

p53: The Challenge of Linking Basic Science and Patient Management

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ABSTRACT

Abnormalities of the p53 tumor suppressor gene are the single most common molecular abnormality seen in human cancer, being found in more than 50% of malignancies. Considerable evidence indicates that the product of this gene has critical roles in coordinating the response of cells to a diverse range of environmental stresses. Loss of p53 function is associated with loss of normal cell cycle control, diminished apoptosis, and genomic instability and is strongly associated with the neoplastic phenotype. We have a detailed knowledge of the biochemical properties of p53 and its activity as a

transcription factor regulating diverse aspects of cellular function, but the *in vivo* physiological relevance of many of these remains uncertain. Nevertheless, p53 represents a highly significant potential target for novel therapeutic intervention; however, the further development of clinical applications and novel therapeutic strategies utilizing our knowledge of p53 is absolutely contingent upon bridging the gap between our biochemical understanding and our much less well-developed insights into the role of p53 in relevant physiological systems *in vivo*. *The Oncologist* 1998;3:218-224

THE STRUCTURE AND FUNCTION OF p53: AN OVERVIEW

The literature relating to the p53 tumor suppressor gene is enormous and is composed of an admixture of clinical studies (of variable quality) and incredibly detailed biochemical and molecular analyses that baffle and confuse even those well acquainted with the field. The reductionist approach to the mechanistic role of p53 in cellular pathways is essential, but sometimes gives the reader a feeling of confusion and despair; when in the midst of the forest, the wood cannot be easily distinguished from the trees. The goal of this review is to provide a helicopter pilot's perspective of the forest below, recognizing that some of it is still covered in mist and remains poorly explored. Building upon this framework, I hope to provide an overview of the potential clinical relevance of p53 biology. An invaluable historical perspective [1] and recent reviews [2-9] can be perused to add detail for those readers who wish to study the field further.

Our current view of the normal function of p53 is that it is a modular protein with regions with distinct but interlocking functions [10, 11]. These functions are coordinated such that p53

protein within a cell acts to integrate signals emanating from a wide range of cellular stresses and allows the cell to respond to these insults by activating a set of genes whose products facilitate adaptive and protective activities [2, 6]. In order to function in such a complex manner, p53 protein is subject to a diverse array of regulatory mechanisms that keeps this potentially dangerous protein in check until needed [2-5]. While the p53 protein has become best known because of its close association with human (and animal) neoplasia, and in particular because of the frequent loss of function of p53 as a consequence of mutation or allelic loss [7, 8], it should be recognized that the normal function of p53 is not simply as a tumor suppressor. Other functions involving response to stress, including in developmental situations, may be of great significance, and there is an increasing body of literature suggesting that p53 has clinical significance without neoplasia [2, 9]. Nevertheless, the biochemical properties that underpin the complex biology are intimately related to the structure of the p53 molecule (Fig. 1). The critical features of the p53 molecule are the DNA-binding domain and the activation domain which together define p53 as a transcription factor—a protein that can regulate the expression of other genes.

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Figure 1. A representation of the structure of p53 protein. In man, p53 is composed of 393 residues. There are five highly conserved "boxes" and five identifiable regions subserving different functions. However, it should be recognized that the functions are interdependent, and regulation in one "domain" can profoundly influence other domains. Interactions with other macromolecules are of great significance, with binding to DNA in a sequence-specific manner being of critical importance. In addition, p53 interacts with a wide range of proteins, facilitating both the regulation of p53 activity and control of its concentration by the control of its degradation.

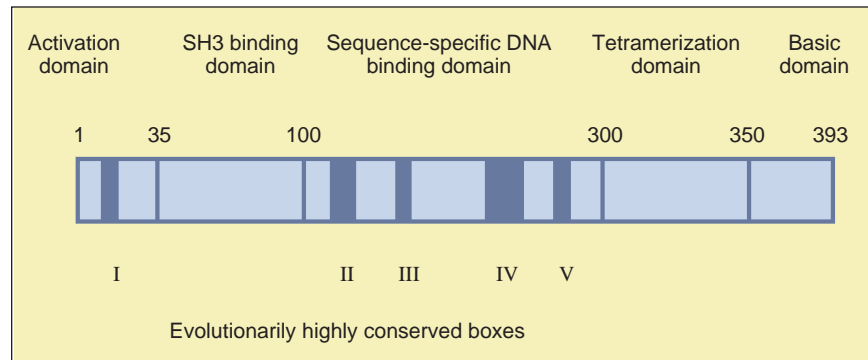
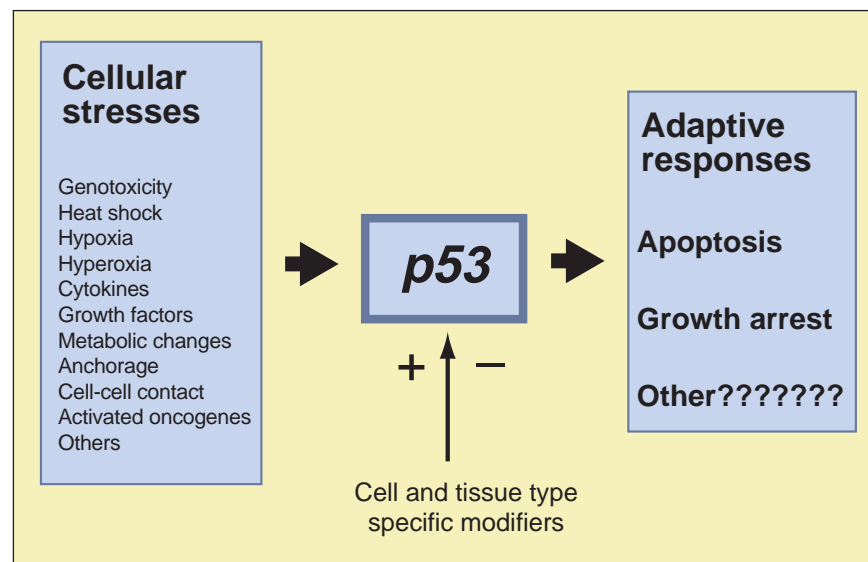


Figure 2. The p53 pathway is not a simple linear system. Rather, there are many "inputs" and many "outputs." It is quite wrong to think only of DNA damage as the initiating stimulus to the pathway, and it is similarly incorrect to view the resultant consequences as restricted to growth arrest and apoptosis. Furthermore, there are many levels of control with inputs at all points from initiating insult to resultant adaptive response. The activity of the system is profoundly altered by poorly understood cell type and tissue-specific effects.



The core of the p53 protein is a region which folds in such a way as to form a domain which can interact with DNA in a sequence-specific manner. The majority of missense mutations seen in human (and animal) tumors occurs in regions of the gene encoding this domain such that it loses its ability to specifically bind DNA in a DNA-sequence-specific manner [12, 13]. The binding to DNA is optimal when the protein is in a tetrameric state as a consequence of interactions of four separate p53 molecules via the tetramerization domain. The C terminal region is composed predominantly of basic residues and forms a region that has regulatory properties. The DNA-binding domain is separated from the transcriptional activation domain by a region containing a series of repeated proline residues typical of a polypeptide that can interact with signal transduction molecules that contain an SH3 region. Through this domain, p53 is influenced by diverse signaling molecules, including the *c-abl* oncogene. The N terminal transcriptional activation domain allows p53 protein, in the context of its specific binding to a target DNA sequence, to recruit the protein machinery required for transcribing new mRNA, and by so

doing, activate the expression of target genes. This region is also critically involved in regulating the stability and activity of p53 protein via interactions with proteins such as mdm2. Binding of mdm2 to p53 allows targeting of p53 to the ubiquitin-mediated proteolytic machinery [14]. mdm2 binding also blocks the ability of p53 to interact with the transcriptional apparatus. Modification of p53 by phosphorylation may alter many of these properties, and, in particular, the interaction of p53 with other proteins such as mdm2. By this means, much of the regulation of the p53 pathway occurs.

Given this biochemical background, what are the functions of p53? While much of the literature is focused on the idea that p53 is activated by DNA damage to elicit alterations in cell cycle control and/or apoptotic cell death, a broader picture is now emerging, as shown in Figure 2. A diverse range of insults can activate p53 to elicit adaptive responses that include, but are by no means restricted to, growth arrest and apoptosis. These properties are profoundly influenced by cell type and tissue-specific modifiers which are of clear importance but remain poorly understood in terms of mechanism

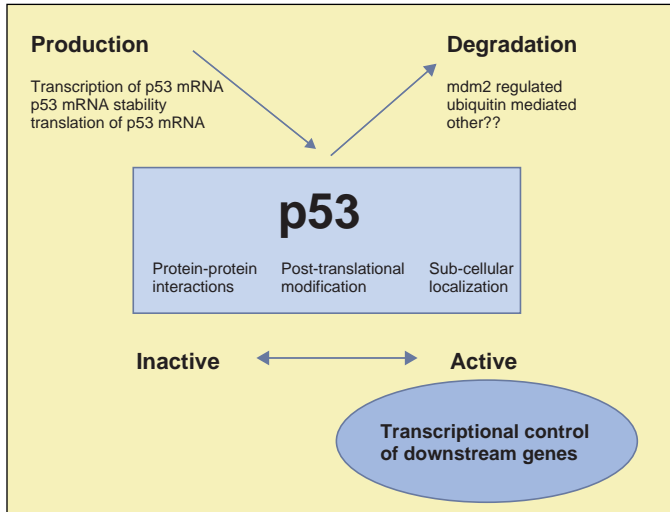


Figure 3. There are diverse levels of control of p53. p53 protein is tightly regulated by control of production of protein (mRNA production, stability, and efficiency of translation) and of its degradation by ubiquitin-mediated proteolysis. Additional levels of control include diverse protein-protein interactions, post-translational modifications (including phosphorylation, RNA binding, and glycosylation), and also by regulation of subcellular localization. By this means, p53 protein can be switched from inactive to active forms, and as a result lead to transcriptional activation (or repression) of downstream target genes. Activities which do not relate to transcriptional control have also been suggested.

[15, 16]. However, we do have some understanding of the mechanisms by which the pathway is controlled (Fig. 3). For example, the level of p53 is dependent upon a balance between protein synthesis and degradation, but additional levels of control exist, with protein-protein interactions and post-translational modifications being very important [17]. In addition, the regulation of subcellular localization of p53 is increasingly viewed as being significant [18]. These mechanisms serve to regulate not just the level and location of p53 protein but its activity. Furthermore, different target genes are induced (or repressed) in different cell types and with differing kinetics and thresholds, leading to considerable subtlety in the p53 response. From this overview of the biochemistry and biology of p53, a model of how p53 works has emerged (Figs. 4A and 4B), and how this is perturbed in neoplasia (Fig. 5). Inevitably, in a fast-moving and complex field, these models should be treated with caution and may be revised in the coming years. Indeed, we are already learning that there are homologs of p53 (p73 and KET) which may have overlapping roles and functions [2, 19-21]. The models presented here hopefully provide an intellectual framework for considering the clinical relevance of p53. One important caveat to these views is that most of our knowledge of p53 is based upon cell culture and biochemical studies or inference from clinical observations. In truth, we know very little of the physiological functions of p53 and the subtlety of p53 biology in vivo. A

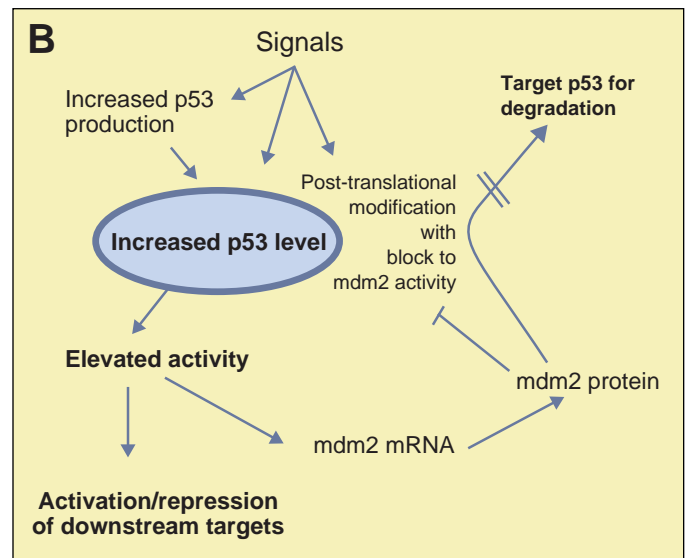
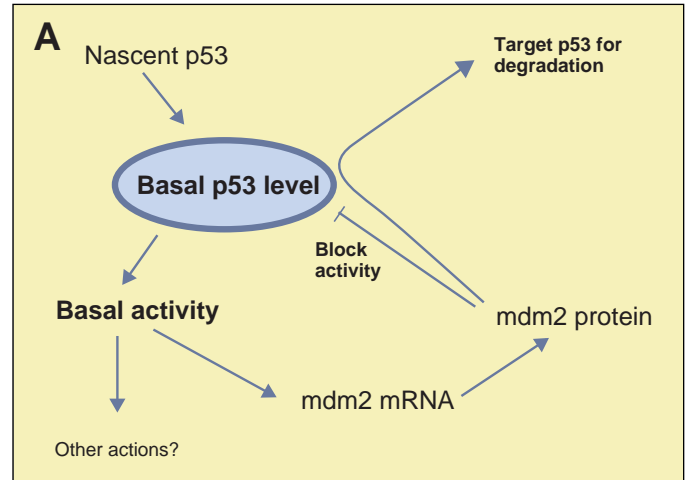


Figure 4. The normal p53 pathway. A tonic loop exists in which the basal level of p53 activates a basal level of downstream target genes, including *mdm2* (Fig. 4A). *mdm2* protein binds p53, inactivating the ability of p53 to function as a transcription factor by blocking access to the basal transcription apparatus and also targeting p53 for ubiquitin-mediated degradation. A range of insults (Fig. 2) alters a set of (as yet poorly defined) signaling pathways such that there is alteration of the level and state of p53, perturbing the tonic loop (Fig. 4B). Activation of p53 occurs (Fig. 3) with the transcriptional regulation of downstream target genes which elicit the required biological functions. It is likely that the kinetics and spectrum of downstream targets activated (or repressed) are modified by cell-type-specific factors, and, in particular, the profile of other transcription factors and transcriptional coactivators present in a cell.

clear consequence of this is that the development of clinical applications of p53 will require a more sophisticated view of p53 biology than we currently possess.

THE CLINICAL RELEVANCE OF p53

What of the clinical implications of our burgeoning, if incomplete, knowledge of p53? Certainly p53 abnormalities

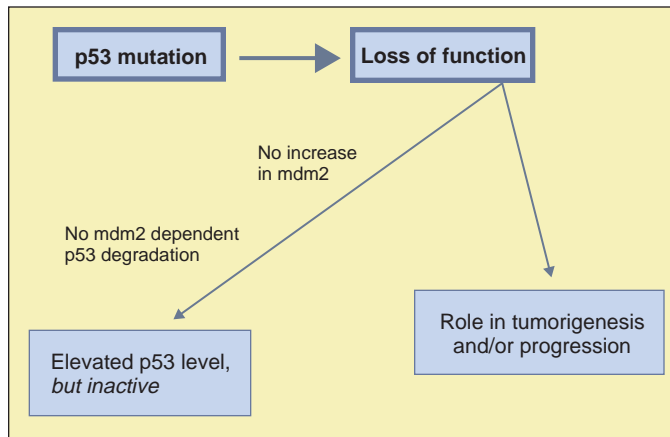


Figure 5. p53 in neoplasia. Loss of function of p53 protein occurs as a consequence of missense mutation, allelic loss, or inactivation as a consequence of viral proteins such as HPV E6. As a consequence, the downstream targets of p53 are not appropriately regulated, and there is loss of their normal function, e.g., loss of p53-activated cell death, growth arrest, and/or control of genomic stability. Loss of these important p53-dependent processes may occur early in the genesis of some tumors, or, alternatively, may be steps in tumor progression. One of the most common features of mutant p53 is its accumulation within cells—a phenotype seen frequently in tumors and detectable by immunohistochemistry. While there are multiple mechanisms for this clinically useful phenotype, one important mechanism is the loss of activation of mdm2 mRNA, and, hence, mdm2 protein. Consequently, the mdm2-dependent degradation pathway of p53 does not operate, and, thus, p53 protein accumulates to high levels, although the protein is inactive.

are very prevalent in human disease, including recently in non-neoplastic disorders [22, 23]. Indeed, it may be that our focus on p53 and neoplasia has been too great, and roles in other “stress-related” situations should not be neglected. For example, p53 certainly has a major role in development [9], and involvement in cardiovascular, neurological disease and in the pathogenesis of viral infections is suggested by many data [24–31]. Nevertheless, it is in neoplasia where most attention has focused, although it must be said that the plethora of publications (more than 11,700 currently available via PubMed) contains many descriptive, poorly controlled, and overinterpreted studies. Nevertheless, a number of points are clear. Of particular note is the remarkable correlation between the phenotype of p53 overexpression and neoplasia (Fig. 5), borne out by a great many studies, including a large prospective analysis [32]. Indeed, while it must be recognized that there are physiological reasons for the accumulation of p53 protein in cells (e.g., hypoxia is common in tumors and is a potent inducer of the p53 pathway), the widespread availability of robust anti-p53 reagents means that p53 “staining” can be operationally employed as an indication of neoplasia. Of course, caveats to this exist, not the least of which is the important point that if extremely sensitive detection systems are employed, p53 immunoreactivity can be seen in very many normal cells and tissues. A

detailed commentary on this general area was published several years ago, and the general points remain valid today [33].

A second area that has received considerable interest and has generated a huge body of literature is the relationship between p53 and prognosis. Again, there is considerable murky water in the available literature, with a number of rather exaggerated claims being made, ranging from p53 overexpression or mutation being associated with adverse or even better prognosis. Based upon an attempt at a critical review of the then-available literature, and while recognizing that there are good theoretical reasons for associating p53 abnormalities with adverse clinical course, it was suggested by *Dowell and Hall* [34] that in most clinical situations, the effect of p53 status on outcome is rather modest. Notwithstanding this rather cynical perspective, other studies have suggested that there is, at least in some tumor types, clinical benefit in assaying p53 status, for example, in breast cancer [35]. Moreover, while we have considerable knowledge of the biochemistry of p53, and it is clear that abnormalities of p53 contribute extensively to the genesis and progression of human tumors, there are many other genes involved, and it is the analysis of the p53 pathway rather than simply p53 per se that is important [2]. It might be that as our understanding of the full pathway evolves we may gain more effective diagnostic and prognostic insights. Moreover, it is not simply that we still do not understand the pathway in biochemical terms, but that we do not understand how this biochemistry functions in a physiological setting in vivo. When we have a better basic knowledge of the full pathway (including the relevance of p53 homologs), then the possibility that the analysis of p53 might allow prediction of therapeutic response may become realized [36, 37].

There is very good evidence that p53 is a tumor suppressor. For example, p53 null mice develop cancer, and the introduction of normal p53 protein into cells devoid of functional p53 can induce growth arrest and/or cell death. While the former studies are convincing, the latter class of experiment can be criticized, since such studies employ considerable overexpression of p53, not the modest physiologically relevant levels normally seen in vivo. Nevertheless, such studies suggest that manipulating p53 might allow novel therapeutic interventions in disease, and, in particular, in cancer. A number of approaches are being explored. The simplest approach (in concept) is the introduction of wild-type p53 into tumor cells using retroviral or adenoviral delivery systems; this has been mooted as one approach to tumor gene therapy [38]. Indeed, exciting preliminary results have been reported [39], and a phase II study has been announced (RPR/GenCell/Introgen Therapeutics Inc., Press Release, June 1998), despite all sorts of theoretical reasons why such an approach might not work. For example,

the targeting of delivery systems to affect all tumor cells is fraught with difficulty, although it may be that “bystander” effects will be such that this is not actually necessary. Another difficulty is that the existence of mutant p53 protein in a cell may inactivate wild-type protein by a “dominant negative” effect. This is a situation in which one mutant protein can, in the context of an oligomer, functionally inactivate wild-type (normal) molecules in the complex. Certainly, this phenomenon can be seen in experimental systems and may compromise the clinical utility of this approach.

A number of groups have postulated that it may be possible to manipulate the inactive mutant p53 protein present in many tumor cells and reactivate at least some of its wild-type characteristics. Of course this is an approach which has theoretical difficulties, but recent biochemical data do suggest that it is feasible, at least in vitro or in cultured cells. For example, the introduction of certain second mutations into p53 that already has an inactivating mutation can restore some normal activity, raising the hope that small molecules might be designed that have similar function-restoring effects [40]. Furthermore, various peptides and antibodies can affect the C terminus of mutant p53 protein in such a

way as to restore its ability to function in some assays; this does lend further support to the notion that a suitable small molecule might be designed (or at least identified in a natural product screen) that may have therapeutic potential [41–43]. Another attractive strategy is to manipulate the critical regulatory interactions that control p53 function and activity. For example, it might be that the manipulation of the phosphorylation status of p53 with suitable kinase or phosphatase inhibitors could be of utility. Alternatively, the manipulation of critical protein-protein interactions that control p53 function could be targeted. For example, the recognition that mdm2 plays a critical role in p53 homeostasis and our detailed biochemical and structural understanding of this interaction make it a particularly attractive target, at least from the point of view of “proof of principle” [44]. At present, these approaches remain experimental.

One approach that has provided some exciting insights as to what may be possible is the use of a mutant adenovirus to kill cells that have a defective p53 pathway [45, 46]. This elegant approach is based upon the need for successful adenovirus replication to require the inactivation of cellular p53

function. Adenovirus achieves this by encoding a protein (E1b) whose function is to inactivate p53 and which, without this functionality, cannot replicate in mammalian cells—a process that will eventually kill the infected cell. By engineering an adenovirus with exactly this defect (no functional E1b), it is found that this virus will not grow in any normal cell but only in those in which p53 is inactivated by some other route—for example, by missense mutation or by allelic loss—events typical of many human tumors. Consequently, introduction of this mutant virus into normal cells has no effect, but neoplastic cells with defective p53 are killed by the productive lytic infection. This is beneficial, since not only are the infected cells killed, they die and release more virus than capable of infecting additional tumor cells and killing them: a system with intrinsic ampli-

fication. Encouraging experimental and phase I clinical studies using this approach have been reported [45, 46].

An alternate strategy to the utilization of our knowledge of p53 for therapeutic benefit may be to take advantage of the simple fact that it is easier to inhibit a system than to activate it. Drugs or other agents that inactivate the p53

When we have a better basic knowledge of the full pathway (including the relevance of p53 homologs), then the possibility that the analysis of p53 might allow prediction of therapeutic response may become realized.

pathway may allow the harmful (and p53-dependent) apoptotic consequences of radio- and chemotherapy on normal cells to be reduced. A limitation on this theoretical strategy may be the existence of apoptotic pathways independent of p53. For example, even in p53 null mice where there is a clear relationship between apoptosis and p53 function [47]; at later time points apoptosis is seen in the gut in the absence of p53 function [48].

If the major hurdles relating to technical issues such as agent delivery, viral safety, suitable drug discovery, etc., are overcome—in themselves major tasks—then manipulating p53 will be of clinical benefit. Or are there reasons to be a little more skeptical? Despite the importance of p53 in human neoplasia and the evidence that overexpression of p53 in cell lines in vitro can reverse the transformed phenotype, it may be inappropriate to conclude that restoration of p53 activity will necessarily be beneficial. The elegant studies of *Ewald et al.* [49] provide a particularly striking example of this perspective. These investigators employed a transgenic mouse system in which p53 function was inactivated by the expression of the p53 binding domain of SV40 large T antigen in salivary

gland epithelium using a tissue-specific, regulatable promoter. This elegant approach allowed p53 function to be inactivated (or activated) at will. When p53 was inactivated by the expression of T antigen, there was progressive cellular hyperplasia and nuclear atypia. When p53 function was restored (by turning T antigen off), there was histological regression of these lesions. In separate experiments, if p53 was inactivated for longer periods there were more severe changes which appear to be overtly neoplastic while benign. Again, these regressed if p53 function was restored by turning T antigen off. However, if p53 was inactivated for longer periods, then overtly malignant tumors arose which persisted even when p53 activity was restored; presumably, other molecular events occurred as part of tumor progression, leading to the tumors persisting irrespective of p53 function. Remembering that the clinical phase of tumors is short compared with the life span of the tumor, any manipulation of p53 will be late and presumably in the milieu of multiple genetic changes and heterogeneity derived from the existence of multiple clonal sub-lines within the tumor.

Useful Web Sites

<http://perso.curie.fr/Thierry.Soussi/index.html>
<http://bioinformatics.weizmann.ac.il/hotmolebase/entries/p53.htm>
<http://www.iarc.fr/p53/homepage.htm>
<http://athens.wistar.upenn.edu/~p53/>

CONCLUSION

This brief overview has developed the idea that the considerable complexity of the p53 pathway (which,

inevitably, we have only touched upon) must be interpreted in the light of its physiological relevance in vivo systems [2]. Without doubt, p53 has clear relevance to the biology of neoplasia, but this should not obscure other possible biologically important and potentially clinically relevant areas (such as development and cardiovascular and neurological disease). While at present the direct clinical relevance of assaying the p53 pathway and its abnormalities is unclear (witness the conflicting data on p53 and prognosis), the potential therapeutic opportunities are of great interest and may prove to be immensely beneficial. Perhaps, however, it might be prudent to view some of the enthusiasm with a degree of healthy skepticism. Clearly, the challenge for the future will be the linking of the detailed and rigorous biochemistry to the complex and difficult-to-study physiological systems of whole organisms. We know a lot about p53 in cells in culture, but very little (in truth) about p53 in complex tissues in vivo; bridging this gap will be the key to utilizing our knowledge of p53 to benefit the patient.

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