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REVIEW

Suppression of p53: a New Approach to Overcome Side Effects of Antitumor Therapy

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Abstract—The p53 protein is traditionally believed to be a tumor suppressor. Activation of p53-dependent apoptosis in response to damage to cell DNA provides for the elimination of possible tumor cell precursors. However, in some cases the activity of p53 can be dangerous for the organism. Thus, p53-dependent apoptosis induced in normal tissues during chemo- and radiotherapy can cause severe side effects of antitumor therapy and, therefore, limits its efficiency. This review analyzes experimental data on the role of p53 in the primary and late tissue response to DNA-damaging exposures. Comparison of normal and p53-deficient mice indicated that the apoptosis in radiosensitive tissues during the first hours after irradiation is really caused by the activity of p53 which, in turn, is determined by a high level of expression of mRNA of p53. We supposed that a temporary suppression of p53 can decrease the damage to sensitive tissues and accelerate their recovery after the antitumor radio- and chemotherapy. To test this hypothesis, we have isolated a chemical inhibitor of p53 and determined its activity *in vitro* and *in vivo*. This compound, called pifithrin-α, protects wild-type mice against lethal doses of radiation, has no effect on p53-deficient animals, and does not induce visible tumors. These results show that the suppression of p53 is a promising approach in the prevention of side effects of antitumor therapy.

Key words: p53, apoptosis, antitumor therapy

The p53 protein plays a key role in the control of the cell response to various kinds of stress: the activation of p53 in response to stress results in the arrest of proliferation or in apoptosis. Thus, p53 has an important "social" function in the multicellular organism, eliminating damaged and, consequently, potentially dangerous cells, inducing them to die for the organism's safety. The inactivation of p53 which is found in most tumors speaks in favor of its antitumor activity. And just because of this, the inactivation of p53 is traditionally considered to be an undesirable and dangerous event. Many efforts have been directed toward recovering its functions in tumors for therapeutic reasons. However, we will consider here the role of p53 in the organism from another standpoint, taking into account that its activity is not restricted only to tumor cells. We will consider findings which show the involvement of p53 in the regulation of the response of normal tissues to damaging exposures, with special attention to its role in the development of side effects during antitumor therapy.

The efficiency of radio- and chemotherapy is limited by severe complications caused by damage to various sensitive tissues including the hemopoietic and immune systems, different kinds of epithelium (especially of the small intestine), and cells of the reproductive system. If p53 is involved in the induction of this damage, it may be considered as a target for therapeutic suppression in order to decrease the undesirable effects. Obviously, this approach is promising for the treatment only of those tumors which have lost the function of p53, and hence its suppression should not have undesirable consequences.

First, we will consider in brief the molecular mechanisms of the activation of p53, then describe the functions of this protein in tumor suppression, normal development, and differentiation in order to predict the possible complications which could arise during attempts to suppress p53. Afterwards we will consider changes in normal tissues in response to DNA damage and the role of p53 in the induction of these effects. In particular, the following questions will be considered.

Are side effects of antitumor therapy associated with the activation of p53?

Why are the p53-dependent effects of genotoxic exposures tissue-specific?

How does p53 affect the ability of normal tissue to regenerate after stress?

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What consequences can result from the temporary suppression of p53 during the acute period of antitumor therapy?

What complications can be caused by the therapeutic suppression of p53?

MOLECULAR MECHANISMS OF p53 ACTIVITY

Activation of p53 occurs in response to various stresses [1] including damage to DNA by chemical and physical agents (genotoxic stress) [2, 3], disorders in the regulation of assembly/disassembly of microtubules [4], the activation of oncogenes [5], hypoxia [6], hyperthermia [7], etc. (see below). The activation of p53 results either in the arrest of the cell cycle at one of its "check points" or in the induction of apoptosis. The choice between these alternatives depends on the cell type and the character of the stress signal. For example, while thymocytes die from rapid apoptosis caused by damage to DNA [8, 9], fibroblasts become irreversibly "arrested". And the character of the stress determines the p53-dependent response in the case of Baf-3 line of human lymphoid cells. In the presence of interleukin-3, γ-irradiation of Baf-3 inhibits the cell cycle, whereas in the absence of the cytokine the same exposure results in apoptosis [10, 11].

Mechanisms of activation of p53. The activation of p53 is mainly regulated on the post-translational level. In response to stress, the p53 protein is stabilized, which is at least partially regulated by phosphorylation of p53 by a number of cell protein kinases [12-14]. The induction of p53 in response to activation with dominant oncogenes has another mechanism which includes the interaction of p53 with regulatory proteins (see below). The available information on molecular mechanisms of the activation of p53 has been summarized in some recent reviews [1, 12, 15].

The stabilization of p53 provides for its accumulation in the nucleus where it binds to specific sequences of DNA and modulates the transcription (strengthens or weakens) of various p53-regulated genes. The activity of these genes at least partially explains the cell response to stress. Thus, the p53-dependent induction of an inhibitor of cyclin-dependent kinases p21/Waf-1 [16] causes the arrest at the G1 phase of the cell cycle. Another p53-dependent factor, the nuclear protein 14-3-3-σ [17], is involved in arrest of the cell cycle at the G2 phase. The p53-regulated gene *bax* is involved in the activation of p53-dependent apoptosis [18]. However, the mechanisms of p53-dependent cell effects are not limited by the effects of p53 on transcription. Mutants of p53 deficient in transcriptional activation can induce apoptosis in some cell systems, and this indicates that p53 is also involved in other mechanisms of cell regulation which are still unknown [19].

Regulation of p53. The regulation of the p53-dependent response includes the interaction of p53 with a number of cell proteins such as Mdm2, p19ARF, CBP/p300, p33ING1, and Ref-1 [20-27]. Mdm2 is an important negative regulator of p53 which is encoded by a p53-inducible gene. Binding to p53, the Mdm2 protein stimulates the export of p53 from the nucleus and accelerates its proteasomal degradation [26, 27]. The protein p19ARF is induced together with p53 in response to the transformation of dominant oncogenes. It binds to Mdm2 and results in the accumulation of p53 and induction of a p53-dependent response [20]. CBP/p300 [21, 22] and p33ING1 [23] are involved in the activation of p53-dependent transcription. The p53-binding protein Ref-1 is involved in the induction of p53-dependent apoptosis [24, 25].

The p53 protein is also regulated on the level of nuclear transport. The accumulation of p53 in the nucleus is limited by a "window" during the G1 to the early S phase of the cell cycle and prevents the modulation of p53-regulated genes outside of this "window" [28]. Moreover, the transport of p53 into the nucleus is inhibited in early embryonic cells [29] and in neuroblastomas [30], resulting in its functional inactivation. The molecular mechanisms of these events remain unclear.

THE ROLE OF p53 IN NORMAL DEVELOPMENT

To assess to what extent the suppression of p53 can be dangerous for a normal organism, consider data on the normal function of this protein and on pathological consequences of its insufficiency.

p53 and spontaneous carcinogenesis. The toxicity of p53 expression for many tumor cells and the functional inactivation of p53 in most tumors suggest its antitumor activity. The activity of p53 as a tumor suppressor is directly illustrated by the phenotype of mice with genetically inactivated p53 (p53-knockout). The inactivation of p53 is associated with a dramatic increase in the incidence of spontaneous tumors in homozygous and even in heterozygous "knocked-out allele" animals. The homozygous "knocked-out" animals die during the first six months mainly because of lymphomas. In the heterozygous animals different tumors appear among which sarcomas and lymphomas are the most common [31, 32]. The high incidence of tumors in the p53-deficient animals is suggested to result from the p53-absence-caused disorders in the mechanism which prevents the accumulation of spontaneously mutating cells by the irreversible arrest of the cell cycle or induction of apoptosis. The accumulation of such cells produces a cell population which has a high risk of spontaneous transformation. And in fact, somatic cells of the p53-knocked-out mice are characterized by an extremely high incidence of chromosome aberrations [33]. The

dependence of cell control of genome stability on p53 was first shown in studies on the induction of gene amplification with suppressors of p53 [34, 35]. The antitumor activity of p53 is also displayed in its response to the activation of dominant oncogenes. Thus, the expression of activated *ras*, *myc*, *E1A* in fibroblasts results in the induction of p53 and in the irreversible arrest of cell proliferation that is similar to premature aging [5, 36]. In this case the activation of p53 requires the tumor suppressor p19ARF to be expressed [37].

p53 and replicative aging. The control of replicative aging is another important mechanism of the antitumor activity of p53. Natural cell aging ends with irreversible growth arrest after a certain number of divisions. The inactivation of p53 disturbs this process. Thus, fibroblasts from the p53-knocked-out mice fail to age in cell culture and continue to proliferate without limit [38]. For selection of immortalized cell lines, p53 is often deliberately inactivated by expressing oncoproteins of DNA-containing viruses. The irreversible arrest of proliferation of aged cells is accompanied by the p53-dependent transcriptional activation of target genes for p53 [39]. In aged cells p53 seems to be activated in response to chromosome breaks associated with the shortening of telomeres in the aging cells [40].

p53 and tumor progression. The status of p53 significantly effects the features of a tumor. The maintenance of the wild-type p53 in tumors is a positive predictor for tumors of the large intestine, mammary glands, urinary bladder, etc. [41-49]. The intactness of p53 usually characterizes less aggressive tumors which are sensitive to antitumor therapy [50]. p53 also decreases the incidence of tumor metastatic variants, probably by preventing the accumulation of additional mutations that are required for tumor progression [51]. Moreover, p53 is an antiangiogenic factor because it activates the transcription of thrombospondins 1 and 2 which are known to be suppressors of angiogenesis [52-54].

p53 and secreted growth regulators. The effect of p53 is not restricted by its direct influence on the proliferation of damaged cells. The activation of p53 induces damaged cells to secrete growth-inhibiting factors which affect the proliferation of the surrounding cells. p53-dependent factors which inhibit the growth of various cell lines have been found in the culture medium of continuous and primary cell cultures after γ-irradiation and also in the urine of irradiated mice [55]. In addition to the antiangiogenic factors, the target genes of p53 also include other suppressors of growth (IGBP-3, TGF-β2, inhibin-β, inhibitors of serine proteases) [55]. The nature of the p53-dependent growth inhibitors is still unknown. The p53-dependent secretion of stress-dependent growth-inhibiting factors is likely to determine the known "bystander effect" which is observed during gene therapy [56] when the extent of cell death is significantly greater than the number of cells directly expressing the exogenous p53. In fact, the death of tumor cells induced by chemotherapeutic agents gets greater efficiency when the cells are grown mixed with fibroblasts expressing the wild-type p53, whereas p53-deficient fibroblasts lack this feature [55].

p53 and normal development. The phenotype of p53-deficient mice is described not only by an increased incidence of spontaneous tumors. Although the development of most of the p53-deficient embryos is normal [31, 32], exencephalia and later anencephalia occur in many of females (23%) due to improper closure of the neural tube [57, 58]. Improper development of eyes and teeth is also common in the p53-deficient embryos [57, 59].

Moreover, the absence of p53 effects the differentiation of some cell types [60]. Thus, p53-negative mice have significantly increased white pulp and fraction of immature B-cells in the bone marrow [61]. The possible involvement of p53 in the differentiation of thymocytes is also reported [62], and its involvement in the differentiation of neurons and oligodendrocytes is known [63]. The suggested role of p53 in spermatogenesis is based on data on the cyclic expression of p53 in tetraploid primary spermatocytes [64] and on the changed ratio between the stem and differentiated cells in spermatogonia of p53-deficient mice [65]. The inhibition of p53 activity in embryos of *Xenopus laevis* inhibits the differentiation of early blastomeres [66]. All these observations suggest the involvement of p53 in the differentiation and morphogenesis of various types of cells and tissues, although the mechanism of this involvement remains unknown.

To summarize, there are three basic functions of p53 in the normal organism. The first function is associated with its role of a "guardian of the genome", i.e., providing for elimination of potentially dangerous cells during the development of an embryo and in proliferating adult tissues; this function seems to be involved also in the control of cell aging that explains the ability of p53 to increase the efficiency of antitumor therapy. The second function of p53 is the control of cell cooperation by secreting antiproliferative factors: this function seems to be associated with the aging of tissues, response to stress, and the interaction between normal and tumor tissues. The third function of p53 is its involvement in differentiation and morphogenesis.

p53 DETERMINES RADIOSENSITIVITY OF TISSUES AND EMBRYOS

Activity of p53 *in vivo*. To follow the activity of p53 *in vivo*, three years ago three research groups independently obtained transgenic mice which had the gene *lacZ* under the p53-responsive promotor [67-69]. The activity of p53 in tissues of these mice can be detected by blue staining (the color test for β-galactosidase) which corre-

sponds to regions of p53-dependent induction of the transgene [67-69]. In these "blue" mice a pronounced local activation of the transgene was found after irradiation or injection of adriamycin in the spleen, thymus, small intestine, and also in early embryos, whereas the p53-dependent transgene was not activated. Interestingly, just those tissues with the active p53 are the most sensitive to radiation and chemotherapy, and their damage can cause severe side effects of antitumor therapy. Thus, the p53-dependent activation of the transgene mapped the radiosensitive tissues of the mice.

A correlation between the radiosensitivity and the activity of p53 was also found in mouse embryos. Early embryos of mammals have been long known to be highly sensitive to γ-radiation. But the situation sharply changes during organogenesis (8-13 days), and late embryos do not differ in radiosensitivity from adult tissues [70]. In our experiments the induction of the transgene and the level of apoptosis after γ-exposure concurrently decreased by the middle of embryonic development. Moreover, the p53–/– embryos were significantly more radioresistant than their p53+/– twins [67]. Thus, the increased activity of p53 is a molecular basis for the well-known phenomenon of high radiosensitivity of early mammalian embryos.

The difference in the activity of p53 in various tissues is suggested to be of great biological importance. The high activity of p53 seems to be a protective mechanism in rapidly proliferating tissues which prevents the accumulation of genetically damaged cells. Actually, the accumulation of damaged cells which in normal mice are eliminated due to p53-dependent apoptosis seems to be the cause of the accelerated development of lymphomas in p53-deficient mice after γ-exposure [71]. Also, the high survival of embryos of p53-deficient mice after the irradiation correlates with the appearance of multiple developmental defects. Improper location of organs seems to originate from genetically damaged cells which are retained in the p53-deficient animals [72]. These observations impelled D. Lane to call p53 the "guardian of babies" [73].

Radiosensitivity correlates with increased expression of protein p53. Why is p53 active only in certain tissues? What occurs in the middle of embryogenesis when embryos which earlier were sensitive to irradiation become resistant to it? Stabilized p53 is found in all murine tissues, but the amount of this protein in different tissues is very different. The amount of stabilized p53 is much higher in radiosensitive tissues than in radioresistant ones [69]. This finding is also confirmed by *in vitro* studies on tumor cell lines [74-76] and *in vivo* on tissues of small and large intestine of mice [77]. Thus, the amount of the p53 protein in the tissue is suggested to determine its response to genotoxic stress.

An interesting observation to illustrate this hypothesis was made in comparing p53+/– and p53+/+ mice which express the p53-dependent gene *lacZ* [68]. The transgene activation in the irradiated p53+/– versus the p53+/+ mice was decreased significantly more than it would be expected in the case of the twofold decreased gene dose. This phenomenon seems to be explained by the activity of p53 as a tetramer, and therefore, the twofold decrease in the cell concentration of the protein sharply decreases the probability of formation of the active complex. Consequently, low levels of p53 expression in most tissues are likely to be responsible for their radioresistance.

Regulation of p53 on the level of mRNA. The accumulation of p53 in normal tissues after treatment with DNA-damaging agents correlates with levels of tissue expression of mRNA of p53. It seems that the concentration of mRNA of p53 in a tissue determines the efficiency of accumulation of the stabilized p53 protein. The expression of mRNA of p53 in radiosensitive tissues of spleen and thymus is many times higher than in radioresistant tissues of liver, brain, and muscles ([78], E. A. Komarova et al., unpublished observations). Moreover, the high expression level of mRNA of p53 in embryos during the first half of pregnancy significantly decreases during its second half [78, 79], and this correlates with the difference in radiosensitivity of the early and late embryos. Since this sensitivity depends on the function of p53, it seems that just the level of mRNA of p53 determines the tissue fate after irradiation. Consequently, the regulation of p53 at the level of mRNA plays an essential role in the determination of its effects *in vivo*.

It is interesting that up to now the regulation of p53 at the level of mRNA has not been given due attention because it was thought to be regulated mainly on the post-transcriptional level. Therefore, the question of mechanisms providing the different expression in tissues of p53 mRNA remains open.

The difference in the levels of p53 mRNA is not the only pattern to regulate the tissue specificity of p53 effects which can depend on any member of the signal pathway of p53. Using microchips to analyze gene expression, we compared the spectrum of genes induced in response to irradiation in radiosensitive (spleen, thymus) and radioresistant (liver) tissues of p53+/+ and p53–/– mice [55]. Many of the identified p53-dependent genes were found to be tissue-specific [55].

p53-dependent and p53-independent apoptosis. Massive apoptosis occurs in radiosensitive tissues of mice with the wild-type p53 soon after irradiation and is not observed in p53-negative animals; this suggests the determining role of p53 in the organism's primary response to γ-radiation [67, 80-82]. However, the p53-dependent first wave of cell death is often followed by a second wave of p53-independent apoptosis [81, 83, 84] which levels the difference in the radiation-induced damages of the tissues. For example, the level of apoptosis

differed threefold in bone marrow cells of the p53+/+ and p53–/– mice 4 h after the irradiation (6 Gy). However, 8 h later the level of apoptosis in the p53–/– cells increased [81]. The level of the p53-independent apoptosis markedly depends on the radiation dose applied. Thus, the p53-independent apoptosis is virtually absent in the small intestine after irradiation at the dose of 1 Gy and is clearly pronounced in mice exposed to 8 Gy [83].

p53 and tissue recovery after genotoxic stress. p53 increases the damage of radiosensitive tissues, inducing acute apoptosis after genotoxic stress. What is the effect of p53 on tissue recovery after stress? Does apoptosis in stem cells depend on p53? To answer these questions, consider findings on various tissues.

The survival of hemopoietic multipotent stem cells and committed precursors after irradiation can be evaluated using the clonogenic approach on spleen cells and also by determination of the extent of hemopoiesis recovery. The multipotent stem cells and more differentiated colony-forming cells isolated from p53-deficient mice are significantly more resistant to radiation and chemotherapeutic agents than similar cells from animals with wild-type p53 [85, 86]. The same was found for fibroblastoid precursors for bone marrow cells. Based on these findings, it is concluded that the recovery of hemopoietic cells [86] after genotoxic stress should be more efficient in the absence of p53.

Analysis of findings on clonogenic survival of cells of other radiosensitive tissues after irradiation suggests an unexpected conclusion. Notwithstanding the great difference in the extent of radiation-induced apoptosis in the epithelium of small intestine, skin, and testicular cells of the p53-deficient mice and mice with wild-type p53, the late survival of clonogenic cells responsible for recovery of these tissues nearly does not depend on their p53-status [65, 82, 87, 88]. The recovery of spermatogonia was even delayed in the p53-deficient mice [65, 89]. Differentiated skin keratinocytes with the "wild" p53 were five times more sensitive to the ultraviolet-induced apoptosis than the p53-deficient cells. However, the induction of apoptosis in nondifferentiated cells of the epidermal basal layer did not depend on p53 [88]. The induction of apoptosis in differentiated and stem cells of the epithelium of small and large intestine also differently depended on p53. Although the acute apoptosis in the differentiated cells depended on the function of p53, the recovery of these tissues from stem cells after irradiation did not depend on the status of p53. Stem cells of the large intestine epithelium are known to be more radioresistant and, thus, they should less depend on p53 than stem cells of small intestine epithelium [87]. This difference is suggested to cause the increased incidence of secondary tumors in the large intestine compared to the small one after radio- and chemotherapy. It seems that apoptosis of the damaged cells in the large intestine due to the decreased dependence of this tissue on p53 increases the risk of cell transformation. Why do the differentiated cells depend on p53 much stronger than the stem cells? It is suggested that the p53-dependent apoptosis is not induced in the stem cells because most of them are not proliferating. The differentiated and differentiating cells are in the state of proliferation, and this seems to explain their high sensitivity to damage of DNA and the strong dependence on p53. However, the protection of early precursors against p53-dependent death is likely to represent the more common phenomenon that also occurs during early embryogenesis. The induction of p53 was found to be inhibited in nondifferentiated stem embryonal cells *in vitro* and in early embryos *in vivo*, and this seems to be caused by the limitation of the nuclear transport of p53 [29].

Summarizing these data, it is concluded that during the first hours after genotoxic stress p53 plays the role of a killer of differentiating cells of radiosensitive tissues and also of stem cells of the hemopoietic system. It is suggested that a temporary suppression of p53 should decrease the damage of radiosensitive tissues caused by the p53-dependent apoptosis.

IS INHIBITION OF p53 DANGEROUS?

Based on all of the experimental data, the p53-dependent apoptosis is concluded to be the cause of the rapid death of cells of radiosensitive organs during the first hours after γ-radiation. Chemotherapy with DNA-damaging agents (doxorubicin, fluorouracil, cytosine arabinoside, cisplatin, etoposide, etc.) and other inducers of p53 (vinca-alkaloids) seems to cause similar consequences. We suppose that a temporary suppression of the functions of p53 during the first hours after genotoxic stress should decrease the damage of normal tissues by antitumor therapy because it should provide the maintenance of the cells which are able to reduce the damage during the period of p53 being "switched off". Obviously, this approach can be used only in the treatment of p53-deficient tumors because their sensitivity to the therapy should not change in the presence of inhibitors of p53.

Is the available information sufficient to justify the principle of the suppression of p53 during antitumor therapy? We summarize the "pro" and "con" arguments as a dispute between two standpoints: *pessimistic* (**P**) and *optimistic* (**O**).

P. The loss of p53 in tumors is associated with the increase in their progression and resistance to chemotherapy. Suppression of p53 should cause the same changes in tumors.

O. More than 50% of human tumors are free of functional p53. The suppression of p53 should not affect the treatment efficiency of such tumors. Moreover, in

some tumors disorders in the function of p53 are associated with increased sensitivity to antitumor therapy [90]. Thus, in such cases the inhibition of p53 is likely even to increase the therapeutic effect of antitumor treatment.

P. Insufficiency of p53 is associated with a high risk of spontaneous tumors. The suppression of p53 during antitumor therapy may result in the survival of genetically changed cells in radiosensitive tissues which normally would be eliminated by p53-dependent apoptosis. This can increase the risk of appearance of new tumors.

O. Except for hemopoietic stem cells, the differentiating and differentiated cells of radiosensitive tissues are characterized by sensitivity to p53-dependent apoptosis; the survival of clonogenic cells does not depend on p53. Therefore, the suppression of p53 should not affect the amount of genetically changed cells among the surviving stem cells, and, consequently, such a treatment should not increase the risk of appearance of secondary tumors. For a long time colony-stimulating growth factors have been used during chemotherapy with the purpose of stimulating the recovery of hemopoiesis. However, the therapeutic effect of these factors is more likely to be associated with the inhibition of the p53-dependent apoptosis [91] due to activation of the so-called survival pathways, that is, of the signal pathways responsible for cell survival.

P. The p53 protein determines only the rapid tissue response to genotoxic stress, the second wave of the p53-independent apoptosis eliminates differences in the damage to tissues in animals with both the wild-type and deficient p53.

O. This is true only for high doses of chemo- and radiotherapy. The second wave of apoptosis is not observed after low or middle doses of radiation. This indicates that the suppression of p53 should be protective for the organism.

P. The degree of survival of stem cells in the intestinal epithelium and in spermatogonia does not depend on the status of p53. This means that tissue regeneration cannot be improved at the cost of suppression of p53.

O. Tissue regeneration originates from stem cells and occurs for a long time. The suppression of apoptosis in the population of committed precursors and differentiated cells by suppression of the functions of p53 should support the function of normal tissue during regeneration.

CHEMICAL INHIBITOR OF p53 PROTECTS MICE AGAINST LETHAL RADIATION DOSES

When writing this review, we had no experimental data to confirm the possibility to use the suppression of p53 with the purpose to decrease the damage to normal tissues during antitumor radio- and chemotherapy. However, we have recently succeeded in the identification of a compound, pifithrin-α (PFT-α), which inhibits the function of p53. To find an inhibitor of p53, a "library" of 10,000 random compounds was used; each compound was tested on the earlier obtained screening system of ConA cells. These cells contain the bacterial gene *lacZ* which is controlled by the p53-regulated promotor. The activation of this gene (detected by the blue staining with X-gal) occurs in response to the damage of DNA caused by radiation or chemotherapeutic agents. We have isolated a number of compounds which inhibit *lacZ* activation in ConA cells, and one of these compounds was described in detail. Using PFT-α, we found that the temporary suppression *in vitro* of p53 inhibits in sensitive cells the apoptosis induced by the damage to DNA and thus increases the fraction of cells surviving the stress. The testing of PFT-α *in vivo* has shown that the single injection of the preparation protected 100% of mice against the 60% lethal radiation dose [92]. It is not yet clear what the place of PFT-α in the signal pathway of p53 is. It seems that the mechanism of its effect is associated with a disturbance in the nuclear transport of p53.

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