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Review

The *p53* tumour suppressor gene

R. J. C. STEELE, A. M. THOMPSON, P. A. HALL and D. P. LANE

Dundee Cancer Research Institute, Dundee Teaching Hospitals Trust and University of Dundee, Dundee, UK
Correspondence to: Professor R. J. C. Steele, Department of Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

Background Abnormalities of the *p53* tumour suppressor gene are thought to be central to the development of a high proportion of human tumours. This article reviews current understanding of its function and potential clinical significance.

Methods Material was identified from previous review articles, references cited in original papers, a Medline search of the literature over the 12 months to January 1998, and by scanning the latest issues of relevant journals.

Results and conclusion *p53* is considered to be a stress response gene, its product (the p53 protein) acting to induce cell cycle arrest or apoptosis in response to DNA damage, thereby maintaining genetic stability in the organism. These functions are executed by a complex and incompletely understood series of steps known as the 'p53 pathway', part of which involves induction of the expression of a number of other genes. As *p53* is the most commonly mutated gene in human cancer, it has attracted a great deal of interest as a prognostic factor, diagnostic tool and therapeutic target. However, despite many promising studies, its potential in practical cancer management has still to be realized.

In recent years the rather prosaic term 'p53' has reached the attention of most clinicians but many have only the haziest notion of what it represents. Molecular biologists now believe that the p53 protein has a major role in cellular function and homoeostasis, and that defects in the system to which it is central occur in most if not all human cancers. Its importance is reflected in over 9000 p53-related papers published since 1992. The purpose of this article is to provide an explanation of current understanding of the physiological and clinical significance of p53. Given the size of the literature an exhaustive review has not been attempted; references have been restricted to key articles and representative examples where work has been replicated.

Oncogenes and tumour suppressor genes

The development of cancer is now seen as a complex, multi-step process which depends on both external carcinogenic influences and subcellular genetic defects. The genetic defects may be caused directly by mutagenic carcinogens, but they may also be inherited or may occur sporadically (perhaps induced by background radiation). Indeed, not all carcinogenic stimuli produce mutations; they may merely enhance cellular proliferation or survival such that the likelihood of a dangerous mutation occurring and persisting is increased. It is generally accepted, however, that genetic mutations are necessary before cancer can arise[1].

The genes that are associated with the development of malignancy when dysfunctional are broadly categorized as oncogenes, or tumour suppressor genes. Although this classification may be imperfect, it is a useful means of thinking about the genetic basis of cancer.

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Oncogenes

Oncogenes were first identified when it was realized that the tumorigenicity of many retroviruses could be attributed to specific genes, and the first of these to be cloned was v-*src* from the Rous sarcoma virus which causes sarcomas in chickens. It was then discovered that chicken DNA contains a very close relative of v-*src*, and that similar versions of the same gene are present in the DNA of other vertebrates[2,3]. Thus it was realized that the retroviral genes which can transform normal cells into cancer cells (i.e. oncogenes) are actually derived from normal cellular genes. These normal genes are now known as proto-oncogenes, and may become oncogenes either by incorporation of a retrovirus into the genetic material or, more commonly, by mutation at their normal site of residence within the cellular DNA.

Because an oncogene by definition confers malignant properties onto a cell, mutation of a proto-oncogene generally results in gain of function; this may occur by amplification where the affected gene overproduces a protein that drives cell proliferation or enhances survival, or it may occur by production of a mutant protein which escapes control mechanisms that normally constrain its proliferative activity. It follows that proto-oncogenes encode proteins that stimulate cellular growth or survival. These may be broadly categorized as growth factors, growth factor receptors, intracellular signal transducers (which transmit the signal from an activated receptor to the nucleus) and transcription factors (which induce protein synthesis by stimulating the DNA in the nucleus to produce messenger RNA).

An oncogene (i.e. a mutated proto-oncogene) typically acts as a dominant gene, and so a mutation in one allele will be sufficient for it to become manifest. However, with few exceptions[4], oncogenes are not inherited and usually contribute to the pathogenesis of cancer by somatic mutations within the cells of the target tissues.

Tumour suppressor genes

In contrast to oncogenes, tumour suppressor genes, in their normal state, encode proteins that act to maintain cell numbers by suppressing proliferation or promoting loss. These genes become involved in the tumorigenic process when they sustain mutations that result in loss of function. In this case the normal gene tends to act in a dominant fashion and only when both alleles are damaged will the effect of the mutant gene be apparent. Because of this, mutations in single alleles of tumour suppressor genes may be passed through the germline; virtually all of the genes that have been identified as responsible for inherited cancer belong to this category[1]. Sporadic loss of tumour suppressor function in a genetically normal individual can and does occur but, as this requires both alleles in a single cell to malfunction due to either mutation or deletion (loss), it occurs much less frequently than in an individual who has an inherited defect in all cells.

p53 belongs to the category of tumour suppressors and it appears to occupy a pivotal role in deciding the fate of cells that have been stressed. Thus elimination of cells that have sustained genetic damage depends on functional p53, and damage to the *p53* gene itself may allow cells bearing other mutant genes to proliferate unchecked.

Physiological role of p53

p53 is a phosphoprotein made up of 393 amino acids; it resides in the nucleus of the cell. It was first discovered as a protein that could bind with the virally encoded large 'T' antigen (or protein) which is responsible for the transformation of cells by simian virus 40[5,6]. These early studies were attempting to understand the mechanism by which this T antigen exerted its transforming properties by searching for cellular proteins that might be directly affected. Antibodies raised against the large T antigen immunoprecipitated a protein of 53 kD (hence the term 'p53') and for several years this protein was thought to be the product of an oncogene. It was later recognized, however, that many transformed cells contained *p53* gene mutations and that normal (or 'wild-type') p53 functioned to suppress cellular proliferation.

It is now established that the p53 protein is central to the cellular response to a wide variety of stressful stimuli[7,8]. These stimuli, which include DNA damage, hypoxia, heat shock, metabolic changes and certain cytokines, activate the p53 protein, which in turn drives a series of events that culminate either in cell cycle arrest or apoptosis (programmed cell death). This is illustrated in *Fig. 1*; it can be appreciated that disruption of the p53 pathway significantly affects the ability to repair or discard a damaged cell, which can then go on to replicate. If this cell has sustained damage to one or more proto-oncogenes or to other tumour suppressor genes, a cancer may result.

So one of the physiological roles of p53 is to prevent the formation of tumours and, if this hypothesis is correct, damage to the *p53* gene itself would predispose to tumour formation. As will be obvious from the following section, considerable evidence has accumulated to support this view, explaining the recent phenomenal interest in this protein. However, from an evolutionary point of view, it would be surprising if this were the only function of p53.

Tumours with p53 abnormalities tend to occur in old age and do not affect animals in their reproductive phase.

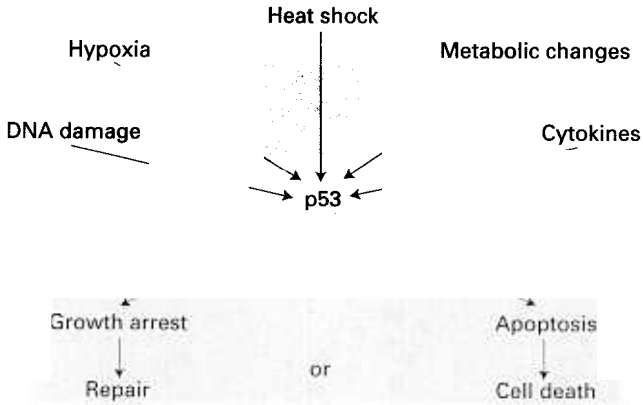

Fig. 1 Diagrammatic representation of the central role of p53 in the coordination of the cellular response to various stresses

However, studies using 'knockout' mice (in which specific genes have been inactivated) have shown that p53 null mice, while viable, display a high rate of developmental abnormalities, especially of the nervous system[9,10]. This suggests that p53 might protect against teratogenesis and experiments using benzo[a]pyrene have shown increased teratogenicity in p53 null mice[11]. In addition, after *in utero* irradiation p53 null mice have a high incidence of anomalies and a low death rate, whereas normal mice have a low incidence of anomalies and a high death rate[12]. Thus p53 may have evolved primarily as a suppressor of teratogenesis, with tumour suppression being a secondary property; it has been suggested that it may have an even more fundamental role as a facilitator of developmental complexity in higher animals[13].

Control of p53 and the 'p53 pathway'

As indicated in *Fig. 1*, p53 is thought to act as a nodal point between stressful stimuli and the final fate of the cell, and multiple events occur both 'upstream' and 'downstream' of p53 induction. Under normal circumstances cells contain very low levels of p53 protein, but stressful stimuli trigger 'upstream' events that lead to the accumulation or activation of p53[7,8] which then triggers the 'downstream' pathway. A graphic illustration of the upstream pathway in action is provided by the rapid appearance of immunodetectable levels of p53 in the epidermis and superficial dermal fibroblasts of normal adult human skin when exposed to doses of ultraviolet irradiation sufficient to cause mild sunburn[14] (*Fig. 2*).

As mentioned above, various forms of stress initiate the upstream pathway and, although the components of the pathway (i.e. the signals that communicate with p53) have not been identified, it is likely that protein kinases which are activated by DNA damage and subsequently phosphorylate p53 may be responsible[15,16]. As one end-result is increased expression of p53, it might seem reasonable to suppose that the upstream signals cause increased transcription and subsequent translation of the *p53* gene. There is, however, little evidence to support this hypothesis and other mechanisms must be invoked. Another nuclear protein, mdm-2, appears to be crucial in the control of p53 and has a key role in the observed accumulation of p53 in response to stress.

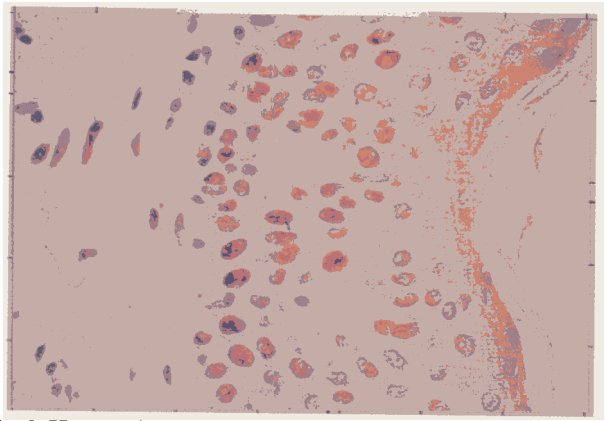

Fig. 2 Human skin immunostained for p53 protein after exposure to sufficient ultraviolet irradiation to cause mild sunburn. The dark staining indicates overexpression of p53 in the nuclei

Mdm-2 is a 491-amino-acid phosphoprotein which can bind to p53[17]; it not only blocks its biological activity, but also targets p53 for destruction via the ubiquitin proteosome pathway[18,19]. Mdm-2 may be thought of as a component of the downstream pathway as its transcription is increased by p53[20] (*Table 1*) and it thereby acts as a negative feedback mechanism controlling p53 levels (*Fig. 3*). That this is vitally important has been illustrated by knockout experiments showing that mdm-2 null mice are not viable unless they are also null for p53, indicating that mdm-2 is necessary to prevent unregulated p53 activity[21].

On the basis of these findings it is possible to speculate that mdm-2 may be important in controlling the response of p53 to stress, and that phosphorylation of mdm-2 or p53 itself by stress-activated protein kinases could prevent their interaction and hence allow accumulation of p53[22,23]. Certainly other influences that affect the survival of cells may act through mdm-2, as evidenced by the finding that basic fibroblast growth factor induces mdm-2 independently of p53 and so renders the cell insensitive to stimuli that would normally trigger apoptosis through the p53 pathway[24].

Whereas the mechanism of the upstream pathway is still largely speculative, the downstream pathway is better understood. p53 is a transcription factor; it can bind to specific DNA sequences and activate the transcription of genes containing such binding sites in their promoter regulatory regions[25,26]. The number of genes thought to be activated in this way is growing rapidly and there is an equally impressive range of genes which seem to have their function repressed by p53[7,27]. Some of the more robust candidates for the downstream p53 pathway are shown in *Table 1*; it can be seen how activation of these genes can affect the cell cycle and the rate of apoptosis. It has become clear, however, that p53 may also act in other ways not related to transcriptional activity. For instance, recent evidence indicates that it may inhibit nuclear DNA replication directly[28] and that p53-dependent apoptosis can occur without transcriptional activation of p53 target genes[29,30].

Despite the vast amount of data now available, it must be stressed that little of the mechanism of p53 function is certain; the accumulation of knowledge in this field is currently very rapid. Recently, homologues (i.e. distinct proteins with shared functions) of p53[31–34] and an mdm-2-related protein (mdm-x)[35] have been described, and these are likely to have important implications. It is possible that the p53 homologues make up a family of molecules with similar effects but induced by different signals and therefore play fundamentally different roles in cellular homoeostasis.

It must also be appreciated that much of our knowlege of p53 function comes from *in vitro* work and that the *in vivo* situation presents a whole new set of problems. In particular, it has become clear that the p53 response varies not only according to the insulting stimulus but also according to the tissue and cell type involved[36,37]. These discoveries, coupled with the increasingly complex interrelated pathways that are emerging, leave room for significant changes in our view of the precise significance of p53 over the next few years.

Table 1 Key genes transcriptionally activated by p53 which mediate the pathway leading to cell cycle arrest or apoptosis

Gene	Function of gene product
	Binds to and inactivates p53, forming an autoregulatory loop
p21/WAF1/Cip1	Arrests cell cycle by inhibiting cyclin–cyclin-dependent kinase complexes and binding to PCNA
GADD45	Arrests cell cycle by binding to PCNA
Bax	Promotes apoptosis
IGF-BP3	Enhances apoptosis by blocking the mitotic activity of insulin-like growth factor

PCNA, proliferating cellular nuclear antigen

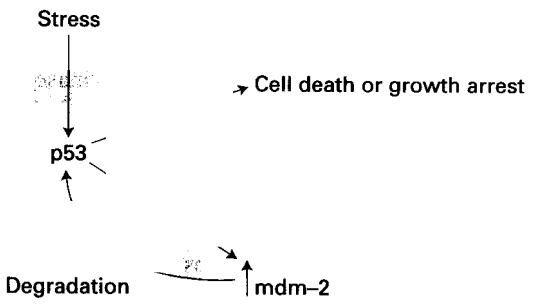

Fig. 3 Diagrammatic representation of the role of mdm-2 in preventing unregulated activation of p53

Role of p53 in cancer

The main reason for the phenomenal recent interest in p53 is the finding that a high proportion of human cancers (up to 50 per cent) contain mutations of the *p53* gene[38] (*Table 2*). Most commonly these genetic changes are missense mutations in one allele, although deletions or chain-termination mutations can occur. The mutational spectra at the *p53* locus indicate that many different environmental mutagens are likely to be involved[8], but these have yet to be identified specifically. The actual site of the mutation is also important; as p53 acts mainly as a transcription factor, mutations in the DNA-binding domain have the greatest effect on function. Most missense mutations in cancers are located in this domain and these lead to the production of p53 protein which fails to bind to DNA in the normal sequence-specific

Table 2 Frequency of *p53* mutations in different human tumour types

Tissue or site	Frequency (%)
Lung	
Colorectum	
Oesophagus	
Ovary	
Pancreas	
Skin	
Stomach	
Head and neck	
Bladder	
Prostate	
Hepatocellular	
Brain	
Adrenal	
Breast	
Endometrium	
Kidney	
Thyroid	
Haemopoietic system	
Carcinoid	
Melanoma	
Parathyroid	
Cervix	

fashion[39]. In addition, work with knockout mice has shown that p53 null animals display a high rate of tumour formation[40]. It has also been shown that the Li–Fraumeni cancer family syndrome is caused by a germline mutation in the *p53* gene[41,42].

Given the involvement of p53 in the cell cycle arrest or apoptotic response to genotoxic damage outlined above, these findings are not surprising. It is reasonable to suppose that loss of effective p53 would allow damaged cells to survive and open the door to the accumulation of mutations in other tumour suppressor genes and proto-oncogenes. It has been shown in transgenic mice that apoptosis slows the growth of a tumour induced by a T antigen which cannot inactivate p53 function and that rapid tumour growth with reduced apoptosis occurs in p53 null animals with the same antigen[43]. In addition, the p53 mutations found in squamous cell carcinoma are also found in skin lesions caused by ultraviolet radiation, and in p53 null mice ultraviolet light does not cause the typical apoptotic changes seen in the skin of normal mice[44].

However, it is naive to regard *p53* mutation simply as an 'enabling' event in carcinogenesis. While it appears to be an early event in the development of skin cancer[44], in colorectal cancer it has been found to occur late in the adenoma–carcinoma sequence[45]. The timing of a *p53* mutation is related to tumour type and must depend on a complex series of variables. It has been suggested, because p53 is induced by hypoxia, that the need for angiogenesis is balanced by the elimination of p53 function[8]. Thus a rich blood supply early in tumour development may leave *p53* mutation to arise at a later stage.

A key discovery in the oncological significance of p53 was high levels of the protein in many tumours. This accumulation results from an increase in p53 stability, which in turn is usually associated with a mutation in the *p53* gene[46,47], and it was long thought that the mutant protein was inherently more stable than the wild-type protein. However, recent evidence indicates that p53 protein stability depends not specifically on mutation, but on binding to mdm-2[22]. Mdm-2 is transcriptionally activated by p53 and then targets it for destruction, thereby forming an autoregulatory mechanism. It is now believed that mutant p53 cannot activate the transcription of mdm-2 and it is for this reason that p53 accumulates, a hypothesis supported by experimental work which has shown that p53 disappears from human tumour cells microinjected with mdm-2[48].

Detecting mutations in the *p53* gene is both expensive and time consuming, and the discovery that accumulation of the protein is associated with mutation has led to a proliferation of studies of archival material from human tumours using immunohistochemical detection of p53 as a surrogate for mutation. Because p53 acts as a protective mechanism against the perpetuation of genetic damage, it has been suggested that tumours with functioning p53 may carry a better prognosis than those expressing the mutant protein. In support of this theory there are numerous studies that have demonstrated an association with poor survival and accumulation of p53 in breast cancer[49,50], colorectal cancer[51–53], gastric cancer[54], lung cancer[55], ovarian cancer[56] and several other tumour types. However, there are a number of studies that have not shown this association and it has been concluded that any adverse prognostic effect is probably small[57]. Indeed, recent studies on colorectal and breast cancer using robust reagents have not been able confirm any prognostic significance of p53 accumulation even with a large number of patients[58,59]. This is perhaps not surprising as the fact that malignant transformation has already occurred indicates a fundamental breakdown of cellular control, and there is no good *a priori* reason why if a *p53* mutation has or has not contributed to this process the outcome should be any different.

It is also important to appreciate the limitations of using immunohistochemical detection of p53 as a marker of p53 function. First, it has been shown that detectable expression of p53 can occur in the absence of gene mutations[60,61]. This may be due to increased sensitivity of modern reagents, but other explanations such as malfunction of mdm-2 may apply in some instances. Second, it is conceivable that some mutations may not interfere with mdm-2 transcription and therefore remain susceptible to the controls exerted on the wild-type protein but still be functionally inactive. Third, it is recognized that viral proteins, such as the E6 human papilloma virus protein, can target wild-type p53 for destruction in a similar way to mdm-2[62].

Most important, however, is the concept that it is the p53 pathway that is crucial rather than the protein alone. Some *p53* mutations may have a different downstream effect from others; for example, some mutants can activate the *p21* gene but not the *bax* gene[63] so that the effects on cell cycle arrest may be different to those on apoptosis. Furthermore, rather than sustaining *p53* mutations some tumours, especially sarcomas, inactivate p53 by overexpression of mdm-2[64]. Very recently another tumour suppressor, p33 (encoded by the *ING1* gene), has been shown to be obligatory for the cell cycle inhibitory effects of p53[65] and it may also cooperate in the initiation of apoptosis. So if p33 is necessary to support the anti-tumour effects of p53, mutations in the *p33/ING1* gene will have to be taken into account. The p53 pathway is complex and not fully understood. It is possible that most, if not all, tumours have sustained some damage to this mechanism, but this can be detected by conventional methods only if the *p53* gene itself is mutated and consequently overexpressed.

Potential role of p53 in the management of cancer

Prognostic factor

p53 analysis does not appear to have any clinically significant utility as a prognostic factor and is unlikely to supplant conventional factors, such as stage and histological grade, in the near future. However, there is great interest in the significance of p53 in modulating the response to radiotherapy and chemotherapy. As both of these forms of cancer treatment cause DNA damage, it is reasonable to assume that p53-dependent apoptosis may be responsible for at least part of the therapeutic effect and there is evidence to support this hypothesis. Cells transformed by the viral oncogene *E1A* undergo p53-dependent cell death in response to ionizing radiation or treatment with 5-fluorouracil, etoposide or doxorubicin[66]. Work using transgenic mice has shown that *p53* mutations increase the resistance of haemopoietic cell lineages to γ irradiation[67]. In addition, X-irradiation at 9·5 days of gestation produces fewer deaths but more embryonic abnormalities in p53-deficient mice compared with wild-type animals[12], reinforcing the notion that normal functioning of the p53 pathway is required for efficient DNA repair or cell death after irradiation.

Study of a small series of patients with rectal cancer showed that radiotherapy appeared to increase the number of apoptotic cells only in tumours expressing wild-type p53[68]. In breast cancer *p53* mutations are well correlated with resistance to doxorubicin treatment[69]. It is also of interest that human tumours that are generally sensitive to radiotherapy or chemotherapy, such as testicular cancer or childhood acute lymphoblastic leukaemia, display low rates of p53 mutations[66,70], whereas tumours that often contain *p53* mutations, such as colorectal and lung cancers, tend to respond less well to chemotherapy or radiotherapy.

The use of *p53* mutation analysis to predict sensitivity to potentially toxic therapy is therefore an attractive proposition, but there is some evidence to suggest that p53 status may not always predict outcome reliably. Some reports indicate that inactivation of the *p53* gene can actually render cells more sensitive to genotoxic damage[71,72], and in a study of human squamous carcinoma cells *p53* mutations did not correlate with radiosensitivity[73]. This is an area that requires large-scale clinical studies with careful assessment of p53 function.

Diagnostic tool

The fact that *p53* mutations are expressed by so many human tumours has led to attempts to use them for diagnostic purposes. In cytology, suspicious cases frequently occur for which a satisfactory distinction between benign and malignant cannot be made, and immunocytochemical detection of p53 has been used in a wide variety of tumours[74]. As *p53* mutation is not a consistent finding in all tumours, the sensitivity of this approach is poor, but the specificity is high (in the region of 97 per cent) and staining for p53 in suspicious cytology specimens may prove to be a useful adjunct to morphological assessment.

Another area in which *p53* mutations have been used in an attempt to improve diagnosis is faecal screening for gastrointestinal cancer. As *p53* is one of the genes that is commonly mutated in colorectal cancer, it has been proposed that detection of *p53* mutations along with a panel of other mutated genes might offer a useful screening tool. However, while *p53* mutations can be detected in gut lavage fluid from patients with colorectal cancer[75], effective faecal tests have proved elusive owing to difficulties in extracting appropriate DNA from stool.

Finally, there has been interest in looking for mutant DNA in blood as a marker for minimal residual disease after apparent eradication of primary malignancy[76]. If this were feasible, it might prove useful for selecting patients for adjuvant therapy and for monitoring treatment. The *p53* gene is an obvious candidate for this approach, although little real progress has been made in this direction.

Therapy

In the treatment of cancer, restoration or modulation of p53 function has become something of a holy grail, based on the premise that the tumour cells lacking this function might destroy themselves or at least become more susceptible to the effects of DNA damage inflicted by conventional chemotherapy or radiotherapy. Essentially, three main approaches look promising in this field. First, there is virus-mediated gene transfer in which a viral genome is engineered to contain foreign genes which are expressed in the host cell genome after infection. Second, there is the use of a cytolytic virus which can replicate only in cells that lack p53 function, and by targeting such cells could destroy tumours with mutant p53. Third, there is the discovery or design of small molecules that can interfere with the negative regulation of p53, pharmacologically activating the p53 response.

Virus-mediated gene transfer. A wild-type *p53* DNA fragment has been inserted into a retrovirus (LNSX retroviral vector). Using this to restore the wild-type *p53* gene to lung cancer cells, it has suppressed the growth of both lung cancer cell lines and human lung cancers in nude mice[77,78]. Similar findings in colorectal cancer cells lines have been reported using the replication defective adenovirus Ad5/CMV/p53[79]; it has also been shown that this agent has a synergistic effect when used with cisplatin chemotherapy[80].

There is one reported clinical trial using wild-type *p53* gene transfer in nine patients with non-small cell lung cancer in whom conventional treatment had failed. In this study the LNSX retroviral vector was injected directly into the tumour either percutaneously with radiological guidance or via a bronchoscope[81]. *In situ* hybridization and DNA polymerase chain reaction showed vector–*p53* sequences in post-treatment biopsies, and apoptosis was more frequent in post-treatment than in pretreatment biopsies. No treatment-related toxicity was noted and tumour regression occurred in three patients. Further extensive trials of adenovirus encoding wild-type p53 are currently underway.

Cytolytic virus therapy. The DNA tumour virus adenovirus produces a 55-kDa protein from the *E1B* region of its genome which binds and inactivates p53. It was hypothesized that an adenovirus lacking E1B would not be able to replicate in normal cells but would in cancer cells lacking p53 function. For this reason, ONYX-015, an *E1B* gene-attenuated adenovirus was compared with normal adenovirus in human and colonic cancer cell lines with and without p53 function. As expected, the ONYX-015 virus replicated as efficiently as the normal virus in

the cell line lacking wild-type p53, but not in the line with normal p53 function[82].

Subsequent work showed that, while normal human cells are very resistant to the cytolytic effects of ONYX-015, a wide range of human tumour cell lines with either mutant or normal *p53* gene sequences is destroyed[83]. It is interesting that tumours with wild-type p53 are susceptible; this is presumably due either to the presence of undetected *p53* mutations or to malfunction of other components of the p53 pathway (e.g. mdm-2 overexpression). A phase I trial of ONYX-015 in patients with advanced cancer is currently underway and a report should be forthcoming in the near future.

Interference with the negative regulation of p53. The activity of p53 is dependent, at least in part, on sequence-specific DNA binding and this process is controlled by a negative regulatory domain in the p53 molecule[84,85]. Neutralization of this domain by a specific antibody activates p53[86] and it is likely that stress-related factors which influence the transcriptional activity of p53 act in a similar way. The same antibody can activate mutant forms of p53 synthesized by human tumour cells lines[87], and this opens up the possibility of discovering or designing small molecules that could activate mutant forms of p53, thereby rescuing p53 function. Similarly, the discovery that mdm-2 interacts with p53 via a small molecular interface to block p53 function suggests that small molecules could be used to disrupt this interaction[22]. This would be particularly useful in tumours, especially sarcomas, in which p53 is normal but where there is overexpression of mdm-2[64].

Conclusion

p53 research is tantalizingly close to revolutionizing clinical practice in oncology, but it still has some way to go. The prognostic significance of p53 is uncertain, its role in diagnosis is promising but yet to be developed, and its potential in therapy is just emerging. However, there is no doubt about the central role of p53 in the development of cancer and one of the main questions to answer is: Why do a significant proportion of tumours seem to have normal p53? The answer may come from intensive study of the p53 pathway rather than of p53 in isolation, as it is conceivable that all malignant tumours have a defect somewhere along this pathway. This is the direction being taken in oncologically relevant p53 research and, when the pathway and its defects are fully understood, the tailoring of therapy for an individual tumour based on its molecular and genetic profile will be a practical strategy.

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