased frequency of p53 mutations in an experimental leukemia mouse model [41].

The adverse effects of wtp53 on drug resistance and the survival potential seen in different types of cancer cells raise a number of fundamental questions:

- Is the diversification of wtp53 activities manifested in different types of cancer cells an acquired property (re)gained during the course of tumor cell evolution, or a manifestation of the predetermined developmental pattern in different types of homeostatic tissues or in distinct cell types within the tissue?
- At which stage of tumor development (establishment, expansion or recurrence) is the impact of survival-promoting activities of wtp53 most pronounced?
- Is it possible to selectively activate the apoptotic shoulder of the wtp53 pathway by bypassing the survival-promoting responses mediated by wtp53?
- What is the molecular basis of the apparent functional diversification of wtp53 activities in cancer cells?

3. Spatio-temporal diversification of p53 functions: a matter of balance

As guardian of the genome, wtp53 prevents the accumulation and further propagation of non-programmed alterations in the genomic DNA. The mechanisms utilized by wtp53 to maintain genomic integrity are versatile and include control of cell cycle progression, DNA repair [42,43], and centrosome duplication [44]. The underlying molecular mechanisms include the direct recognition and binding of wtp53 to DNA lesions [45,46] and recombinogenic DNA structures [47,48], the catalytic augmentation of DNA repair activities, as well as the transcriptional activation of DNA repair factors and of cell cycle regulators [42]. The mechanisms underlying wtp53 functions in induction of apoptosis are also versatile and include transcriptional regulation of apoptosis-related genes, or transcription-independent actions of wtp53 at the mitochondria [49]. The multitude of factors influencing p53 conformation, its subcellular distribution, and its DNA binding and transcriptional activity contribute to the dynamic balance between survival-promoting and death-inducing activities of wtp53 [4].

The mechanism utilized in sensory neurons exemplifies how the p53 transcriptional program can be modulated coordinately with a specific function of a given cell type. The transcription factor Brn-3a is expressed during late embryogenesis and required for survival of sensory neurons [50]. The survival-promoting effects of Brn-3a are in part due to its ability to interfere with the ability of p53 to activate transcription of apoptosis-inducing genes, but not of those involved in inhibition of proliferation [51,52]. Another example is the regulatory feedback loop formed by the transcription factor SLUG, which regulates survival in hematopoietic progenitors, and PUMA, a potent mediator of p53-dependent apoptosis [53]. SLUG is a highly conserved zinc finger transcriptional repressor, which inhibits transcription of PUMA [54]. Intriguingly, SLUG and PUMA are both activated by wtp53 apparently via the same mechanism that relies on the sequence-specific binding of p53 to their promoters [53,54]. Likewise, another pair of functionally antagonistic genes, p21 and the p21 ubiquitine ligase p53RFP can be activated via sequence-specific DNA binding by wtp53 [55]. Activation of p53RFP by wtp53 impairs the cells' ability for cell cycle arrest in

to be realized. Furthermore, the death-inducing potency of p53 may also require additional factors such as certain post-translational modifications of p53 [97–100], or, depending on cell type, the presence of cellular factors that influence (facilitate or interfere with) the apoptosis inducing potential of p53 [101,102]. For example, p53 isoforms comprise a distinct group of modulators that are structurally similar to p53 but exert dissimilar or even antagonistic functions. Under acute genotoxic stress that causes damage in genomic or mitochondrial DNA the generic functions of wt p53 as a survival-promoting factor will inevitably be augmented, whereas the apoptosis-inducing activities may or may not be induced, depending on the cellular context (depicted in B). The scenarios depicted in A and B are applicable to cellular responses mediated by wt p53 in different types of cancer cells. (C) Dissociation between the ATM- and the p53-activating effects of chloroquine. In contrast to agents that cause DNA damage and induce p53 activation via the ATM-dependent pathway, chloroquine-induced activation of p53 is independent on ATM. Although the ATM kinase undergoes autophosphorylation in response to chloroquine [87], this signal is not always transmitted to p53. p53 activation by chloroquine may thus occur independently from ATM [85,86]. The efficacy of chloroquine in activating the apoptotic shoulder of p53 responses may be due to uncoupling of DNA repair and p53 stabilization. In conjunction with the ability of chloroquine to induce apoptosis via the lysosome-mediated pathway, the p53-activating effects of chloroquine render this agent a promising candidate for cancer treatment.

response to DNA damage and triggers apoptosis [56]. The p21-p53RFP feedback loop thus seems to counterbalance the anti-apoptotic activities of p21, as p21 is ubiquitilated by p53RFP for proteasomal degradation [55].

The ability of wtp53 to activate functionally antagonistic pairs such as SLUG-PUMA and p21-p53RFP represents a clear example of how the functional dichotomy of cellular responses to wtp53 activation can be realized through the regulation of transcription. The key to understanding the functional diversification of wtp53 activities in different types of normal and neoplastic cells therefore is to find out how *selectivity* of target gene transactivation by wtp53 is achieved. Recent advances in the characterization of the p53 transcriptome, coupled with the assessments of p53 DNA binding on the whole genome scale, revealed that more than 500 genes may be regulated by wtp53 at the transcriptional level [57]. Notably, some of the p53 target genes were consistently identified under various conditions used to activate the transcriptional response of p53, while many others showed oscillating patterns of responsiveness to wtp53. The genes that regulate cell cycle and DNA repair were seen most invariantly under various conditions suggesting that pro-survival functions of wtp53 may be more conserved than those related to induction of apoptosis (Fig. 2A). Consistent with this notion, recent interspecies sequence comparison of p53 response elements (p53-REs) revealed that p53-REs from p53 target genes related to cell cycle control appear to be conserved most among species [58,59,7]. These studies not only revealed the truly global impact of wtp53 on the cellular transcriptome, but also further strengthened the notion that the ability of wtp53 to mediate functionally distinct outcomes requires that it regulates transcription in a target gene-selective mode. Several mechanisms to explain how target gene selectivity of transcriptional control mediated by wtp53 may be achieved have been proposed: a varying affinity of wtp53 to distinct promoters, the impact of cell type specific factors influencing the responsiveness of some but not all p53-regulated promoters to p53, function-specific post-translational modifications of p53, and the impact of dynamic changes of DNA and chromatin structure within individual p53-regulated promoters [4,60].

p53 response elements (p53-REs) identified in most wtp53 regulated genes exhibit significant heterogeneity with respect to both their sequence context and architecture [61]. It has been proposed that the responsiveness of different genes to wtp53 reflects the varying binding affinity of the DNA binding core domain of wtp53 to individual p53 response elements. Indeed, binding affinities of wtp53 to p53-REs from apoptotic genes are generally lower than those to p53-REs from genes with functions in DNA repair or cell cycle control [62]. An important biological implication derived from the analysis of the p53-DNA interface is that the prevalence of pro-survival functions of wtp53 might be pre-determined by the inherent differences in p53 binding affinities to anti-apoptotic and pro-apoptotic p53-REs, and that the generally low propensity of wtp53 to activate apoptotic genes may require additional factors to reach levels sufficient to induce apoptosis. Indeed, the apoptotic response mediated by p53 through transcriptional activation can be facilitated by the interaction with p53-binding proteins that enhance p53 binding to p53-REs to promoters of apoptosis-inducing genes [4].

4. The roles of p53 splice variants in functional diversification of p53

A novel layer of complexity arises from the discovery of p53 isoforms, produced by alternative splicing, that recently have emerged as important components of the p53 regulatory network [63,64]. It appears that such isoforms may influence the balance between survival-promoting and apoptosis-inducing activities of p53. Whereas the roles of splice variants of mouse p53 have been characterized in detail [65–67], the significance of alternative splicing for the functions of human p53 had remained obscure until recently, when several isoforms of human p53 produced by alternative splicing were identified in normal and transformed cells. From the nine splice variants of human p53 identified so far, eight are identical in their central part but differ from p53 and amongst themselves in their N- and C-termini [64]. Reflecting the difference both in the overall structure and composition of individual domains, p53 isoforms are functionally distinct from p53 and amongst each other, but exhibit as a common feature an impaired potential to activate transcription of p53 target genes. [68,63]. However, at least some p53 splice isoforms appear to play an important role in modulating the transcriptional activity of p53 both in a negative and a positive mode. The N-terminally truncated isoform p47 seems to act as a generic negative regulator of p53-dependent transcription by counteracting the transcriptional activity of p53 through the formation of transcriptionally inactive p53:p47 hetero-oligomers, and by affecting the subcellular localization of p53 [63]. The delta p53 (Δp53) isoform has a truncated central DNA binding domain (DBD) and exhibits an altered DNA binding specificity towards different p53-REs. Interestingly, while being capable of binding and activating transcription of p53 target genes with functions in cell cycle regulation, the Δp53 isoform does not bind p53-REs of apoptotic genes [69]. The C-terminally truncated isoform p53β lacks a substantial portion of the oligomerization domain and possesses a unique C-terminal domain lacking any homology to the C-terminus of p53 (p53-CTD) [68]. The recent characterization of p53β yielded some surprising results: it appears that the transcription- and oligomerization-deficient p53β not only can associate with some p53-regulated promoters in chromatin, but also that p53β seems to modulate the transcriptional activity of p53 in a promoter-selective manner [70]. How p53β is able to associate with some promoters is unclear. According to the current view of transcriptional regulation by wtp53, its potential to assemble into homotetramers and the presence of an intact p53-CTD are major pre-requisites for the sequence-specific DNA binding and the transcriptional activity of wtp53 [71,72]. According to the different properties of p53β, it is likely that p53β is tethered to DNA indirectly via the interaction with other DNA binding proteins whose identity still has to be established. The data suggest that the picture of the p53-DNA interface is still far from being complete and that some of the views on transcriptional control mediated by p53 may have to be revisited.

Although the roles of individual p53 isoforms are far from clear, their sole existence has important implications for further understanding the mechanisms underlying the func-

tional diversity of cellular responses mediated by p53, and will possibly change some of the previous conclusions that were based on the assumption that p53 is the only protein of its kind expressed in human cells. In this regard, it should be noted that different p53 isoforms exhibit cell type-dependent expression patterns that do not parallel the expression patterns of p53. Thus, the inherent functional duality of p53 may be modulated by its splice variants in a cell type-specific and spatio-temporal manner, with the ultimate outcome depending on the tissue-specific representation of individual isoforms. The existence of a family of p53 proteins that are structurally similar but functionally distinct calls for re-investigating some of the phenomena that previously have been ascribed solely to p53. Particularly, the possibility exists that not all of the about 600 sites identified as p53 binding sites in the human genome [57] are ''pure'' p53 binding sites, but may actually correspond to sites bound by a p53 isoforms. In this regard, it should be mentioned that antibodies commonly used to precipitate p53-bound chromatin or proteins will not only bind p53, but also some p53 isoforms.

5. p53-dependent apoptosis versus p53-mediated DNA repair: *killing without (DNA) break*

Augmentation of DNA repair and control of cellular metabolism are important constituents of p53's functions in promoting an error-free survival of non-transformed cells (Fig. 2A). The switch to apoptosis inducing functions of wtp53 occurs when irreparable damage or structural aberrations in the genome cannot be fixed (Fig. 2A). Indeed, p53-dependent apoptosis is the major cause of embryonic lethality associated with deficiency of XRCC4 and DNA ligase IV, which are involved in non-homologous end-joining of DNA, DSB repair, and V(D)J recombination during embryogenesis [73,74]. Although this mechanism is also operational in cancer cells, the threshold level of irreparable DNA damage that is sufficient to activate the apoptotic shoulder of the wtp53 response may be different in normal and in cancer cells. The prevalence of wtp53 activities in DNA repair and cell cycle regulation over its potential to induce apoptosis in some types of cancer cells may create a situation, where activation of wtp53 might promote cell survival instead of triggering apoptosis. Such a situation is depicted in Fig. 2B. Thus, bypassing the DNA damage response may be required for efficient activation of the apoptotic shoulder of the p53 response in cancer cells. Indeed, strategies exploiting the possibility of activating wtp53-dependent apoptosis by non-(DNA) damaging agents yielded promising results. The efficient apoptotic killing of tumor cells through re-introduction of high levels of recombinant wtp53 [75,76], through inhibition of Mdm2 [77], through pharmacological (re)activation of the transcriptional activity of p53 by some DNA intercalating agents [78,79], or even by restoring wtp53 activity to mutp53 [80], has been reported. The various aspects related to the restoration of p53 functions in cancer cells as a therapeutic strategy have been extensively addressed in recent reviews [81,82,76,83,84]. Here we would like to briefly discuss cytotoxic effects that involve activation of the p53 pathway in the absence of DNA damage.

Some DNA intercalating agents that do not cause DNA damage are capable of activating wtp53 transcription in cancer cells, such as ellipticine [78], acridine derivatives [79], or quinolines [85,86]. The emerging complex picture of p53 activation by chloroquine is an interesting example. The first hint that chloroquine may activate p53 response came from the finding that chloroquine induces autophosphorylation of the ATM kinase [87] acting upstream from p53 in the DNA damage-inducible signaling cascade (Fig. 2B and C). However, detailed investigations revealed that the chloroquine (ClQ)-dependent activation of the transcriptional activity of p53 is ATM-independent [86] and that activation of p53 by ClQ or the related compound quinacrine does not involve ATM-dependent phosphorylation of p53 [86,85], our own unpublished observations). It thus appears that activation of ATM by chloroquine or other quinoline-based drugs and induction of the apoptotic shoulder of the p53 response might be unrelated phenomena. ATM-independent activation of the p53 apoptotic response by quinolines suggests that the functional diversification of p53 may be achieved by uncoupling p53 signaling from the DNA repair response [87,86]. In this regard, it may be worthwhile to revisit earlier studies showing that chloroquine may actually inhibit DNA repair [88]. The overall efficacy of chloroquine in killing tumor cells is likely to be the result of several pathways (Fig. 2C). Indeed, the death paths activated by quinolines appear versatile and include activation of p53 via inhibition of NF-κB [85], apoptosis induction via the lysosome-mediated inhibition of autophagy [89,90], and also direct effects on DNA binding of p53 induced by intercalation of quinolines into DNA (own unpublished data). It should be noted that the outcome of p53 activation by ClQ might differ in different types of cells. While effectively inducing apoptosis in neurons [91], in peripheral blood lymphocytes [92] and in malignant cells derived from renal [85], lung [93], mammary [94] and brain (own unpublished observations) cancers, ClQ was shown to activate predominantly a p53-dependent proliferative block via cell cycle arrest in breast epithelial cells [95]. The notoriously versatile mode of action of quinolines in targeting not just one but multiple cellular pathways may be an important feature that renders these agents effective in killing cancer cells. Importantly, in contrast to many p53-activating drugs, anti-malarials have a long history of a clinically safe use in non-cancer therapy and might be relatively non-hazardous for normal cells [96]. Induction of the p53 response in the absence of DNA damage may thus be efficient in triggering a death response in tumor cells while allowing to by-pass activation of the survival-promoting path regulated by p53.

6. Conclusion

Functional duality is an essential feature of the tumor suppressor function of p53. A fine-tuned balance between survival-promoting and death-inducing activities of wtp53 is controlled in a spatio-temporal mode both during development and in normal homeostatic tissues. In contrast to the global inactivation of p53 functions by mutations, which abolish both the survival-promoting and death-inducing functions of p53 universally in different types of tumor cells, a selective impairment of death-inducing activities of wtp53

without the loss of p53 activities associated with DNA repair and cell survival in certain types of tumor cells and/or in distinct cell sub-populations within the same type of tumor tissue will provide a survival advantage. Consequently, the expression of wtp53 may not always serve as a predictive marker for a better response to cytotoxic treatments at least in some types of tumors. The potential to induce the apoptotic shoulder of the p53 response rather than induction of p53 activities associated with DNA repair and cell cycle regulation might thus be a relevant measure of the therapeutic benefit of cytotoxic agents targeting p53. The effects of wtp53 in tumor cells clearly vary dependent on the tissue origin of the cells and the cell type. A prevalence of apoptosis-inducing activities of p53 in response to stress may therefore be expected in those tumor cells derived from the apoptosis-prone cell types whose propensity to self-terminate is essential for their normal function under physiological conditions. However, in many solid tumors, the p53 response seems to be further shifted towards its pro-survival activities.

Acknowledgments

We apologize to our many colleagues, whose excellent work we were unable to cite due to space limitations. Experiments performed in the laboratories of the authors were supported by grants from the Deutsche Krebshilfe (A.G. and W.D.), the Fonds der Chemischen Industrie (WD), and by EC FP6 funding (WD). The publication reflects only the authors' views and the *Community* is not liable for any use that may be made of the information contained therein. The Heinrich-Pette-Institut is financially supported by the Freie und Hansestadt Hamburg and the Bundesministerium für Gesundheit.

REFERENCES

[1] Komarova EA, Chernov MV, Franks R, Wang KH, Armin G, Zelnick CR, et al. Transgenic mice with p53-responsive lacZ: P53 activity varies dramatically during normal development and determines radiation and drug sensitivity in vivo. EMBO J 1997;16:1391–400.
[2] Frenkel J, Sherman D, Fein A, Schwartz D, Almog N, Kapon A, et al. Accentuated apoptosis in normally developing p53 knockout mouse embryos following genotoxic stress. Oncogene 1999;18:2901–7.
[3] Komarova EA, Gudkov AV. Suppression of p53: a new approach to overcome side effects of antitumor therapy. Biochemistry (Mosc) 2000;65:41–8.
[4] Vousden KH. Outcomes of p53 activation—spoilt for choice. J Cell Sci 2006;119:5015–20.
[5] Bensaad K, Vousden KH. p53: new roles in metabolism. Trends Cell Biol 2007;17:286–91.
[6] Janicke RU, Sohn D, Schulze-Osthoff K. The dark side of a tumor suppressor: anti-apoptotic p53. Cell Death Differ 2008;15:959–76.
[7] Rogel A, Popliker M, Webb CG, Oren M. p53 cellular tumor antigen: analysis of mRNA levels in normal adult tissues, embryos, and tumors. Mol Cell Biol 1985;5:2851–5.
[8] Schmid P, Lorenz A, Hameister H, Montenarh M. Expression of p53 during mouse embryogenesis. Development 1991;113:857–65.
[9] Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature 2000;408:307–10.
[10] Toledo F, Wahl GM. Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. Nat Rev Cancer 2006;6:909–23.
[11] Mendrysa SM, McElwee MK, Michalowski J, O'Leary KA, Young KM, Perry ME. mdm2 Is critical for inhibition of p53 during lymphopoiesis and the response to ionizing irradiation. Mol Cell Biol 2003;23:462–72.
[12] Mendrysa SM, O'Leary KA, McElwee MK, Michalowski J, Eisenman RN, Powell DA, et al. Tumor suppression and normal aging in mice with constitutively high p53 activity. Genes Dev 2006;20:16–21.
[13] Liu G, Terzian T, Xiong S, Van Pelt CS, Audiffred A, Box NF, et al. The p53-Mdm2 network in progenitor cell expansion during mouse postnatal development. J Pathol 2007;213:360–8.
[14] Armstrong JF, Kaufman MH, Harrison DJ, Clarke AR. High-frequency developmental abnormalities in p53-deficient mice. Curr Biol 1995;5:931–6.
[15] Sah VP, Attardi LD, Mulligan GJ, Williams BO, Bronson RT, Jacks T. A subset of p53-deficient embryos exhibit exencephaly. Nat Genet 1995;10:175–80.
[16] Akhtar RS, Geng Y, Klocke BJ, Roth KA. Neural precursor cells possess multiple p53-dependent apoptotic pathways. Cell Death Differ 2006;13:1727–39.
[17] Geng Y, Akhtar RS, Shacka JJ, Klocke BJ, Zhang J, Chen X, et al. p53 transcription-dependent and -independent regulation of cerebellar neural precursor cell apoptosis. J Neuropathol Exp Neurol 2007;66:66–74.
[18] Meletis K, Wirta V, Hede SM, Nister M, Lundeberg J, Frisen J. p53 suppresses the self-renewal of adult neural stem cells. Development 2006;133:363–9.
[19] Gil-Perotin S, Marin-Husstege M, Li J, Soriano-Navarro M, Zindy F, Roussel MF, et al. Loss of p53 induces changes in the behavior of subventricular zone cells: implication for the genesis of glial tumors. J Neurosci 2006;26:1107–16.
[20] Hemmati HD, Nakano I, Lazareff JA, Masterman-Smith M, Geschwind DH, Bronner-Fraser M, et al. Cancerous stem cells can arise from pediatric brain tumors. Proc Natl Acad Sci USA 2003;100:15178–83.
[21] Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, et al. Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res 2004;64:7011–21.
[22] Yuan X, Curtin J, Xiong Y, Liu G, Waschsmann-Hogiu S, Farkas DL, et al. Isolation of cancer stem cells from adult glioblastoma multiforme. Oncogene 2004;23:9392–400.
[23] Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006;444:756–60.
[24] Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007;170:1445–53.
[25] Ohgaki H, Dessen P, Jourde B, Horstmann S, Nishikawa T, Di Patre PL, et al. Genetic pathways to glioblastoma: a population-based study. Cancer Res 2004;64:6892–9.
[26] Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol 2005;64:479–89.
[27] Shu HK, Kim MM, Chen P, Furman F, Julin CM, Israel MA. The intrinsic radioresistance of glioblastoma-derived cell lines is associated with a failure of p53 to induce p21(BAX) expression. Proc Natl Acad Sci USA 1998;95:14453–8.
[28] Steinbach JP, Weller M. Apoptosis in gliomas: molecular mechanisms and therapeutic implications. J Neurooncol 2004;70:245–54.
[29] Hermisson M, Klumpp A, Wick W, Wischhusen J, Nagel G, Roos W, et al. O^6-Methylguanine DNA methyltransferase

and p53 status predict temozolomide sensitivity in human malignant glioma cells. J Neurochem 2006;96: 766–76.
[30] Roos WP, Batista LF, Naumann SC, Wick W, Weller M, Menck CF, et al. Apoptosis in malignant glioma cells triggered by the temozolomide-induced DNA lesion O6-methylguanine. Oncogene 2007;26:186–97.
[31] Batista LF, Roos WP, Christmann M, Menck CF, Kaina B. Differential sensitivity of malignant glioma cells to methylating and chloroethylating anticancer drugs: p53 determines the switch by regulating xpc, ddb2, and DNA double-strand breaks. Cancer Res 2007;67:11886–95.
[32] Gomez-Manzano C, Fueyo J, Kyritsis AP, Steck PA, Roth JA, McDonnell TJ, et al. Adenovirus-mediated transfer of the p53 gene produces rapid and generalized death of human glioma cells via apoptosis. Cancer Res 1996;56:694–9.
[33] Komata T, Kondo Y, Koga S, Ko SC, Chung LW, Kondo S. Combination therapy of malignant glioma cells with 2-5A-antisense telomerase RNA and recombinant adenovirus p53. Gene Ther 2000;7:2071–9.
[34] Cerrato JA, Yung WK, Liu TJ. Introduction of mutant p53 into a wild-type p53-expressing glioma cell line confers sensitivity to Ad-p53-induced apoptosis. Neuro Oncol 2001;3:113–22.
[35] Grombacher T, Eichhorn U, Kaina B. P53 is involved in regulation of the DNA repair gene O6-methylguanine-DNA methyltransferase (MGMT) by DNA damaging agents. Oncogene 1998;17:845–51.
[36] Blough MD, Zlatescu MC, Cairncross JG. O6-methylguanine-DNA methyltransferase regulation by p53 in astrocytic cells. Cancer Res 2007;67:580–4.
[37] Pellegata NS, Antoniono RJ, Redpath JL, Stanbridge EJ. DNA damage and p53-mediated cell cycle arrest: a reevaluation. Proc Natl Acad Sci USA 1996;93:15209–14.
[38] Scott SL, Earle JD, Gumerlock PH. Functional p53 increases prostate cancer cell survival after exposure to fractionated doses of ionizing radiation. Cancer Res 2003;63:7190–6.
[39] Sak A, Wurm R, Elo B, Grehl S, Pottgen C, Stuben G, et al. Increased radiation-induced apoptosis and altered cell cycle progression of human lung cancer cell lines by antisense oligodeoxynucleotides targeting p53 and p21(WAF1/CIP1). Cancer Gene Ther 2003;10:926–34.
[40] Peller S, Rotter V. TP53 in hematological cancer: low incidence of mutations with significant clinical relevance. Hum Mutat 2003;21:277–84.
[41] Engelmann A, Speidel D, Bornkamm W, Deppert W, Stocking C. Gadd45 is a pro-survival factor associated with stress-resistant tumors. Oncogene 2008;27:1429–38.
[42] Sengupta S, Harris CC. p53: traffic cop at the crossroads of DNA repair and recombination. Nat Rev Mol Cell Biol 2005;6:44–55.
[43] Gatz SA, Wiesmuller L. p53 in recombination and repair. Cell Death Differ 2006;13:1003–16.
[44] Tarapore P, Fukasawa K. Loss of p53 and centrosome hyperamplification. Oncogene 2002;21:6234–40.
[45] Lee S, Elenbaas B, Levine A, Griffith J. p53 and its 14 kDa C-terminal domain recognize primary DNA damage in the form of insertion/deletion mismatches. Cell 1995;81: 1013–20.
[46] Szak ST, Pietenpol JA. High affinity insertion/deletion lesion binding by p53—evidence for a role of the p53 central domain. J Biol Chem 1999;274:3904–9.
[47] Janz C, Susse S, Wiesmuller L. p53 and recombination intermediates: role of tetramerization at DNA junctions in complex formation and exonucleolytic degradation. Oncogene 2002;21:2130–40.
[48] Walter K, Warnecke G, Bowater R, Deppert W, Kim EL. Tumor suppressor p53 binds with high affinity to CTG-CAG trinucleotide repeats and induces topological alterations in mismatched duplexes. J Biol Chem 2005;280:42497–507.
[49] Moll UM, Wolff S, Speidel D, Deppert W. Transcription-independent pro-apoptotic functions of p53. Curr Opin Cell Biol 2005;17:631–6.
[50] McEvilly RJ, Erkman L, Luo L, Sawchenko PE, Ryan AF, Rosenfeld MG. Requirement for Brn-3.0 in differentiation and survival of sensory and motor neurons. Nature 1996;384:574–7.
[51] Hudson CD, Morris PJ, Latchman DS, Budhram-Mahadeo VS. Brn-3a transcription factor blocks p53-mediated activation of proapoptotic target genes Noxa and Bax in vitro and in vivo to determine cell fate. J Biol Chem 2005;280:11851–8.
[52] Budram-Mahadeo V, Morris PJ, Latchman DS. The Brn-3a transcription factor inhibits the pro-apoptotic effect of p53 and enhances cell cycle arrest by differentially regulating the activity of the p53 target genes encoding Bax and p21(CIP1/Waf1). Oncogene 2002;21:6123–31.
[53] Nakano K, Vousden KH. PUMA, a novel proapoptotic gene, is induced by p53. Mol Cell 2001;7:683–94.
[54] Wu WS, Heinrichs S, Xu D, Garrison SP, Zambetti GP, Adams JM, et al. Slug antagonizes p53-mediated apoptosis of hematopoietic progenitors by repressing puma. Cell 2005;123:641–53.
[55] Ng CC, Arakawa H, Fukuda S, Kondoh H, Nakamura Y. p53RFP, a p53-inducible RING-finger protein, regulates the stability of p21WAF1. Oncogene 2003;22:4449–58.
[56] Huang J, Xu LG, Liu T, Zhai Z, Shu HB. The p53-inducible E3 ubiquitin ligase p53RFP induces p53-dependent apoptosis. FEBS Lett 2006;580:940–7.
[57] Wei C-L, Wu Q, Vega VB, Chiu KP, Ng P, Zhang T, et al. A global map of p53 transcription-factor binding sites in the human genome. Cell 2006;124:207–19.
[58] Jegga AG, Inga A, Menendez D, Aronow BJ, Resnick MA. Functional evolution of the p53 regulatory network through its target response elements. Proc Natl Acad Sci USA 2008;105:944–9.
[59] Horvath MM, Wang X, Resnick MA, Bell DA. Divergent evolution of human p53 binding sites: cell cycle versus apoptosis. PLoS Genet 2007;3:e127.
[60] Kim E, Deppert W. The versatile interactions of p53 with DNA: when flexibility serves specificity. Cell Death Differ 2006;13:885–9.
[61] Riley T, Sontag E, Chen P, Levine A. Transcriptional control of human p53-regulated genes. Nat Rev Mol Cell Biol 2008;9:402–12.
[62] Weinberg RL, Veprintsev DB, Bycroft M, Fersht AR. Comparative binding of p53 to its promoter and DNA recognition elements. J Mol Biol 2005;348:589–96.
[63] Courtois S, de Fromentel CC, Hainaut P. p53 protein variants: structural and functional similarities with p63 and p73 isoforms. Oncogene 2004;23:631–8.
[64] Bourdon JC. p53 and its isoforms in cancer. Br J Cancer 2007;97:277–82.
[65] Wolkowicz R, Peled A, Elkind NB, Rotter V. Augmented DNA-binding activity of p53 protein encoded by a carboxyl-terminal alternatively spliced mRNA is blocked by p53 protein encoded by the regularly spliced form. Proc Natl Acad Sci USA 1995;92:6842–6.
[66] Almog N, Li RZ, Peled A, Schwartz D, Wolkowicz R, Goldfinger N, et al. The murine C′-terminally alternatively spliced form of p53 induces attenuated apoptosis in myeloid cells. Mol Cell Biol 1997;17:713–22.
[67] Wu Y, Liu Y, Lee L, Miner Z, Kulesz-Martin M. Wild-type alternatively spliced p53: binding to DNA and interaction with the major p53 protein in vitro and in cells. EMBO J 1994;13:4823–30.

[68] Prives C, Manfredi JJ. The continuing saga of p53—more sleepless nights ahead. Mol Cell 2005;19:719–21.
[69] Rohaly G, Chemnitz J, Dehde S, Nunez AM, Heukeshoven J, Deppert W, et al. A Novel human p53-isoform is an essential element of the ATR-intra-S-phase checkpoint. Cell 2005;122:21–32.
[70] Bourdon JC, Fernandes K, Murray-Zmijewski F, Liu G, Diot A, Xirodimas DP, et al. p53 isoforms can regulate p53 transcriptional activity. Genes Dev 2005;19: 2122–37.
[71] Espinosa J, Emerson B. Transcriptional regulation by p53 through intrinsic DNA/chromatin binding and site-directed cofactor recruitment. Mol Cell 2001;8: 57–69.
[72] McKinney K, Mattia M, Gottifredi V, Prives C. p53 linear diffusion along DNA requires its C terminus. Mol Cell 2004;16:413–24.
[73] Frank KM, Sharpless NE, Gao Y, Sekiguchi JM, Ferguson DO, Zhu C, et al. DNA ligase IV deficiency in mice leads to defective neurogenesis and embryonic lethality via the p53 pathway. Mol Cell 2000;5:993–1002.
[74] Gao Y, Ferguson DO, Xie W, Manis JP, Sekiguchi J, Frank KM, et al. Interplay of p53 and DNA-repair protein XRCC4 in tumorigenesis, genomic stability and development. Nature 2000;404:897–900.
[75] Ternovoi VV, Curiel DT, Smith BF, Siegal GP. Adenovirus-mediated p53 tumor suppressor gene therapy of osteosarcoma. Lab Invest 2006;86:748–66.
[76] Levesque AA, Eastman A. p53-based cancer therapies: is defective p53 the Achilles heel of the tumor? Carcinogenesis 2007;28:13–20.
[77] Vassilev LT. MDM2 inhibitors for cancer therapy. Trends Mol Med 2007;13:23–31.
[78] Peng Y, Li C, Chen L, Sebti S, Chen J. Rescue of mutant p53 transcription function by ellipticine. Oncogene 2003;22:4478–87.
[79] Wang W, Ho WC, Dicker DT, MacKinnon C, Winkler JD, Marmorstein R, et al. Acridine derivatives activate p53 and induce tumor cell death through Bax. Cancer Biol Ther 2005;4:893–8.
[80] Selivanova G, Wiman KG. Reactivation of mutant p53: molecular mechanisms and therapeutic potential. Oncogene 2007;26:2243–54.
[81] El-Deiry WS. The role of p53 in chemosensitivity and radiosensitivity. Oncogene 2003;22:7486–95.
[82] Wang W, El-Deiry WS. Restoration of p53 to limit tumor growth. Curr Opin Oncol 2008;20:90–6.
[83] Gudkov AV, Komarova EA. Dangerous habits of a security guard: the two faces of p53 as a drug target. Hum Mol Genet 2007;16 Spec No. 1:R67–72.
[84] Ljungman M, Lane DP. Transcription—guarding the genome by sensing DNA damage. Nat Rev Cancer 2004;4:727–37.
[85] Gurova KV, Hill JE, Guo C, Prokvolit A, Burdelya LG, Samoylova E, et al. Small molecules that reactivate p53 in renal cell carcinoma reveal a NF-kappaB-dependent mechanism of p53 suppression in tumors. Proc Natl Acad Sci USA 2005;102:17448–53.
[86] Maclean KH, Dorsey FC, Cleveland JL, Kastan MB. Targeting lysosomal degradation induces p53-dependent cell death and prevents cancer in mouse models of lymphomagenesis. J Clin Invest 2008;118:79–88.
[87] Bakkenist CJ, Kastan MB. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. Nature 2003;421:499–506.
[88] Arnold AM, Whitehouse JM. Interaction of VP16-213 with the DNA repair antagonist chloroquine. Cancer Chemother Pharmacol 1982;7:123–6.
[89] Boya P, Gonzalez-Polo RA, Poncet D, Andreau K, Vieira HL, Roumier T, et al. Mitochondrial membrane permeabilization is a critical step of lysosome-initiated apoptosis induced by hydroxychloroquine. Oncogene 2003;22:3927–36.
[90] Boya P, Gonzalez-Polo RA, Casares N, Perfettini JL, Dessen P, Larochette N, et al. Inhibition of macroautophagy triggers apoptosis. Mol Cell Biol 2005;25:1025–40.
[91] Zaidi AU, McDonough JS, Klocke BJ, Latham CB, Korsmeyer SJ, Flavell RA, et al. Chloroquine-induced neuronal cell death is p53 and Bcl-2 family-dependent but caspase-independent. J Neuropathol Exp Neurol 2001;60:937–45.
[92] Meng XW, Feller JM, Ziegler JB, Pittman SM, Ireland CM. Induction of apoptosis in peripheral blood lymphocytes following treatment in vitro with hydroxychloroquine. Arthritis Rheum 1997;40:927–35.
[93] Fan C, Wang W, Zhao B, Zhang S, Miao J. Chloroquine inhibits cell growth and induces cell death in A549 lung cancer cells. Bioorg Med Chem 2006;14:3218–22.
[94] Zhou Q, McCracken MA, Strobl JS. Control of mammary tumor cell growth *in vitro* by novel cell differentiation and apoptosis agents. Breast Cancer Res Treat 2002;75:107–17.
[95] Loehberg CR, Thompson T, Kastan MB, Maclean KH, Edwards DG, Kittrell FS, et al. Ataxia telangiectasia-mutated and p53 are potential mediators of chloroquine-induced resistance to mammary carcinogenesis. Cancer Res 2007;67:12026–33.
[96] Radl S. From chloroquine to antineoplastic drugs? The story of antibacterial quinolones. Arch Pharm (Weinheim) 1996;329:115–9.
[97] Song J, Chao C, Xu Y. Ser18 and Ser23 phosphorylation plays synergistic roles in activating p53-dependent neuronal apoptosis. Cell Cycle 2007;6:1412–4.
[98] Feng L, Hollstein M, Xu Y. Ser46 phosphorylation regulates p53-dependent apoptosis and replicative senescence. Cell Cycle 2006;5:2812–9.
[99] Knights CD, Catania J, Di Giovanni S, Muratoglu S, Perez R, Swartzbeck A, et al. Distinct p53 acetylation cassettes differentially influence gene-expression patterns and cell fate. J Cell Biol 2006;173:533–44.
[100] Tang Y, Luo J, Zhang W, Gu W. Tip60-dependent acetylation of p53 modulates the decision between cell-cycle arrest and apoptosis. Mol Cell 2006;24:827–39.
[101] Braithwaite AW, Prives CL. p53: more research and more questions. Cell Death Differ 2006;13:877–80.
[102] Das S, Raj L, Zhao B, Kimura Y, Bernstein A, Aaronson SA, et al. Hzf Determines cell survival upon genotoxic stress by modulating p53 transactivation. Cell 2007;130:624–37.