Minireview

Nuclear and mitochondrial apoptotic pathways of p53

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Abstract In contrast to p53-mediated cell cycle arrest, the mechanisms of p53-mediated apoptosis in response to cellular stresses such as DNA damage, hypoxia and oncogenic signals still remain poorly understood. Elucidating these pathways is all the more pressing since there is good evidence that the activation of apoptosis rather than cell cycle arrest is crucial in p53 tumor suppression. Moreover, the therapeutic interest in p53 as the molecular target of anticancer intervention rests mainly on its powerful apoptotic capability. This puzzling elusiveness suggests that p53 not only engages a plethora of downstream pathways but itself might possess a biochemical flexibility that goes beyond its role as a mere transcription factor. Recent evidence of a direct pro-apoptotic role of p53 protein at mitochondria suggests a synergistic effect with its transcriptional activation function and brings an unexpected new level of complexity into p53 apoptotic pathways. © 2001 Published by Elsevier Science B.V. on behalf of the Federation of European Biochemical Societies.

Key words: p53; Transcription factor; Mitochondrial localization; Stress-induced; Apoptosis

1. Introduction

In contrast to p53-mediated cell cycle arrest, the mechanism of p53-mediated apoptosis in response to cellular stresses such as DNA damage, hypoxia and oncogenic signals remains poorly understood. The elucidation of this pathway is particularly important as there is in vivo evidence that it is primarily the activation of apoptosis by p53 rather than its arrest function that is crucial in tumor suppression. The importance for p53-induced apoptosis in tumor suppression is further underlined by some human tumor-derived p53 mutants that have a selective loss-of-function only for apoptosis but not for the G1 arrest pathway [1]. Moreover, the therapeutic interest in p53 as the molecular target of anticancer agents lies, of course, in its apoptotic pathways [2].

2. p53 transcription function and apoptotic target genes

Over the last 5 years, a number of different p53-induced genes were proposed to play a role in p53-mediated cell death including Bax [3], Fas/Apo-1 [4], IGF-BP3 [5], Killer/DR5 [6], PIGs [7], PAG608 [8], PERP [9], Noxa [10], PIDD [11], DRAL [12] and p53AIP1 [13] (Fig. 1). Often, these genes were found in screens that compared a particular tumor cell line lacking p53 with its counterpart overexpressing ectopic p53, and some form of subtractive methodology (e.g. subtractive hybridization, differential display) was used. This was the case, e.g. for Bax, PIDD and the PIG group. PERP and Noxa were also found using a subtractive approach but relied on endogenous p53 by comparing p53+/+ MEFs with their p53−/− counterparts.

The candidacy of these genes for being p53 apoptosis genes is based on the following criteria: (i) demonstrating p53-dependency of their induction (usually accompanied by the identification of a putative p53-binding site in their 5′-regulatory region), and (ii) demonstrating that ectopic overexpression of the candidate gene is sufficient to induce apoptosis in p53-deficient tissue culture cells. In some cases (e.g. Noxa and PIDD), downregulation of the endogenous gene by antisense methods decreases (but never abolishes) cell death rate after stress.

However, most known p53 target genes are induced to similar levels during p53-mediated G1 arrest and apoptosis [9]. This strongly suggests that they function more generally in transducing p53 stress signals, but that they are not the decisive death determinant in the cell's decision fork whether to arrest or to undergo cell death. This situation holds true for the p53 target genes Bax, IGF-BP3, Killer/DR5, the PIGs, PIDD, and Noxa. Each of these genes is similarly induced in doxorubicin-stressed p53+/+ MEFs, which only arrest, and in doxorubicin-stressed E1A p53+/+ MEFs, which only apoptose [9]. Notable exceptions in apoptosis specificity is PERP and possibly, p53AIP1. PERP, a member of the tetraspan transmembrane protein family PMP22/gas3, was cloned after subtracting against G1 arrest-associated p53-induced messages. PERP is specifically induced during p53-mediated apoptosis in E1A-harboring MEF cells but not during G1 arrest [9]. Also, stress-mediated serine 46 phosphorylation on p53 is specifically associated with induction of p53AIP1 but not with induction of p21Waf1, Noxa and PIG3, suggesting that p53AIP1 might be an apoptosis gene induced by this particular modification of p53 [13]. The induction of candidate apoptosis genes exhibit variable kinetics with some being rather slow in their inductive response (24 h or longer), e.g. PIG3 and p53AIP1. While many of the above-mentioned candidates are widely expressed, DRAL is an example of a tissue-restricted response gene which is exclusively expressed in cardiomyocytes [12].

The ultimate proof for any p53 apoptosis candidate gene

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Abbreviations: KO, knock out mouse; ROS, reactive oxygen species

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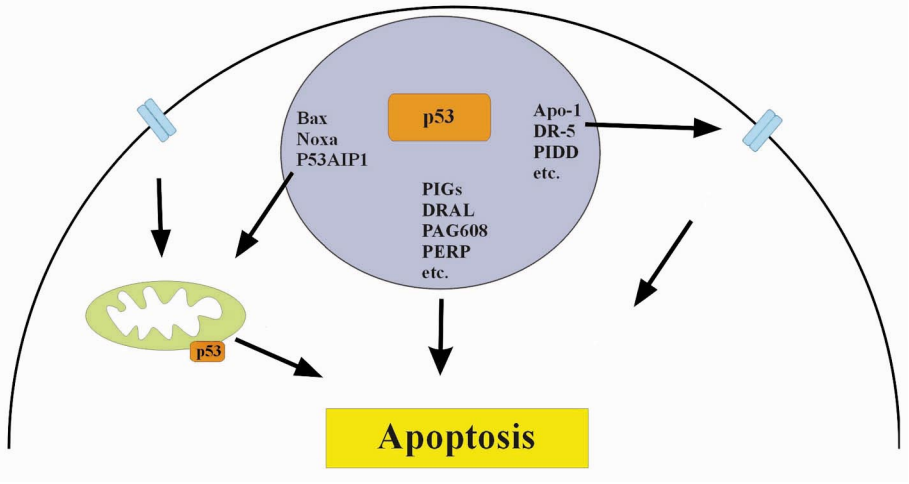

Fig. 1. Transcriptionally dependent and independent mechanisms of p53-mediated apoptosis both activate the mitochondrial pathway of cell death. Alterations in mitochondrial membrane potential, mitochondrial ROS production and/or cytochrome *c* release can result from p53-mediated transcriptional activation of mitochondrial proteins such as Noxa, p53 AIP1 and Bax. Moreover, the rapid translocation of p53 protein directly to mitochondria occurs in a broad spectrum of cell types and death signals and enhances the apoptotic potency of p53. In addition, p53 can enlist a multitude of other p53-induced effector genes. p53 can activate the death receptor pathway via death receptor target genes (DR-5, Apo-1) or death-domain-containing proteins (PIDD). Other target genes operate through unknown apoptotic pathways (PIGs, DRAL, PAG608, PERP).

would be a loss-of-function knock out mouse (KO) for that candidate which shows resistance to a p53-dependent apoptotic stress stimulus. This would definitively demonstrate that specific gene's requirement for p53-mediated apoptosis. So far, of all candidates only the Bax and APO-1 KO mice have been made, but the available results fail to demonstrate such a requirement. Bax requirement is, at best, partial and context-dependent. Bax deficiency only attenuates but does not abrogate the p53-dependent apoptotic pathway in E1A-expressing primary mouse embryo fibroblasts [14] and in choroid plexus tumors of transgenic T-antigen-expressing mice [15]. On the other hand, Bax-deficient thymocytes are fully competent for γ-irradiation (IR)-induced p53-dependent apoptosis [16,17]. Furthermore, the mouse Bax gene lacks a p53-binding site (although the human Bax promoter has a consensus binding site), indicating poor evolutionary conservation. Moreover, human p53 delta Pro, which lacks the proline-rich region 61–94, induces Bax normally but has lost its apoptotic function [18]. Likewise, APO-1 is fully dispensable for γ-IR induced p53-dependent apoptosis as shown by spontaneously Fas-deficient mice (so-called *lpr* mice) [17,19].

Taken together, despite many years of intense search for the critical p53 apoptosis effector(s), we are still faced with a vexing elusiveness of a clear understanding of how p53 does the job of inducing cell death. It strongly argues that this powerful protein simultaneously engages in a multitude of downstream pathways to mediate cell death. In apoptosis, p53 does not sit on top of a simple 'monorail' transcriptional pathway, as it does in p53-mediated G1 and G2 arrest. Instead, p53 enlists a spectrum of different biological effector pathways. It even opens up the possibility that this molecule has pleiotropic biochemical functions, a sort of jack of more than one trade. This might require biochemical flexibility for functioning in transcriptional activation and transcription-independent modes of action, which in turn might be cell type- and damage-specific. What is the evidence for such transcription-independent modes of action of p53-mediated apoptosis?

3. Transrepression

A transrepression mechanism was suggested which involves selective targeting by wild-type but not mutant p53 protein of the corepressor mSin3a, coupled with histone deacetylase, to the regulatory regions of the microtubule-associated protein 4. Map4, a p53-repressed gene, has been correlated with a delay in apoptosis [20]. In contrast to the non-specific repression previously observed in some transient reporter assays when greatly overexpressed p53 and target promoters were used, Map4 repression appears to be specific. However, the precise DNA-binding domain and the exact role of Map4 in apoptosis remain to be identified.

4. Transcription-independent pathways of p53 apoptosis

Evidence for transcription-independent pathways for p53-mediated apoptosis has been accumulating for years. In some cell types, p53-dependent apoptosis occurs in the absence of any gene transcription or protein synthesis [21–23]. Furthermore, inhibitors of protein phosphatases induce p53-dependent apoptosis in the absence of transcriptional activation [24]. Moreover, the transcriptionally inactive p53 mutants del(1–214) and $p53_{gln22,\ ser23}$, which fail to specifically bind to DNA or act as transcription factor of Waf1 and other target genes, act as potent inducers of apoptosis in several cell systems [25–27]. Interestingly, p53 protein from cell-free postnuclear extracts (which contain mitochondria), made from transformed fibroblasts that undergo p53-dependent apoptosis after γ-IR, directly mediates the activation of effector caspases. Immunodepletion of p53 protein from these extracts blocks this activity, suggesting direct protein–protein signaling from p53 to the Casp9/Casp3 activation cascade. This pathway requires caspase 8 [28].

5. Mitochondria, protein translocation and apoptosis

Mitochondria are central integrators and transducers for

pro-apoptotic signals, forming the nexus between the non-specific inducer phase and the final execution phase of apoptosis. This is particularly but not exclusively the case with those inducers of cell death that activate apoptosis independently of death receptor pathways on the cell surface. Such inducers include cell damage from γ-IR, anticancer drugs, hypoxia and growth factor withdrawal. A major reason for the central role of mitochondria is that these organelles store a host of critical apoptotic activators and effectors of cell death in their intermembranous space. These include cytochrome *c* (see e.g. [29]), Smac/Diablo (a cytochrome *c*-dependent caspase co-activator) [30,31], apoptosis inducing factor (AIF), a flavoprotein which activates nuclear endonucleases [32] and procaspases 2, 3 and 9 (reviewed in [33]). Permeabilization of the outer mitochondrial membrane, which is associated with mitochondrial dysfunction and collapse of the inner membrane gradient $\Delta\varphi M$, causes the release of these pro-apoptogenic factors. This release constitutes the point of no return and triggers the execution phase of cell suicide because it directly activates the latent apoptotic machinery.

One striking feature of apoptosis signaling is protein translocation of signal and effector molecules between three major cellular compartments. This includes translocation to and from mitochondria, the cytoplasm and the nucleus. Of particular interest are a growing list of pro-apoptotic proteins that undergo translocation to mitochondria, where they exert their pro-apoptotic functions by inducing organellar dysfunction. The classic pro-apoptotic bcl family members Bax [34,35], Bad (reviewed in [33]), Bim [36] and truncated tBid [37,38] do this by increasing mitochondrial permeability which, among others, leads to the release of cytochrome *c*. For example, inactive cytosolic Bid undergoes N-terminal cleavage by caspase 8 to tBid, leading to a newly exposed glycine residue which now becomes the target of posttranslational *N*-myristoylation [39]. This modification promotes its mitochondrial targeting and pro-apoptotic effect. Moreover, ionizing IR induces translocation of the stress kinase SAPK/JNK to mitochondria which in turn causes phosphorylation and inactivation of anti-apoptotic Bcl-xL [40]. Similarly, phorbol esters induce translocation of protein kinase C delta to mitochondria, altering a yet unknown substrate [41]. The evolving theme here is that these mitochondrially translocating proteins belong to unrelated biochemical classes of molecules, most of which were previously not associated with mitochondrial functions. Most unexpectedly, this diversity is now even extending to transcription factors.

6. p53 and mitochondria

We recently showed that a fraction of stress-induced endogenous p53 protein targets to mitochondria in response to various types of damage in human and mouse, malignant and non-malignant cell lines [42]. This result was obtained using all methods available for determination of subcellular localization, including carefully controlled subcellular fractionation. p53 translocation strictly occurs at the onset of p53-dependent apoptosis, but not during p53-independent apoptosis triggered e.g. by the death receptor pathway, nor does it occur during p53-mediated cell cycle arrest. The translocation of p53 to mitochondria is rapid (within 1 h after cell damage) and precedes changes in mitochondrial membrane potential, cytochrome *c* release and procaspase-3 activation [42].

Mitochondrial localization of endogenous p53 can be visualized by in situ immunofluorescence of whole cells after 5–6 h of hypoxic stress [43]. Immuno-flow cytometry analysis of isolated mitochondria show that a significant amount of mitochondrial p53 localizes to the membranous compartment. This result was confirmed by direct localization of p53 via immuno-electronmicroscopy of stressed mitochondria, while untreated mitochondria failed to give a signal. Further suborganellar localization of p53 by limited trypsin digestion suggests that a significant amount of mitochondrial p53 is located at the surface of the organelle, while a subfraction appears to be intraorganellar (trypsin-resistant) [42]. Mitochondrial association of p53 and its significant surface localization can be reproduced in vitro in an organellar pull-down assay with purified baculoviral p53 added to isolated mitochondria. Control recombinant PCNA protein fails to associate. Co-immunoprecipitation from stressed whole cells or mitochondria shows that mitochondrial p53 is found in an in vivo complex with the mitochondrial import motor mt hsp70. This p53 subpopulation possibly corresponds to the trypsin-resistant subfraction [42]. A similar in vivo complex between mt hsp70 (also called mot-2) and p53 was independently observed in NIH 3T3 cells [44]. Interestingly, forced overexpression of ectopic mot-2 abolished the transcriptional ability of p53 in reporter assays and nuclear translocation, suggesting that p53 can be completely siphoned off into mitochondria [44].

Similar results were seen in clean ectopic systems in the absence of additional DNA damage. In p53-deficient EB1 cells which harbor a stable, inducible wild-type p53 transgene, mitochondrial p53 accumulation occurs concomitantly with nuclear p53 accumulation and precedes the onset of apoptosis after sole induction of ectopic p53 [42]. On the other hand, mitochondrial regulators of apoptosis influence the induction of mitochondrial p53 accumulation. Overexpression of anti-apoptotic Bcl-2 or Bcl-xL abrogates stress-signal-mediated mitochondrial p53 accumulation and apoptosis. In contrast, Bcl-2 or Bcl-xL overexpression does not abrogate total cellular p53 accumulation nor the ability to undergo stress-induced cell cycle arrest [42].

Importantly, nuclear bypass experiments demonstrate that mitochondrial p53 localization is sufficient for launching p53-dependent apoptosis from the level of mitochondria. Deliberate targeting of ectopic p53 to mitochondria (via fusions with mitochondrial import leader peptide, designated L-p53) bypasses the nucleus and is sufficient to induce apoptosis in three different p53-deficient tumor cell lines (Saos-2, H1299 and HeLa) ([42] and unpublished observation). Interestingly, a mitochondrially targeted but truncated p53 protein (L-p53 1–305), which misses the entire C-terminus, has a higher apoptotic activity than L-wtp53, suggesting that the C-terminus containing the tetramerization domain is dispensable for mitochondrial action. This is in contrast to the nuclear action of p53, which requires the C-terminus for tetramerization in order to optimally function as a transcription factor. Finally, the mitochondrial p53 action is transcription-independent since targeted mutant L-p53 R175H, which is completely inactive as transcription factor, retains its apoptotic activity as a mitochondrial protein [42].

Based on these results, we propose a model in which p53 can contribute to cell death by rapid direct signaling at the mitochondria. This pathway likely acts in synergy with the transcription-dependent mode of p53, thereby amplifying the

apoptotic potency and speed of p53. Moreover, based on its implication in a broad spectrum of cell types and death signals, this enhancer pathway has the potential for being generic, accompanying the action of most or all p53-induced apoptotic genes (Fig. 1). Important questions for the future are: which are the protein(s) that mitochondrial p53 is talking to and what secondary apoptotic regulators are being activated as a result of this.

In a general sense, what do we currently know about p53 death signaling via mitochondria? Downstream of mitochondria, p53-dependent apoptosis clearly goes through caspase activation involving the caspase-9/Apaf-1 apoptosome, since loss of both factors substitute for loss of p53 and cause resistance to Myc-induced apoptosis of mouse embryo fibroblasts [45]. At the mitochondrial level, however, the exact nature of p53-induced alterations are unclear. Several independent apoptogenic events have been described. Using adenoviral transduction of wtp53 into HeLa cells (functionally null for p53), Li et al. found that p53 signaling generates production of reactive oxygen species (ROS), which in turn causes collapse of the mitochondrial membrane potential $\Delta\varphi$M. Of note, this group found no evidence of mitochondrial cytochrome *c* release nor Bax translocation (despite Bax induction) or Bid cleavage [46]. In contrast, using similar adenoviral transduction of wtp53 into Saos-2 cells (null for p53), Schuler et al. [47] found that the p53-transduced cytosolic extracts contained a cytochrome *c*-releasing activity that was not p53 itself but was dependent on the presence of cytosolic Bax. These varying results from two similar experimental systems will require more clarification.

Aside from Bax, the p53-induced gene products Noxa and p53AIP1 are also mitochondrial proteins and probably generate their own set of mitochondrial dysfunctions, at least in some circumstances. Bax and Noxa are BH3-domain-containing proteins, while p53 AIP1 has no significant homology to any protein in the public database. However, the onset of mitochondrial dysfunction by these genes might be delayed, since their transcription and translation requires time. This notion is in line with the fact that p53AIP1 mRNA induction was slow and only seen 24 h after γ-IR [13].

Does mitochondrial accumulation of p53 represent a precedent for other transcription factors implicated in apoptosis? The answer is yes. The nuclear orphan steroid receptor TR3 (also called Nur77 or NGFIB), a member of the steroid/thyroid receptor superfamily is a bona fide transcription factor with a zinc finger DNA-binding domain flanked by transactivation domains and a binding domain for an as yet unknown ligand. TR3 is induced and acts as a transcription factor in response to epidermal growth factor and all-*trans*-retinoic acid. On the other hand, TR3 mediates apoptosis in different cell types in vivo, e.g. in neurons, autoreactive developing T cells and human cancer cells ([48] and references within). TR3 is upregulated by apoptotic stimuli like seizures, neuronal ischemia and ligation of the T cell receptor. Unexpectedly, when TR3 works as an apoptotic factor, its transcriptional activation function is turned off [48]. Instead, in response to a wide variety of apoptotic stimuli, TR3 relocates from the nucleus to the surface of mitochondria, where it triggers membrane permeability, cytochrome *c* release and apoptotic cell death. The TR3 DNA-binding domain, required for transcriptional activity, is not required for mitochondrial targeting. As is true for mitochondrial p53, mitochondrial TR3 is also sufficient to cause cell death. Moreover, as for mitochondrial p53, its action is blocked by bcl-2 [48]. Thus, there are now two nuclear transcription factors that, by virtue of their subcellular relocalization, are capable of mediating lethal signaling directly through mitochondria. For one thing, these two examples add another level of complexity to the regulation of apoptosis. However, their greater significance might lie in the fact that it forces us to rethink our neat biochemical classification scheme of one protein – one mode of action.

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References

[1] Ryan, K.M. and Vousden, K.H. (1998) Mol. Cell. Biol. 18, 3692–3698.
[2] Lowe, S.W., Ruley, H.E., Jacks, T. and Housman, D.E. (1993) Cell 74, 957–967.
[3] Miyashita, T. and Reed, J.C. (1995) Cell 80, 293–299.
[4] Owen-Schaub, L.B., Zhang, W., Cusack, J.C., Angelo, L.S., Santee, S.M., Fujiwara, T., Roth, J.A., Deisseroth, A.B., Zhang, W.-W., Kruzel, E. and Radinsky, R. (1995) Mol. Cell. Biol. 15, 3032–3040.
[5] Buckbinder, L., Talbott, R., Velasco-Miguel, S., Takenaka, I., Faha, B., Seizinger, B.R. and Kley, N. (1995) Nature 377, 646–649.
[6] Wu, G.S., Burns, T.F., McDonald III, E.R., Jiang, W., Meng, R., Krantz, I.D., Kao, G., Gan, D.D., Zhou, J.Y., Muschel, R., Hamilton, S.R., Spinner, N.B., Markowitz, S., Wu, G. and el-Deiry, W.S. (1997) Nat. Genet. 17, 141–143.
[7] Polyak, K., Xia, Y., Zweier, J.L., Kinzler, K.W. and Vogelstein, B. (1997) Nature 389, 300–305.
[8] Israeli, D., Tessler, E., Haupt, Y., Elkeles, A., Wilder, S., Amson, R., Telerman, A. and Oren, M. (1997) EMBO J. 16, 4384–4392.
[9] Attardi, L.D., Reczek, E.E., Cosmas, C., Demicco, E.G., McCurrach, M.E., Lowe, S.W. and Jacks, T. (2000) Genes Dev. 14, 704–718.
[10] Oda, E., Ohki, R., Murasawa, H., Nemoto, J., Shibue, T., Yamashita, T., Tokino, T., Taniguch, T. and Tanaka, N. (2000) Science 288, 1053–1058.
[11] Lin, Y., Ma, W. and Benchimol, S. (2000) Nat. Genet. 26, 122–127.
[12] Scholl, F.A., McLoughlin, P., Ehler, E., de Giovanni, C. and Schafer, B.W. (2000) J. Cell Biol. 15, 495–506.
[13] Oda, K., Arakawa, H., Tanaka, T., Matsuda, K., Tanikawa, C., Mori, T., Nishimori, H., Tamai, K., Tokino, T., Nakamura, Y. and Taya, Y. (2000) Cell 102, 849–862.
[14] McCurrach, M.E., Connor, T.M., Knudson, C.M., Korsmeyer, S.J. and Lowe, S.W. (1997) Proc. Natl. Acad. Sci. USA 94, 2345–2349.
[15] Yin, C., Knudson, C.M., Korsmeyer, S.J. and Van Dyke, T. (1997) Nature 385, 637–640.
[16] Knudson, C.M., Tung, K.S., Tourtellotte, W.G., Brown, G.A. and Korsmeyer, S.J. (1995) Science 270, 96–99.
[17] Reinke, V. and Lozano, G. (1997) Oncogene 15, 1527–1534.
[18] Sakamuro, D., Sabbatini, P., White, E. and Prendergast, G.C. (1997) Oncogene 15, 887–898.
[19] O'Connor, L., Harris, A.W. and Strasser, A. (2000) Cancer Res. 60, 1217–1220.
[20] Murphy, M., Ahn, J., Walker, K.K., Hoffman, W.H., Evans, R.M., Levine, A.J. and George, D.L. (1999) Genes Dev. 13, 2490–2501.
[21] Caelles, C., Helmberg, A. and Karin, M. (1994) Nature 370, 220–223.
[22] Wagner, A.J., Kokontis, J.M. and Hay, N. (1994) Genes Dev. 8, 2817–2830.
[23] Gao, C. and Tsuchida, N. (1999) Jpn. J. Cancer Res. 90, 180–187.
[24] Yan, Y., Shay, J.W., Wright, W.E. and Mumby, M.C. (1997) J. Biol. Chem. 272, 15220–15226.

[25] Haupt, Y., Rowan, S., Shaulian, E., Vousden, K.H. and Oren, M. (1995) Genes Dev. 9, 2170–2183.
[26] Haupt, Y., Rowan, S., Shaulian, E., Kazaz, A., Vousden, K. and Oren, M. (1997) Leukemia 11 (Suppl. 3), 337–339.
[27] Chen, X., Ko, L.J., Jayaraman, L. and Prives, C. (1996) Genes Dev. 10, 2438–2451.
[28] Ding, H.F., Lin, Y.L., McGill, G., Juo, P., Zhu, H., Blenis, J., Yuan, J. and Fisher, D.E. (2000) J. Biol. Chem. 275, 38905–38911.
[29] Goldstein, J.C., Waterhouse, N.J., Juin, P., Evan, G.I. and Green, D.R. (2000) Nat. Cell Biol. 2, 156–162.
[30] Du, C., Fang, M., Li, Y., Li, L. and Wang, X. (2000) Cell 102, 33–42.
[31] Verhagen, A.M. et al. (2000) Cell 102, 43–53.
[32] Susin, S.A. et al. (1999) Nature 397, 441–446.
[33] Porter, A.G. (1999) Trends Cell Biol. 10, 394–401.
[34] Hsu, Y.T., Wolter, K.G. and Youle, R.J. (1997) Proc. Natl. Acad. Sci. USA 94, 3668–3672.
[35] Gross, A., Jockel, J., Wei, M.C. and Korsmeyer, S.J. (1998) EMBO J. 17, 3878–3885.
[36] O'Connor, L., Strasser, A., O'Reilly, L.A., Hausmann, G., Adams, J.M., Cory, S. and Huang, D.C. (1998) EMBO J. 17, 384–395.
[37] Li, H., Zhu, H., Xu, C.J. and Yuan, J. (1998) Cell 94, 491–501.
[38] Luo, X., Budihardjo, I., Zou, H., Slaughter, C. and Wang, X. (1998) Cell 94, 481–490.
[39] Zha, J., Weiler, S., Oh, K.J., Wei, M.C. and Korsmeyer, S.J. (2000) Science 290, 1761–1765.
[40] Kharbanda, S., Saxena, S., Yoshida, K., Pandey, P., Kaneki, M. and Wang, Q. et al. (2000) J. Biol. Chem. 275, 322–327.
[41] Majumder, P.K., Pandey, P., Sun, X., Cheng, K., Datta, R., Saxena, S., Kharbanda, S. and Kufe, D. (2000) J. Biol. Chem. 275, 21793–21796.
[42] Marchenko, N.D., Zaika, A.I. and Moll, U.M. (2000) J. Biol. Chem. 275, 16202–16212.
[43] Sansome, C., Zaika, A., Marchenko, N.D. and Moll, U.M. (2001) FEBS Lett. 488, 110–115.
[44] Wadhwa, R., Takano, S., Robert, M., Yoshida, A., Nomura, H., Reddel, R.R., Mitsui, Y. and Kaul, S.C. (1998) J. Biol. Chem. 273, 29586–29591.
[45] Soengas, M.S., Alarcon, R.M., Yoshida, H., Giaccia, A.J., Hakem, R., Mak, T.W. and Lowe, S.W. (1999) Science 284, 156–159.
[46] Li, P.F., Dietz, R. and von Harsdorf, R. (1999) EMBO J. 18, 6027–6036.
[47] Schuler, M., Bossy-Wetzel, E., Goldstein, J.C., Fitzgerald, P. and Green, D.R. (2000) J. Biol. Chem. 275, 7337–7342.
[48] Li, H. et al. (2000) Science 289, 1159–1164.