Surfing the p53 network

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The p53 tumour-suppressor gene integrates numerous signals that control cell life and death. As when a highly connected node in the Internet breaks down, the disruption of p53 has severe consequences.

Tumour-suppressor genes are needed to keep cells under control. Just as a car's brakes regulate its speed, properly functioning tumour-suppressor genes act as brakes to the cycle of cell growth, DNA replication and division into two new cells. When these genes fail to function properly, uncontrolled growth — a defining feature of cancer cells — ensues.

The p53 gene, first described in 1979, was the first tumour-suppressor gene to be identified. It was originally believed to be an oncogene — a cell-cycle accelerator (Box 1) — but genetic and functional data obtained ten years after its discovery showed it to be a tumour suppressor. Moreover, it was found that the p53 protein does not function correctly in most human cancers (Fig. 1). In about half of these tumours, p53 is inactivated directly as a result of mutations in the p53 gene. In many others, it is inactivated indirectly through binding to viral proteins, or as a result of alterations in genes whose products interact with p53 or transmit information to or from p53.

The realization that p53 is a common denominator in human cancer has stimulated an avalanche of research since 1989. During that time there have been over 17,000 publications centred on p53 — 3,300 in the past year alone — and over 10,000 tumour-associated mutations in p53 have been discovered, in organisms ranging from humans to clams[1,2]. As might be expected, this work has led not only to considerable insights into tumour development, but also to considerable confusion and controversy. Here we suggest that signalling pathways involving p53 — like cellular signalling pathways in general — cannot be understood by looking at isolated components. Instead, it is essential to consider the tangled networks into which these signalling components are integrated.

Mechanism of inactivating p53	Typical tumours	Effect of inactivation
Amino-acid-changing mutation in the DNA-binding domain	Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus and many others	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes
Deletion of the carboxy-terminal domain	Occasional tumours at many different sites	Prevents the formation of tetramers of p53
Multiplication of the MDM2 gene in the genome	Sarcomas, brain	Extra MDM2 stimulates the degradation of p53
Viral infection	Cervix, liver, lymphomas	Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation
Deletion of the $p14^{ARF}$ gene	Breast, brain, lung and others, expecially when p53 itself is not mutated	Failure to inhibit MDM2 and keep p53 degradation under control
Mislocalization of p53 to the cytoplasm, outside the nucleus	Breast, neuroblastomas	Lack of p53 function (p53 functions only in the nucleus)

Figure 1 **The many ways in which p53 may malfunction in human cancers.**

Activating the p53 network

The p53 network is normally 'off'. It is activated only when cells are stressed or damaged. Such cells pose a threat to the organism: they are more likely than undamaged cells to contain mutations and exhibit abnormal cell-cycle control, and present a greater risk of becoming cancerous. The p53 protein shuts down the multiplication of stressed cells, inhibiting progress through the cell cycle. In many cases it even causes the programmed death (apoptosis) of the cells in a desperate attempt to contain the damage and protect the organism. The p53 protein therefore provides a critical brake on tumour development, explaining why it is so often mutated (and thereby inactivated) in cancers.

What sort of stresses, then, activate the p53 network? Early work focused on DNA damage as the 'on' switch. A single break in a double-stranded DNA molecule may be sufficient to trigger a rise in levels of p53 protein. This remarkable sensitivity to DNA damage confounded subsequent studies that sought to establish whether the p53 response could be triggered by other signals. It was difficult to show that these other signals did not cause at least a few breaks in double-stranded

Box 1 The genes that cause cancer

Oncogenes. These are analogous to the accelerators in a car. Oncogenes stimulate appropriate cell growth under normal conditions, as required for the continued turnover and replenishment of the skin, gastrointestinal tract and blood, for example. A mutation in an oncogene is tantamount to having a stuck accelerator: even when the driver releases his foot from the accelerator pedal, the car continues to move. Likewise, cells with mutant oncogenes continue to grow (or refuse to die) even when they are receiving no growth signals. Examples are Ras, activated in pancreatic and colon cancers, and Bcl-2, activated in lymphoid tumours.

Tumour-suppressor genes. When the accelerator is stuck to the floor, the driver can still stop the car by using the brakes. Cells have brakes, too, called tumour-suppressor genes. These keep cell numbers down, either by inhibiting progress through the cell cycle and thereby preventing cell birth, or by promoting programmed cell death (also called apoptosis). Just as a car has many brakes (the foot pedal, handbrake and ignition key), so too does each cell. When several of these brakes are rendered non-functional through mutation, the cell becomes malignant. Examples are the gene encoding the retinoblastoma protein, inactivated in retinoblastomas, p53 (Fig. 1), and $p16^{INK4a}$, which inhibits cyclin-dependent kinases and is inactivated in many different tumours.

Repair genes. Unlike oncogenes and tumour-suppressor genes, repair genes do not control cell birth or death directly. They simply control the rate of mutation of all genes. When repair genes are mutated, cells acquire mutations in oncogenes and tumour-suppressor genes at an accelerated rate, driving the initiation and progression of tumours. In the car analogy, a defective repair gene is much like having a bad mechanic. Examples are nucleotide-excision-repair genes and mismatch-repair genes, whose inactivation leads to susceptibility to skin and colon tumours, respectively.

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DNA. Recent research, however, has confirmed the existence of at least three independent pathways by which the p53 network can be activated.

One pathway is indeed triggered by DNA damage, such as that caused by ionizing radiation. Here the activation of the network is dependent on two protein kinases — enzymes that add phosphate groups to other proteins. Two of the major kinases in question are called ATM (for ataxia telangiectasia mutated, named after a disease in which this enzyme is mutated) and Chk2 (ref. 3). ATM is stimulated by double-strand breaks, and Chk2 is in turn stimulated by ATM.

The second pathway is triggered by aberrant growth signals, such as those resulting from the expression of the oncogenes Ras or Myc. In this case, activation of the p53 network in humans depends on a protein called $p14^{ARF}$ (refs 4,5).

The third pathway is induced by a wide range of chemotherapeutic drugs, ultraviolet light, and protein-kinase inhibitors. This pathway is distinguished from the others because it is not dependent on intact ATM, Chk2 or $p14^{ARF}$ genes, and may instead involve kinases called ATR (ataxia telangiectasia related) and casein kinase II[6].

All three pathways inhibit the degradation of p53 protein, thus stabilizing p53 at a high concentration. The increased concentration of p53 — covalently modified as described below — allows the protein to carry out its major function: to bind to particular DNA sequences and activate the expression (transcription) of adjacent genes. These genes, directly or indirectly, lead ultimately to cell death or the inhibition of cell division — but more on this later.

Stabilizing and modifying p53

The amount of p53 protein in cells is determined mainly by the rate at which it is degraded, rather than the rate at which it is made. The degradation proceeds through a process called ubiquitin-mediated proteolysis. Through a series of steps, several copies of a small peptide (ubiquitin) are attached to the protein to be degraded (in this case p53). This ubiquitin chain acts as a 'flag', enabling p53 to be detected by the protein-degrading machinery. The MDM2 protein is one of the enzymes involved in labelling p53 with ubiquitin[7].

This process is subject to a feedback loop like those found in electrical circuits. The p53 protein binds to the regulatory region of the MDM2 gene and stimulates the transcription of this gene into messenger RNA, which is then translated into protein. This MDM2 protein then binds to p53 and stimulates the addition of ubiquitin groups to the carboxy terminus (the end) of p53, which is then degraded. This lowers the concentration of p53 and reduces transcription of the MDM2 gene, closing the feedback loop and allowing p53 levels to rise again.

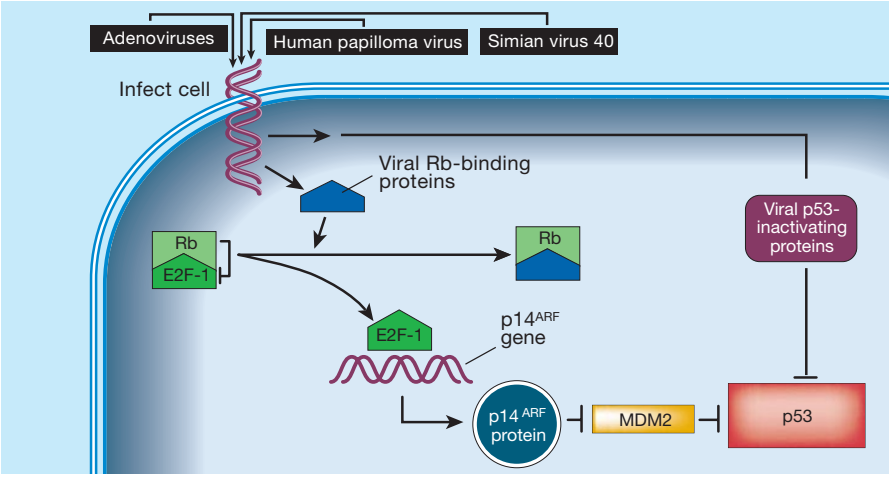

Figure 2 **Viral oncogenes and the p53 network. Several viruses encode proteins that block the interaction between an infected cell's retinoblastoma protein (Rb) and transcription factors of the E2F family, such as E2F-1. This frees E2F-1 to activate target genes required for cellular proliferation (not shown). But it also results in the production of the $p14^{ARF}$ protein, interference with the activity of MDM2 (a negative regulator of the p53 protein), and consequent stabilization of p53. This slows cell (and hence viral) replication. The viruses counteract these cellular defences by producing proteins that inhibit the function of p53. This predisposes the infected cells to become cancerous.**

But an increased level of cellular p53 protein alone is not sufficient for it to become a transcriptional activator. This requires conformational changes in the protein, resulting from modifications such as the addition or removal of phosphate, acetyl, glycosyl, ribose, ubiquitin or 'sumo' chemical groups[6,8,9] ('sumo' is a ubiquitin-like polypeptide that can reversibly modify proteins). The carboxy terminus of p53 normally folds back and inhibits the DNA-binding domain located in the central part of the p53 protein. Acetylation of lysine residues or phosphorylation of serine residues near the carboxy terminus of p53 can enhance the binding of p53 to DNA, presumably by interfering with this folding. Interestingly, such conformational changes can also be achieved by antibodies, peptides and drugs that interact with the carboxy terminus[10]. These compounds might represent a new way to enhance the function of normal p53 and to restore normal function to mutant p53.

Phosphorylation of the amino terminus (the start) of p53 does not affect its DNA-binding abilities, but does affect its affinity for MDM2 and subsequent degradation. Other changes to the p53 protein and its MDM2 partner are also important in the p53 network. For example, sumolation of MDM2 might reduce its ubiquitination (and hence degradation)[11]. This would mean that there is more MDM2 around to ubiquitinate p53, so stimulating p53 degradation.

When a protein promotes the synthesis of its own negative regulator, the levels of the two proteins in a cell would be expected to oscillate out of phase with each other. This has been observed for p53 and MDM2 (ref. 12). Similarly, any perturbation of either p53 or MDM2 should have dramatic effects on the other, as well as on the behaviour of cells and organisms. This is shown by the fact that mice genetically engineered to lack both MDM2 and p53 survive to adulthood, whereas mice lacking only MDM2 die as embryos[13] — presumably because of the unchallenged activity of p53.

Linking activation to stabilization

The most intensively investigated pathway to p53 activation is the one that is initiated by DNA damage[3]. This damage is sensed by 'checkpoints' that retard progress through the cell cycle until the damage is mended. The checkpoint proteins that sense and signal DNA damage have been remarkably conserved during evolution, being found in organisms spanning yeast to humans. They include several kinases, particularly DNA-dependent protein kinase, ATM, Chk1 and Chk2 (ref. 3). All four of the mammalian forms of these kinases phosphorylate p53 at amino-terminal sites that are close to the MDM2-binding region of the protein[6,8,9]. These results have led to a seductive model in which these kinases, activated by DNA damage, phosphorylate the p53 protein and thereby block its interactions with MDM2, leading to stabilization of p53.

But it has been shown that p53 molecules lacking most phosphorylation sites can still be stabilized in response to DNA damage and still activate p53-dependent gene transcription. This suggests that the activation of p53 is not fully controlled by any single phosphorylation site or protein[6,8,9]. On the other hand, patients with inherited mutations of the Chk2 gene are predisposed to cancer. This syndrome is remarkably similar to that seen in patients with inherited mutations of p53 (ref. 14) — compelling evidence for the importance of checkpoints that sense DNA damage in the p53 network.

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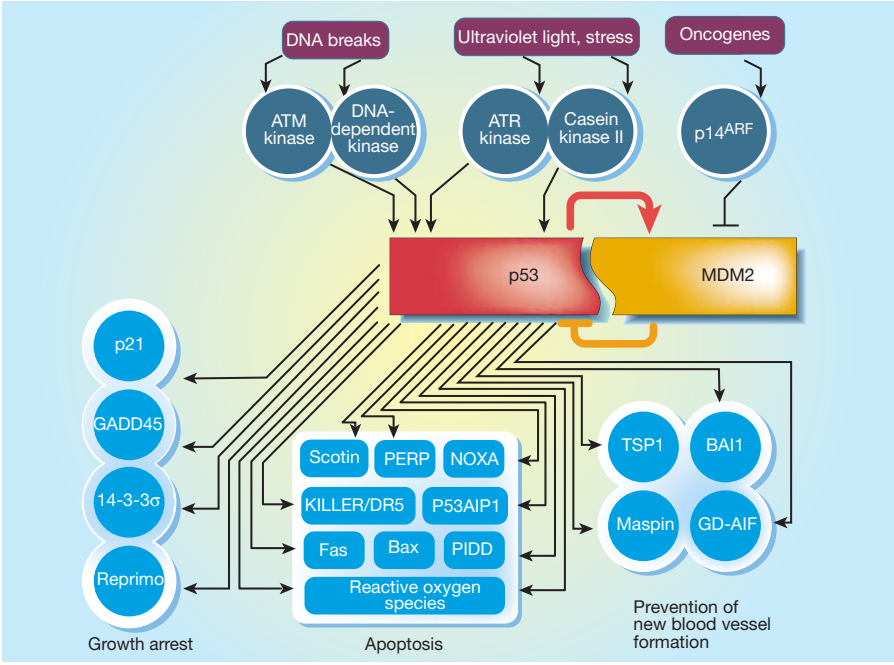

Figure 3 **The p53 network. Activation of the network (by stresses such as DNA damage, ultraviolet light and oncogenes) stimulates enzymatic activities that modify p53 and its negative regulator, MDM2. This results in increased levels of activated p53 protein. The expression of several target genes is then activated by binding of the activated p53 to their regulatory regions. These genes are involved in processes that slow down the development of tumours. For example, some genes inhibit cell-cycle progression or the development of blood vessels to feed a growing tumour; others increase cell death (apoptosis). A negative feedback loop between MDM2 and p53 restrains this network. Many other components of this network, not shown here, have been identified. Similarly, p53 activation results in a variety of other effects, including the maintenance of genetic stability, induction of cellular differentiation, and production of extracellular matrix, cytoskeleton and secreted proteins. The components of the network, and its inputs and outputs, vary according to cell type. p53 is a highly connected 'node' in this network. It is therefore unsurprising that the loss of p53 function is so damaging, and that such loss occurs in nearly all human cancers.**

The second pathway for activating p53 involves the expression of oncogenes in the absence of DNA damage[4,5]. These oncogenes stimulate the transcription of the $p14^{ARF}$ gene or stabilization of the $p14^{ARF}$ protein, which then binds to MDM2 and inhibits its activity. There is also a spatial element to the regulation of MDM2 by $p14^{ARF}$. The $p14^{ARF}$ protein is located within the nucleolus — a subcompartment within the nucleus. In some situations, $p14^{ARF}$ appears to sequester MDM2 into this subcompartment. This keeps MDM2 away from p53, which remains outside the nucleolus (but within the nucleus) where it can activate the transcription of its target genes (see next section). Both MDM2 and p53 proteins also contain nuclear-import and nuclear-export signals — address labels that enable them to be directed into the nucleus and out again[15]. This offers yet another avenue for regulation. Indeed, p53 has been shown to reside outside the nucleus in some tumours[15] (Fig. 1).

The study of viral oncogenes has also shown that interconnected signalling pathways control the activity of p53. Some DNA viruses — such as simian virus 40, human papilloma virus and adenoviruses — encourage the cells they infect to become cancerous (Fig. 2). After infecting the cells of their hosts, these viruses produce proteins that bind to and inhibit another tumour suppressor, the retinoblastoma protein[16], as well as proteins that inactivate p53.

These results have obvious implications for tumour development. But they also suggest that even a complete characterization of the genome (all the genes in an organism), the transcriptome (the genes that are actually expressed as mRNA at a given time) and the proteome (the proteins that are produced from the expressed genes) would not provide a very accurate portrait of the state of the p53 protein in any cell. The condition of this protein cannot be accurately predicted from just its sequence, as it is extensively 'decorated' by different chemical groups, rather as a Christmas tree is decorated by lights and tinsel.

As well as the covalent modifications described above, numerous proteins bind to p53 and may modify its stability as well as its ability to activate transcription[8]. Moreover, in a damaged or stressed cell there is not a single, monolithic p53 species but rather a variety, each modified in a specific fashion. And any detailed characterization of p53 must also include the fourth dimension — time. The state of p53 can change rapidly as cells adapt to the network-initiating stimulus and respond to the numerous feedback and feedforward systems that are thereby set in motion.

What happens next?

Many biochemical functions have been ascribed to activated p53, but the best documented is its ability to bind to specific sequences in DNA and activate the transcription of adjacent genes[17]. The regions of p53 responsible for binding to specific sequences and activating transcription have been precisely defined. Virtually all naturally occurring mutations in the p53 gene reduce the ability of the encoded p53 protein to activate transcription, supporting the idea that this activity is critical to p53's role as a tumour suppressor.

Several dozen genes that are controlled directly by p53 have been identified[17], and they fall broadly into four categories.

Cell-cycle inhibition. One of the first effects of p53 expression, in nearly all mammalian cell types, is a block in the cell-division cycle. The p53 protein directly stimulates the expression of $p21^{WAF1/CIP1}$, an inhibitor of cyclin-dependent kinases (CDKs). CDKs are key regulators of the cell cycle, working together with their partners — cyclin proteins — to ensure that, for example, DNA replication ('S phase') follows smoothly from the cellular resting phase known as G1.

Through its negative effects on various CDKs, $p21^{WAF1/CIP1}$ inhibits both the G1-to-S and the G2-to-mitosis transitions. Other genes, the newest of which is Reprimo, can also arrest cells in G2 phase[18]. In epithelial cells — those that line organs such as the intestine and bladder — p53 also stimulates the expression of protein 14-3-3σ, which sequesters cyclin B1–CDK1 complexes outside the nucleus and thereby helps to maintain a G2 block[19,20]. Interestingly, the inhibition of 14-3-3σ can, in a single step, make primary human epithelial cells grow indefinitely in culture[21]. This immortality may be a key feature distinguishing tumour cells from normal cells.

Apoptosis. Some cells in which p53 is activated undergo programmed death[22]. There are several potential mediators of p53-induced apoptosis[17]. The Bax protein — the prototype of this class of mediator — is an apoptosis-inducing member of the Bcl-2 protein family. Transcription of the Bax gene in some human cells is directly activated by p53-binding sites in the regulatory region of the gene[23]. However, there is no analogous p53-binding site in the regulatory region of the murine Bax gene[24]. More recently, the NOXA and P53AIP1 genes have been discovered to be directly activated by p53 (refs 25, 26). Like Bax, the NOXA and P53AIP1 proteins are located in mitochondria — the cellular powerhouses. When overexpressed, these proteins induce apoptosis.

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Other potential mediators of p53-induced apoptosis include proteins with similarities to the classic 'death-signal' receptors, the TNF (tumour necrosis factor) receptor and Fas. The most recently discovered of these proteins is called PIDD[27]. Finally, p53 may cause death by directly stimulating mitochondria to produce an excess of highly toxic reactive oxygen species.

Genetic stability. Not all genes that limit tumour development control cell birth or death directly. For example, repair genes involved in correcting certain types of error in DNA lead only indirectly to tumour development when inactivated (Box 1). This is because inactivation of these genes leads to genetic instability — an accumulation of errors in all genes, including those that control cell growth. The p53 protein may be important in maintaining genetic stability[28,29]. The mechanisms are not clear, but they may involve the induction of genes that regulate 'nucleotide-excision' repair of DNA, chromosomal recombination and chromosome segregation[28,29]. Further evidence for a role for p53 in DNA repair comes from the induction of a specific 'ribonucleotide reductase' gene by p53 after DNA damage[30]. Such genes maintain cellular control over the responses to DNA errors in a wide range of organisms[31].

Inhibition of blood-vessel formation. To reach dangerous sizes, tumours must encourage the growth of new nutrient-bringing blood vessels in their vicinity. The normal p53 protein stimulates the expression of genes that prevent this process[17,32]. Cells in which p53 is inactivated by mutation would therefore be more likely to recruit new blood vessels, providing a critical growth advantage at a late point in tumour development. This stage is the time when most natural p53 mutations occur. Studies of other tumour suppressors support the idea that preventing the formation of new blood vessels can be an important component of the activity of a tumour suppressor[33].

As well as the genes that are directly activated by p53, there are many that are repressed, although the mechanisms involved are unclear[34,35]. Why does p53 regulate the expression of so many genes — are most of them 'artefacts', which coincidentally have p53-binding sites, but do not have an important role in the p53 network?

Some p53-responsive genes are, in fact, activated only by artificially high levels of added p53, so the possibility of artefacts must be considered for any individual candidate gene. But alternative theories are more attractive and instructive, for the following reasons. First, even the most basic features of the cellular response to DNA damage are not the same in different species and vary even in different cells of the same organism[34,35]. For example, high levels of normal p53 cause some human cells to undergo apoptosis, whereas others simply undergo prolonged cell-cycle arrest. Therefore, one should expect variations in the expression of p53 target genes. Second, the genes most likely to be mutated in cancers, such as p53, are those that serve as nodal points for the integration of a large number of different signals. On this basis, one would expect there to be numerous downstream mediators of such genes, as explained below.

The p53 network

How can the vast number of activating signals, covalent and non-covalent modifications, and downstream regulators of p53 be put into context? One way to understand the p53 network is to compare it to the Internet. The cell, like the Internet, appears to be a 'scale-free network': a small subset of proteins are highly connected (linked) and control the activity of a large number of other proteins, whereas most proteins interact with only a few others[36]. The proteins in this network serve as the 'nodes', and the most highly connected nodes are 'hubs'. In such a network, performance is almost unchanged by random removal of nodes. But such systems contain an Achilles' heel: "the most effective way of destroying a network is to attack its most connected nodes"[37]. It is clear that p53 is one of the most highly connected nodes in the cell (Fig. 3, previous page), and that an attack on p53 (by mutation) will disrupt basic cellular functions, particularly the responses to DNA damage and tumour-predisposing stresses.

This theoretical framework has several implications. We should not be surprised that the inactivation of less connected nodes does not necessarily have draconian effects on the cell, and does not recapitulate all the effects of p53 inactivation. Instead, any outcome that mimics a part of what happens after p53 inactivation should be considered positive evidence of a link. For example, inactivation of the $p21^{WAF1/CIP1}$ or Bax genes does not have exactly the same effects as inactivation of p53. Yet inactivation of each of these genes has tumour-enhancing effects in some cells under specific conditions[23,38].

One should also expect that combined attacks on many nodes linked to p53 should have progressively more severe effects that more and more closely resemble an attack on p53. This is exactly what has been observed[39,40]. And finally, one should be especially cautious about experiments in which p53-linked nodes are overexpressed rather than disrupted. Such overexpressed gene products might interact with many other nodes in an abnormal and unregulated manner. Making sense of such experiments is much more difficult and error-prone than interpreting gene-disruption experiments. The same principles probably apply to most other tumour suppressors, which also function as highly connected nodes that respond to diverse influences within cell-type-specific networks.

An appreciation of the existence and complexity of cellular networks should enable more rational design and interpretation of experiments in the future, and should allow more realistic approaches to treatment. After all, the most important question in p53 research is: how do we attack a cellular network that is already compromised by inactivation of one of its most highly connected nodes? New work[41] suggests possible tactics for such an attack — and ways to dramatically affect the management of a diverse array of cancers. ■

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- **http://www.cancergenetics.org/p53.htm**
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