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p53 as the main traffic controller of the cell signaling network

Sinto Sebastian[1], Amalia Azzariti[1], Nicola Silvestris[2], Letizia Porcelli[1], Antonio Russo[3] Massimo Tommasino[4] and Angelo Paradiso[1]

[1]Clinical Experimental Oncology Laboratory, National Cancer Institute "Giovanni Paolo II", Via Hahnemann, 10 - 70126 Bari, Italy,[2]Medical and Experimental Oncology Unit, National Cancer Institute "Giovanni Paolo II", Via Hahnemann, 10 - 70126 Bari, Italy,[3] Section of Medical Oncology, Department of Surgery and Oncology, University of Palermo, Palermo, Italy,[4]Infections and Cancer Biology Group, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France

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1. ABSTRACT

Among different pathological conditions that affect human beings, cancer has received a great deal of attention primarily because it leads to significant morbidity and mortality. This is essetnially due to increasing world-wide incidence of this disease and the inability to discover the cause and molecular mechanisms by which normal human cells acquire the characteristics that define cancer cells. Since the discovery of p53 over a quarter of a century ago, it is now recognized that virtually all cell fate pathways of live cells and the decision to die are under the control of p53. Such extensive involvement indicates that p53 protein is acting as a major traffic controller in the cell signaling network. In cancer cells, many cell signaling pathways of normal human cells are rerouted towards immortalization and this is accomplished by the corruption of the main controllers of cell signaling pathways such as p53. This review highlights how p53 signaling activity is altered in cancer cells so that cells acquire the hallmarks of cancer including deregulated infinite self replicative potential.

2. INTRODUCTION

In the dynamic development of multi-cellular organisms including humans, certain proteins act as coordinators and/or major traffic controllers of different cellular networks. p53 and the p53 family network are thought to be the primary players of the cell signaling pathway that control both internal and external signals received by cells. p53, (53 Kd), also known as tumor protein 53 (TP53), was first identified in 1979 as a cellular protein that bound large T antigen to the simian virus (SV40) and accumulated in cancer cell nuclei (1). The gene encoding p53 (TP53) was cloned from rodent and human neoplastic cells, and found to have weak oncogenic activity when expressed in rodent cells. However, in the late 1980s, it was discovered that, instead of the wild-type gene, the form of p53 that was studied had missense mutilation. The missense mutations found in the original TP53 cDNA clones proved to be the key to understanding the pathobiological activity of p53 (2). The ability of p53 to form tetramers allows this protein to behave in a dominant-negative fashion in which the allele-producing mutant p53

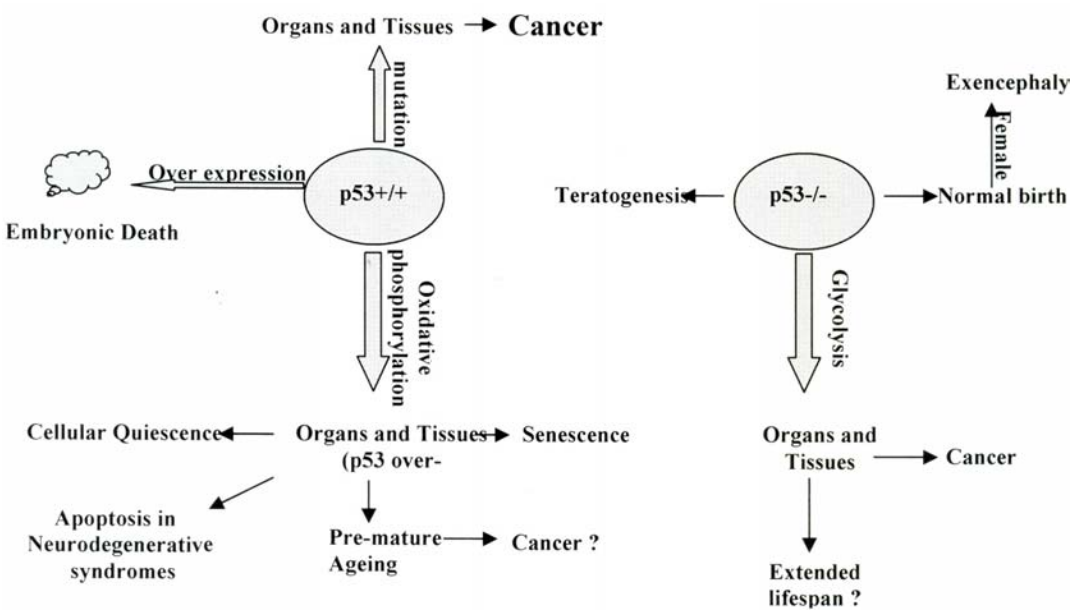

Figure 1. p53 function as a major traffic controller of cell signaling pathways from cellular origin to death: Schematic representation of possible cell fate determination pathways that can be activated and/or repressed by p53 wild type protein.

suppresses the activity of wild-type p53. The ability of p53 to act as a tumor suppressor transcription factor was finally revealed in 1989 by Bert Vogelstein (3). p53 is considered to be a tumor suppressor due to its ability to induce cell cycle inhibition and/or apoptosis. Most cancers acquire inactive p53 (mainly by mutation) and introduction of p53 to these cells induces apoptosis and/or senescence. Many mechanisms mask tumor suppressor functions of wild-type p53. Abundance of p53 and numerous posttranslational modifications most notably, phosphorylation and acetylation, modulate p53 activity (4). p53 protein function is also regulated by expression of other members of the p53 family, such as p63 and p73, which specifically depends on: a) the balance between the expression of transcriptionally active (p53, TAp63, and TAp73) and inactive isoforms (DNp63, DNp53 and DNp73); b) their interaction and competition at DNA-responsive elements; c) their interaction with regulatory, both inhibitory and activating, proteins (5, 6). In non-stressed cells, p53 is essentially kept inactive through the actions of the ubiquitin ligase MDM2, which inhibits transcriptional activity of p53 and ubiquitinates p53 leading to its degradation. p53 is considered to be "the guardian of the genome," "the guardian angel gene," and the "master watchman," mainly due to its role in preventing genome mutation. In this paper, also the recent emerging role of p53 as major traffic controller of cell signalling pathway are reviewed. Understanding the molecular mechanisms responsible for each p53 opens the possibility to develop better therapeutic strategies.

3. UNEXPECTED ROLES OF P53 AS A MAJOR TRAFFIC CONTROLLER

p53 protein has been intensively studied mainly as a tumor suppressor in humans and other mammals (7). Loss or mutation of p53 is strongly associated with increased susceptibility to cancer, and most functions of p53 have been considered in the light of use of p53 to prevent malignant progression (8). Since some p53-null mice were able to develop normally (9), it was originally thought that p53 did not have any major function in normal physiology, a view that had recently been changed. p53 is involved in regulating longevity and aging, glycolytic pathways that might determine endurance and overall fitness, and in apoptotic responses during ischemic and other types of stress. Evidence for genetic variations in the activity of the p53 pathway in humans makes these ideas as being more relevant (10). As a transcription factor, p53 is a major mechanism that both positively and negatively regulates the expression of a large and disparate group of responsive genes (11). Numerous studies, including the recently reported genome wide ChIP analyses (12-13), have identified p53-regulated genes that may play a role in a number of different and sometimes unexpected responses. Although some of these functions still need to be fully validated, there is now clear evidence that p53 plays a role in the regulation of glycolysis (14-15) and autophagy (16), the repair of genotoxic damage (17), cell survival, regulation of oxidative stress (18), invasion and motility (19), cellular senescence (20), angiogenesis (21), differentiation (22), and bone remodeling (23) (Figure 1). Such extensive involement of p53 in cell functions, therefore, suggests that in addition to the role of p53 as a "guardian of the genome", p53 acts as a main traffic controller in the cell signaling network.

4. P53 AS TRAFFIC CONTROLLER: MODES OF ACTIVATION AND SIGNALING MECHANISM

Efficient control of p53 is critical in normal cell growth. A number of mechanisms that lead to the stabilization and activation of p53 have been identified that

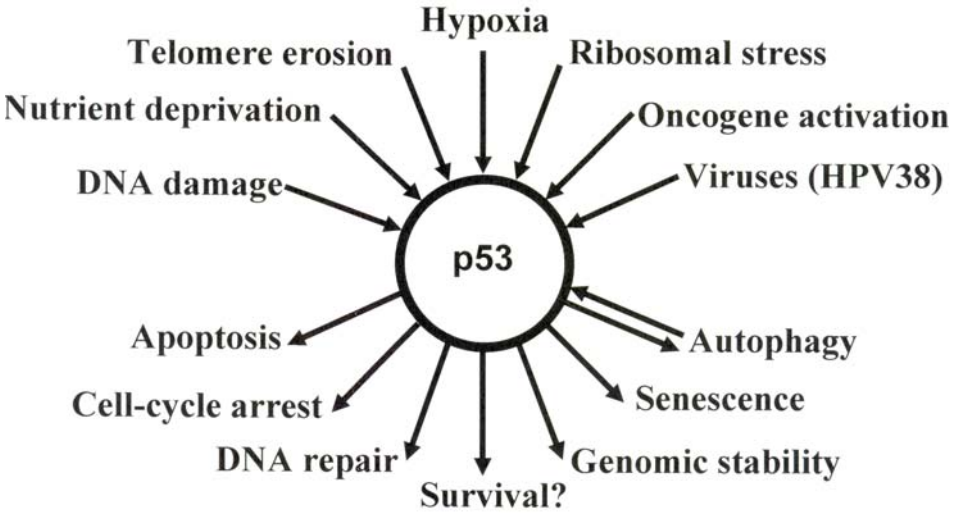

Figure 2. Duties of p53 traffic controller. p53 has a key role in integrating the cellular responses (arrows pointing out from p53) to different types of stress (arrows pointing towards p53). Activation of p53 can result in a number of cellular responses and it is possible that different responses are induced by different stress signals. There is evidence that p53 can play a part in determining which response is induced through differential activation of target-gene expression. Although the importance of these responses to tumour suppression is clear, previously unanticipated contributions of these responses to other aspects of human health and disease are being uncovered. The role of p53 in tumour suppression, development and ageing depends on which cellular response is activated and on the context in which the activation occurs.

participate in such a control. Release of the tight control over p53 with activation of p53 is a well-established response to stress (Figure 2). Analysis of the p53 orthologue in flies and worms shows that, as seen in mammalian systems, p53 is an integral component of the response to genotoxic stress (24-26). p53 is extremely sensitive to low levels of DNA damage, a response that is thought to contribute to tumor suppression by either promoting repair or by eliminating cells harboring potentially oncogenic alterations. However, many other signals can also activate p53, including inappropriate cell proliferation driven by oncogene activation, telomere erosion, DNA damage, nutrient deprivation and hypoxia (27). Importantly, these signals do not all engage p53 through the same pathways, but use different signaling molecules to stabilize and activate p53. For example, ARF, a small protein that binds and inhibits MDM2, has an important role in signaling to p53 in response to some oncogenes, but it is not necessary for the activation of p53 in response to DNA damage (28-29). Similarly, without a requirement for ARF, the ribosomal protein, L11, has a role in activating p53 in response to ribosomal stress (30). Although a response to genotoxic stress certainly seems to be the most historic function of p53 in evolutionary terms, a recent study using a mouse model in which p53 can be switched on and off has indicated that the response of p53 to DNA damage might not be responsible for tumor suppression (31). This study shows that p53 becomes important only after the bulk of the damage has been resolved, and concludes that the key tumor-suppressor function of p53 is to respond to oncogene activation that occurs as a consequence of the original genotoxic stress. In support of this idea, there are studies showing that ARF, which is necessary for oncogene-induced (but not DNA-damage-induced) activation of p53, is responsible for almost all the tumor-suppressor activity of p53 (32). Thus, it appears that different signals use different pathways to activate p53, leading to the interesting question whether all of these pathways are equally important for the inhibition of tumor development.

4.1. DNA damage

Warren Maltzman demonstrated that TP53 was responsive to DNA damage caused by ultraviolet radiation (33). DNA damage was the first type of stress found to activate p53 and based on this finding, p53 is widely regarded as "the guardian of the genome" (34). In the extensive characterization of the signaling routes that connect DNA damage with p53, a cascade of Ser/Thr kinases, which includes ATM, ATR, Chk1 and Chk2, has been identified that all lead to phosphorylation of p53 (35-38). This signaling cascade may be permanently activated in some cancers, suggesting that the cancerous state might be intrinsically associated with the generation of DNA damage (39-40). The constitutive DNA damage in cancer cells is thought to originate primarily from strong generation of reactive oxygen species (ROS) (41) as well as from aberrant firing of DNA replication origins (42-43). Recent characterization of mice, genetically manipulated with a knocked-in p53 that cannot be phosphorylated at two of the main residues targeted by ATM/ATR/Chk1/Chk2, namely, Ser18 and Ser23 (Ser15 and Ser20 in human p53), indicates an important role of these phosphorylation sites in some, but not all, DNA damage induced and p53-dependent responses (44). In agreement with this, mice carrying p53S18A/S23A alleles are tumor prone (44) although this phenotype is considerably milder than in the case of p53-null mice (45-46). These data suggest that the activation of

p53, in response to DNA damage, occurs through multiple pathways, which in addition to the well-established kinase cascade of ATM/ATR/Chk1/Chk2, probably includes other kinases such as p38, JNK/SAPK, and c-Abl (47-52). Regarding human cancer, the available information gathered from the analysis of (epi)genetic aberrations indicates that the DNA damage signaling kinases are not, in general, significant targets of genetic and epi-genetic inactivation (53-55). The only exception to this is found in hematological malignancies, which present a high incidence of mutations in ATM (13–40% depending on the particular type of malignancy) (56). In agreement with this, a recent large-scale sequencing effort of 210 diverse human cancers has identified ATM as one of the three most frequently mutated kinases (5% incidence) (57). Based on such genetic evidence, it can be concluded that DNA damage is conveyed to p53 through multiple redundant pathways. Many transducers participate in such a response but none of these plays a critical role and for this reason, alteration of a single component may have relatively minimal impact on p53 function.

4.2. Oncogene activation

Among the many and varied stimuli that have been reported to activate p53, oncogenic signaling (58) has received a great deal of attention because, similar to the DNA damage, alteration of such signaling pathways is universally found in cancer. It is for this reason that a function as a traffic controller of oncogenes can be assigned to p53. When activated or over-expressed oncogenes such as Ras, c-Myc, or E1a stabilize and activate p53, and depending on the cell type, induce senescence (Ras) or apoptosis (c-Myc or E1a) through hyperproliferative signaling pathways that activate ARF, the product of the alternative reading frame of the cell-cycle regulatory gene INK4a/CDKN2a (59). Oncogenic signaling activates p53 through ARF, (60-62) which, in turn, interacts with MDM2 inhibiting its p53-ubiquitin ligase activity. Consequently, ARF-dependent stabilization of p53 results in a dramatic increase in p53 activity. Many transcription factors activate ARF in response to oncogenic signaling (63-64), most notably DMP1 (Dentin matrix acidic phosphoprotein-1) (65-66). Mice lacking ARF have a remarkable tumor-prone phenotype (67-68) although this is not as severe as p53-deficient mice, (45-46) and there is good genetic evidence in mice supporting the relevance of the ARF/MDM2/p53 axis in tumor suppression (29). Importantly, ARF-deficient-mice present a normal DNA damage response, indistinguishable from ARF-proficient mice (28). Regarding human cancer, the analysis of (epi)genetic alterations indicate that ARF is indeed inactivated at an extraordinary high frequency (~30%) in cancer (63). However, inactivation of ARF almost invariably occurs in combination with the loss the cell cycle inhibitor, p16INK4a, leading to the uncertainty as what exactly is the key targeted tumor suppressor. It should be mentioned, in this regard, that germline point mutations that inactivate ARF alone (i.e. sparing p16INK4a) exist in human kindreds predisposed to cancer (69-70). Nevertheless, the number of germline mutations that inactivate only p16INK4a (i.e. sparing ARF) outnumbers those that inactivate ARF alone by a factor of ~20 (71). The currently available evidence indicates that ARF is an important upstream regulator of p53, whose lack of activity has a significant impact on cancer. Based on the observation that Ser15 in p53 was not phosphorylated in response to adenovirus E1A expression, it was concluded that oncogenic activation of p53 occurs in the absence of DNA damage (71). However, brief c-Myc overexpression in normal fibroblasts induced DNA damage signals which correlated with induction of ROS (72), raising the question as whether or not oncogenes activate p53 through DNA damage and whether the ability of oncogenes to promote apoptosis or senescence correlates with different posttranslational modifications of p53. Ferbeyre *et al* (73) reported that expression of oncogenic Ras in IMR90 cells induced phosphorylation of p53 at Ser15. In contrast, Bulavin *et al* (74) found p53 was phosphorylated at Ser33 and Ser46 but not at other N- or C-terminal sites, nor was it acetylated at Lys382. Interestingly, a similar induction of permanent cell cycle arrest resembling cellular senescence was produced in murine fibroblasts engineered to express the MAP kinase Mek1 (73). The induction of senescence by Ras required wild-type p53 and ARF, but p53 was not required to maintain the senescent state. These data indicate that other signals may influence the outcome of p53 activation, which probably occurs through the association of p53 with various coactivators. However, whether or not this leads to the expression of different p53 target genes remains to be determined. Based on such understanding, p53 is now known as “the traffic controller” of cell signaling pathway.

4.3. Hypoxia

Cells that reside at a distance of 150 □m or more from blood supply in tumors often experience hypoxia, a condition that is common in most solid tumors because of the abnormal development of vasculature. Hypoxia is also an important pathophysiological feature of ischemic disorders. Hypoxia and several hypoxia mimetics have been shown to induce accumulation of p53 as a result of the down-regulation of MDM2 (75) with concomitant phosphorylation of Ser15 but not acetylation of Lys382 (76). However, in contrast to Ionizing radiation (IR), hypoxia treatment fails to induce the transcription of downstream effectors, GADD45, Bax, and p21 (76). Hypoxia does not induce detectable DNA damage, and in contrast to DNA damage-inducing agents, hypoxia primarily causes an association of p53 with mSin3A rather than p300. Consistent with this finding, p53-mediated transrepression was induced. In hypoxia treated human papillomavirus HPV-16 transformed cells, p53 was resistant to E6-mediated degradation, and its association with E6AP was reduced (75). Interestingly, a recent study has shown that inhibition of ATR kinase activity reduced the hypoxia-induced phosphorylation of p53 protein on Ser15 as well as accumulation of p53 protein (77). This data suggests that hypoxia can become selective because of the loss of ATR-dependent checkpoint controls, thus promoting cell transformation.

4.4. Microtubule disruption

Activation of p53 occurs in response to such factors as colcemid, nocodazole, and taxol that deregulate

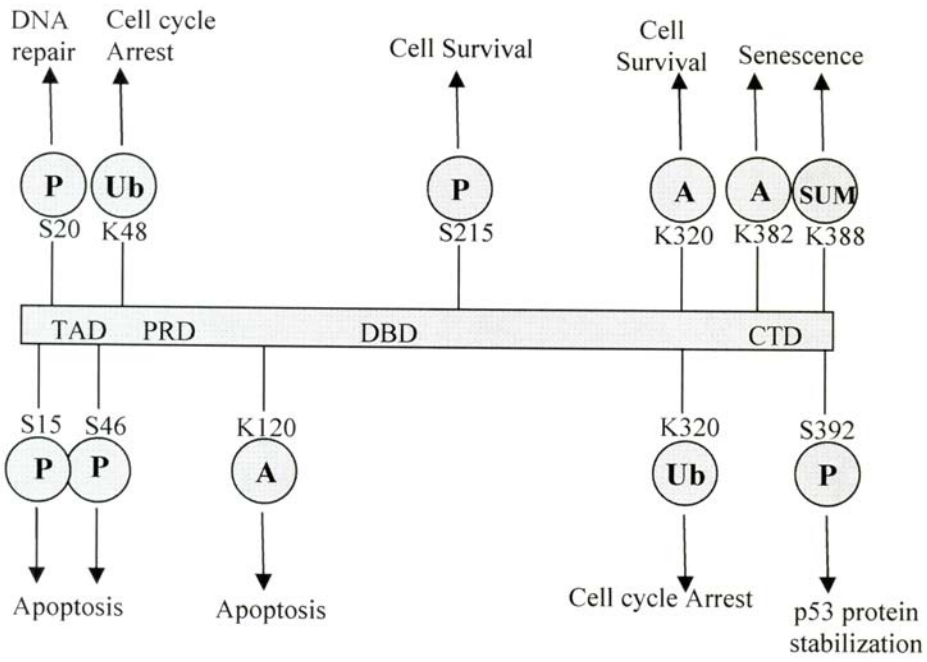

Figure 3. Signals of activated p53 traffic controller for different cell fate determination. Specific residues are modified as shown, with phosphorylation (p), acetylation (A), ubiquitination (Ub), Sumoylation (SUM). Different cell fate determinations after these modifications are shown in matching. TAD, Transactivation domain; PRD, prolin-rich domain; DBD, DNA-binding domain; CTD, C-terminal regulatory domain

cell adhesion or architecture and dynamics of microtubule. Taxol (Paclitaxel), which inhibits microtubule depolymerization, is one of the chemotherapeutic drugs, commonly used in treating ovarian, breast, head and neck cancers. After nocodazole treatment, which depolymerizes microtubules, quiescent human fibroblasts accumulated transcriptionally active p53 and arrested in G_1 with a 4 N DNA content (78). Activation of p53 after colcemid treatment was accompanied by a moderate increase in phosphorylation at Ser15 and correlated with activation of Erk1/2 MAP kinases and the development of focal adhesions rather than disruption of the microtubule system (79). Curiously, murine fibroblasts did not undergo the same response. Taxol and vincristine, but not nocodazole, were found to induced multi-site phosphorylation of p53 in several tumor-derived human cell lines, including HCT-116 and RKO cells, and the pattern of p53 phosphorylation was distinct from that observed after DNA damage (80). Nevertheless, both nocodozole and taxol increased phosphorylation at Ser15. Interestingly, microtubule inhibitor-induced p53 stabilization and Ser15 phosphorylation did not occur in ATM-deficient fibroblasts nor in normal human dermal fibroblasts. Studies with ectopically expressed p53 phosphorylation site mutants indicated that several p53 amino-terminal residues, including Ser15 and Thr18, were required for the taxol-mediated phosphorylation of p53 (80). In contrast, Damia *et al* (81) reported taxol induced p53 phosphorylation in HCT-116 cells at Ser20 but not at Ser15. Phosphorylation at Ser20 was accompanied by increased Chk2 activity and was not inhibited in A-T cell lines or by wortmannin treatment. Therefore, the signaling pathways that impinge on p53 after hypoxia and microtubule disruption are distinct from those induced by genotoxic stresses.

4.5. Replicative senescence

Replicative senescence in human fibroblasts correlates with activation of p53-dependent transcription and was shown to be associated with increased phosphorylation at Ser15, Thr18, and probably at Ser376, and with decreased phosphorylation at Ser392 (82). Since staining with the DO-1 monoclonal antibody, which detects phosphorylation at Ser20 failed to show positive staining, it was inferred that phosphorylation on Ser20 was not inducible upn senescence. These results together with findings showing that changes in p53 phosphorylation are abrogated in cells immortalized by overexpression of telomerase indicate that these modifications may result from telomere erosion. Shortened or disrupted telomere structures may signal to p53 via pathways that are partially shared with DNA damage responses.

5.THE ELEGANT MODEL OF P53 REGULATION

The post-translational modifications that can positively or negatively regulate cell fate determination and tumorigenic role of p53 protein as a tumor suppressor has been studied in great detail (Figure 3). As partially described in Section 3, human p53 has 23 different phosphorylation and dephosphorylation sites. Regulation of p53 function by phosphorylation and dephosphorylation occurs at many sites, most of which reside outside the DNA binding domain (DBD). Most residues are phosphorylated by many different kinases in response to many different

Table 1. p53 mediated transcriptionaly repressed and activated genes

p53 mediated down regulated genes
Cdc25C phosphatase [88], ABCB1, MDR1 [89], ANLN [90], IER3, IEX-1 [91], MAD1L1, MAD1 [92], ODC1 [90], PLK2, SNK [93], PTK2, FAK [94], SCD [90], TRPM2 [90], UBD, FAT10 [95], proto-oncogene c-Myc [96], EpCAM [97], RHAMM [98], MCM-7 [99], Androgen receptor (AR) [100].
p53 mediated up regulated genes (represented few genes in different cell fate determination)
Apoptosis
Apoptosis-inducing factor, mitochondrion-associated, 2 (AIFM2, AMID) [101], PUMA [102], Cathepsin D (CTSD, IRDD) [103], Receptor tyrosine kinase EphA2 [104]
Senescence and/or cell cycle control
CDKN1A, p21 [105-106], PML [107], SESN1, PA26 [38]
Cell Cycle control
GML [108], IBRDC 2, p53RFP [109], PLK3 [110], S100A2 [111], SFN, 14-3-3sigma [112]
DNA repair
BTG2, TIS21 [113], DDIT4, REDD1 [114], FANCC, FAC [115], GADD45A [116], GPX1 [117], MSH2 [118].

p53 has been reported to act as repressor and activator of different cell fate determining genes. In this table major genes repressed by p53 transcription factor and activated in different cell functions has been summarized

stresses and are associated with p53 activation (83). This defines two levels of potential redundancy: first, a specific residue can be phosphorylated by several different kinases (for example, serine 15 is phosphorylated by at least 8 kinases), and second the same kinase can phosphorylate p53 at several residues (for example, CHK2 phosphorylates 7 different residues). Such redundancy might provide a fail-safe mechanism to enable different stresses to activate p53 (83). As some residues seem to be phosphorylated by a single kinase, a unique phosphorylation pattern might determine a subset of cellular responses. Alternatively, this could reflect our incomplete knowledge of relevant kinases and their targets. For example, Ser378 was thought to be phosphorylated by a single kinase just 2 years ago (83), but recent data indicate that three different kinases are involved (84). Furthermore, the dephosphorylation of some residues has been correlated with activation. Therefore, Ser376 is phosphorylated in unstressed cells and dephosphorylated after ionizing irradiation, correlating with the interaction of p53 with 14-3-3 proteins (85). C-terminal lysines of p53 are modified by ubiquitination, acetylation, sumoylation, neddylation, and methylation. Neddylation seems to inhibit transactivation, whereas sumoylation positively or negatively affects p53 function (83). It has recently been suggested that p53 sumoylation induces senescence in normal human fibroblasts but apoptosis in RB (retinoblastoma 1)-deficient cells (86). Rather than apoptosis, it was suggested that modifications to Lys320 promote cell-cycle arrest (87-89). In contrast to Lys372, 373, 381, and 382, which are all acetylated by p300 and ubiquitylated by MDM2 (83), Lys320 is acetylated by the p300 and CBP associated factor (PCAF) (87-88, 90) and ubiquitylated by E4F1 (89). Methylation at nearby lysines may also have dramatically different effects: Lys372 methylation by SET9 stabilizes p53 (91), whereas the methylation of Lys370 by SMYD2 destabilizes it. The increasing variety and complexity of p53 modifications at serines, threonines and lysines shows elegant models involved in p53 regulation.

6.P53 ABILITY TO SWITCH ON AND OFF GENES

The most studied and characterized mode of action of p53 is its function as a transcription factor. The role of modifications and cofactors, which ensure its presence in the nucleus, is just one aspect of the signboard in a signaling network. However, the possibility that p53 switches a particular gene expression on or off (Table 1) is determined by its post-translational modifications, the action of cofactors, or a combination of both of these two mechanisms. Modifications of specific residues in p53 can also directly influence the promoter to which p53 will bind. In response to UV and genotoxic stress, p53 is respectively phosphorylated on Ser46 by the kinases homeodomain-interacting protein kinase-2 (HIPK2) and the dual-specificity tyrosine-phosphorylation-regulated kinase-2 (DYRK2) (119-121). This occurs in the later stages of p53 activation and influences the response by specifically promoting the induction of the apoptotic genes p53AIP1, PUMA, Noxa, and PTEN (122-125). This is accompanied by down regulation of p21 expression, ultimately resulting in p53-dependent apoptosis. Furthermore, p53-dependent apoptosis can be specifically enhanced following DNA damage through the acetylation of Lys120 by the MYST family acetyltransferases MoF and TIP60. Lys120 lies in the DNA-binding domain of p53, and its acetylation leads to increased specific recruitment of p53 to pro-apoptotic target genes such as Puma and Bax, suggesting that this modification alone can influence how p53 responds to DNA-damage signals (Figure 3). This modification appears to be required for p53-dependent apoptosis i.e. mutants that can no longer be modified in this way, exhibit impaired apoptotic activity while maintaining the proper regulation of Mdm2 and cell-cycle-arrest genes (126-127). These data show that a defined p53 modification can be linked to a specific cellular outcome. In contrast, Lys320 of p53 can be modified independently by both acetylation and Ubiquitination to influence promoter selectivity. The e3 ligase, e4F1, ubiquitinates p53 at Lys320, and specifically increases the activation of cell-cycle-arrest genes, such as p21, Gadd45, and cyclin G1 while the expression of apoptotic targets remains unchanged (89). Chromatin immunoprecipitation experiments demonstrated that Lys320-ubiquitinated p53 was bound to the p21 gene promoter but not to that of the apoptotic target gene, Noxa. Similarly, acetylation of Lys320 following drug-induced DNA-damage promotes cell survival, with Lys320-acetylated p53 binding more efficiently to the p21 promoter than to the non-acetylated form of p53 (88). Despite their apparent overlapping functions, the modification of Lys320 by these two distinct mechanisms appears to be mutually exclusive as ubiquitination abolishes acetylation, and vice versa (89). Thus, the two modifications may represent a way that p53 can selectively target cell-cycle arrest genes in response to different incoming signals. Furthermore, the same modification on the same residue can also result in different cellular outcomes. Acetylation of Lys320 in neuronal cells does not cause cell-cycle arrest, but it is specifically involved in promoting neurite outgrowth by elevating the expression of two p53 target genes: firstly, coronin 1b, which encodes an actin-binding protein, and secondly Rab13, which encodes a GTPase (128). Thus,

even the same modification can cause markedly different outcomes depending on the tissue in which activation occurs. Ultimately, these differences must be due to the presence of cofactors in the cell that are differentially expressed from one cell type to another. Therefore, analysis of p53 cofactors must be taken into consideration when attempting to predict the p53 response.

7. EVENTS DOWNSTREAM FROM P53 ACTIVATION

Once the p53 protein is activated, it initiates a transcriptional program that reflects the nature of the stress signal, protein modifications, and of the proteins associated with the p53 protein. The p53 protein binds to a specific DNA sequence, termed the p53-responsive element (RE) (129-130) and induces the expression of downstream genes. The genes in this p53 network mainly initiate one of three programs that result in cell cycle arrest, DNA repair or apoptosis.

7.1. Growth arrest

p21WAF1/CIP1 is known to be a p53-downstream gene, and has been suggested to mediate p53-induced growth arrest triggered by DNA damage. The p21 protein is a cycline-dependent kinase inhibitor that associates with a class of CDKs and inhibits their kinase activities. This will facilitate the accumulation of the hypophosphorylated form of pRB that in turn associates with E2F, inhibiting its transcriptional activity and leading to cell cycle arrest. As long as pRb is bound to E2F, the cell is prevented from entering into S phase. This G1 arrest provides the cell the opportunity to repair DNA damage. Thus, if the repair is successful, p53 level drops and CDK-cyclin protein kinase activity resumes, leading to entry into S phase. If DNA is not repaired, p53 triggers apoptosis (131-132). As a block occurs in G2 phase, there is recent evidence that p53 can control entry into mitosis in the presence of damaged DNA or in S phase due to depletion of the substrates required for DNA synthesis. Part of the mechanism by which p53 blocks cells at the G2 checkpoint involves inhibition of Cdc2, the cyclin dependent kinase required to enter mitosis (133). Cdc2 is simultaneously inhibited by three transcriptional targets of p53, Gadd45, p21, and by 14-3-3σ (134). Binding of Cdc2 to Cyclin B1 is required for its activity, and repression of the cyclin B1 gene by p53 also represses the cdc2 gene thereby helping to ensure that cells do not escape the initial block (135).

7.2. DNA repair

Soon after TP53 was established in the 1990s as the most frequently altered gene in human tumors (136-137), it was found that p53 is a major component of the DNA damage response pathway (34, 138). Once DNA injuries occur, the level of p53 protein rises, which in turn induces a transient cell cycle arrest or apoptotic cell death. The p53 protein senses DNA damage and can halt progression of the cell cycle in G_1 as a result of post-translational modifications caused by specific kinases such as the strand break sensor, ataxia telangiectasia mutated protein (Atm), acetyltransferases like CREB-binding protein (Cbp)/p300, and the poly (ADPribose) polymerase 1 (Parp-1), which prevent proteolysis via the Arf-mouse double minute 2 (Mdm2) pathway and/or enhance binding of p53 to consensus sequences within the genome (139-141). The C-terminal 30 amino acids of p53 were shown to recognize several DNA damage-related structures such as DNA ends, gaps, and insertion/deletion mismatches (142-145). p53 was also demonstrated to catalyze reannealing of short stretches of single- and double-stranded DNA and to promote strand exchange between them (142, 146-147). Furthermore, p53 binds to three-stranded heteroduplex joints and four-stranded Holliday junction DNA structures, specifically localized at the junction, suggesting that p53 directly participates in recombination repair (148-150). Moreover, several research groups demonstrated Mg^{2+}-dependent 3'–5' exonuclease activity intrinsic to p53 (138, 151). In addition to p53 biochemical activities, numerous reports on physical and functional protein interactions further strengthened the suggestion that p53 plays a direct role in nucleotide excision repair (NER), base excision repair (BER), and double-strand break (DSB) repair (152-154). However, it must be emphasized that p53 is not the only potential gene directly involved in DNA repair as other genes are also involved.

7.3. Apoptosis

Pivotal to the tumor-suppressor activity of p53 is its ability to activate apoptosis via multiple pathways (155). However, although a large number of genes, regulated by p53 during induction of apoptosis, are known (155), no single target gene has been identified whose altered expression alone is sufficient to explain p53 mediated transcription dependent apoptosis, and whose genetic deficiency phenocopies p53 deficiency *in vivo*. As an additional mode of p53 pro-apoptotic activity, recent studies have placed non-transcriptional pro-apoptotic activities of p53 at the center of an active debate to establish a comprehensive understanding of p53- mediated apoptosis (155).

7.3.1. p53 role in transcription dependent apoptosis

Several mechanisms have been implicated in p53-mediated apoptosis. p53 activation leads to up-regulation of pro-apoptotic Bax and down-regulation of pro-survival factor Bcl-2 (156-157). More recently, it was demonstrated that p53-mediated apoptosis of M1 cells involves rapid activation of the pro-apoptotic Fas/CD95 death pathway-via up-regulation of membrane bound Fas (158) and the intrinsic mitochondrial pathway, which results in activation of caspase 8, 9, and 10. Fas blocking antibody or inhibition of the apical caspases 8 and 10 were almost effective in abrogating p53 mediated apoptosis, as that which occurs with IL-6. These observations suggest that p53 regulation of the Bcl-2 members, Bax and BcI-2, associated with the intrinsic mitochondrial apoptotic pathway is ancillary to the extrinsic Fas/CD95 apoptotic pathway in mediating p53 induced apoptosis of M1 myeloid leukemia cells (159). In other cell types, up-regulation of IGF-BP3 has been associated with p53 mediated apoptosis by sequestering the cell survival factor, insulin-like growth factor-1 (160-161). The gene encoding for the cathepsin-D protease, PAG608, has also been implicated as a mediator of p53 induced apoptosis in

various cell types (107). Furthermore, it has been documented that a series of p53-induced genes (PIG genes) encode proteins that respond to oxidative stress, suggesting that p53-mediated apoptosis involves activation of redox controlling targets followed by increase in ROS, oxidative damage to mitochondria, and consequent caspase activation (162). It has also been recently observed that p53 suppresses Nrf2-dependent transcription of antioxidant response genes, presumably, to prevent the generation of antioxidants that can hinder induction of apoptosis (163).

A number of p53 transcriptional targets represent genes with the potential to promote or inhibit apoptosis in stressed cells, such as BAX, PUMA, and NOXA, and the p53-repressed genes BCL2 and Survivin. Puma and Noxa are thought to indirectly induce mitochondrial outer membrane permeabilization (MOMP), induced by the activation of Bax and Bak, via interaction with prosurvival Bcl-2 family members interfering with Bax and Bak (164). Interestingly, it was observed that Puma and Noxa contribute differentially to the regulation of p53-mediated apoptotic pathways. In normal cells, Puma was found to induce mitochondrial outer membrane permeabilization via an ER-dependent pathway. However, upon E1A oncoprotein expression, cells also became susceptible to mitochondrial outer membrane permeabilization induction by Noxa via an ER-independent pathway (165). In addition, p53-dependent apoptosis can occur in the presence of inhibitors of transcription and translation (166). In recent years, it has become clear that p53 also harbors a direct pro-apoptotic function at the mitochondria via engaging in protein-protein interactions with anti- and pro-apoptotic Bcl2 family members, including BclXL and Bak (167).

7.3.2. Role of p53 in transcription independent apoptosis

It has been reported that certain transcriptionally inactive mutants of p53 can still induce apoptosis when over- expressed in tumor cells (168-169). Furthermore, in response to certain stresses such as hypoxia, p53 induces apoptosis but does not function as a transactivator (76). Intriguingly, Moll *et al* demonstrated that during p53-dependent apoptosis a fraction of cellular p53 protein is localized into motochondria and induces release of cytochrome C whereas, this has not been observed during p53-mediated cell cycle arrest (167). Additional support to this finding has been gained from functional analysis of polymorphic variants of p53 (168). Within exon 4 of the p53 gene, a common single-nucleotide polymorphism (SNP) at codon 72 leads to the incorporation of either an arginine (R72) or a proline (P72) at this position of the protein. Further investigation has revealed that the R72 form of p53 induces apoptosis markedly better than the P72 variant (168). When potential mechanisms underlying the observed functional difference between the two p53 variants were explored, the greater apoptotic potential of the R72 form surprisingly correlated with its much better ability to traffic to mitochondria. Based on these data, it is possible to conclude that the enhanced apoptosis-inducing activity of the R72 protein is related, at least in part, to its greater mitochondrial localization. Consistently, an analysis of whole cell or mitochondrial extracts by immunoprecipitation-Western blot analysis, demonstrated that the R72 form of p53 binds to the mitochondrial death-effector protein BAK more effectively than to the P72 variant, correlating with the difference in apoptotic potential of the two p53 variants. Bak resides at mitochondria in healthy cells as an inactive monomer. In response to various death stimuli, it undergoes an activating allosteric conformational change that promotes homo-oligomerization. This leads to formation of a pore in the outer mitochondrial membrane, and allows the release of cytochrome C and other pro-apoptogenic factors from the mitochondria resulting in the activation of a caspase cascade (169). Two other BCL2 family members, BAX and BCL-XL, have also recently been implicated in mitochondrial induction of apoptosis caused by p53 (170-171).

8. DYSFUNCTION OF P53 TRAFFIC CONTROLLER IN HUMAN CANCER

In the two decades since its original discovery, p53 has found a singularly prominent place in understanding human cancer. Although the biochemistry of p53 has been extensively studied, knowledge of the biological consequences of p53 dysfunction is still quite rudimentary. p53 dysfunction in cancer cells is mainly due to its mutations (50%), epigenetic modulation at expression level, and low persistence of p53 protein level due to its enhanced turnover. Most p53 mutations found in human cancers are not null mutations but are responsible for mutant versions of the p53 protein that may have unwanted activities such as gain-of-function or dominant negative inhibitory activity for wild type p53. In many cases, this is achieved through polymorphisms and point mutations in p53, which often result in pronounced conformational changes. Such mutant polypeptides, which tend to accumulate at high levels in cancer cells, are believed to exert a dominant negative effect on normal p53. Other than polymorphism and mutation mediated inactivation, other mechanisms are also involved in inactivating expressed wild-type p53 such as virus infection and over-expression of dominant negative regulators of p53 family isoforms (e.g. DNp73 and other post-translational modifications of p53).

8.1. Polymorphisms in TP53

The cDNA for p53 was first cloned in 1984 (172-174), and then approximately 2 years later a mobility shift in p53 protein was identified due to a polymorphic sequence at amino acid 72, changing proline to arginine (175-177). However, the polymorphism was deemed functionally insignificant. It was only in 1994, when allele frequencies of the proline 72 and arginine 72 variants (P72 and R72, respectively) in human populations were analyzed that Beckman *et al* noted statistically significant differences in allele frequency between different ethnic groups. For example, the P72 allele occurs in African Americans with a frequency of approximately 60% but only 30–35% in Caucasian Americans. Interestingly, Beckman noted that the P72 allele frequency increases linearly in multiple populations as they get close to the equator (178). This led to the hypothesis that the polymorphism at codon 72 might have an impact on p53 function, and that the high degree of

exposure to UV light near the equator is the cause for selection favoring the P72 allele. As other studies have suggested, in HPV-positive vulvar cancers, loss of 72P may occur as a result of the increased sensitivity of the wild-type 72R p53 protein to degradation, which is mediated by HPVE6, as also suggested for esophageal carcinomas (179-180). The first comparison of the biological activity of endogenous P72 and R72 proteins was performed by Bonafe *et al* in 2002. They found that compared to P72, blood leukocytes, homozygous for R72, undergo increased apoptosis in response to the cytotoxic drug, cytosine arabinoside (181). However, further analysis revealed that the R72 variant demonstrated greatly increased trafficking to mitochondria according to findings reported by Marchenko *et al.* (167). A number of studies have attempted to determine whether or not there is an association between codon 72 polymorphic variants of TP53 and risk of particular cancer types. These studies have come to contradditory conclusions (182-187). The reasons for these discrepancies are not clear, but it can safely be said that they may be influenced by unknown variables not examined in such studies. A second exonic polymorphism at codon 47, changing a proline to serine, has also been described (188-189). The frequency of this polymorphism is very low, ranging in various studies from 0.5% to 5%. This polymorphism is close to serine 46, a phosphorylation site crucial in the apoptotic function of p53 (189). The clinical significance of this p53 variant is still unknown.

8.2. Mutations in TP53

The p53 tumor suppressor gene is mutated in about half (50%) of all cancer types arising in a variety of tissues, and it manifests a high frequency of missense mutations (136, 138, and 190). Non-missense mutations are also found in the p53 gene but at a lower frequency compared to those present in other tumor suppressor genes such as APC, BRCA, and ATM. These types of mutations occur in the distribution of missense mutations rather more frequently in exons 2–4 (54%) and 9–11 (77%) than in exons 5–8 (20%). Multiple point mutations in the N-terminus of the p53 protein are required to inactivate its transcriptional transactivation function (191) and mutations in the carboxy-terminus modify the oligomerization and nuclear localization of the p53 protein (192-194), the recognition of DNA damage (142-143), the negative regulation of p53 binding to promoter sequences of genes regulated by p53, the transcription of p53-transactivated genes (195), and the induction of apoptosis (196). More studies on p53 mutation analysis have demonstrated that some carcinogens are able to cause specific mutations. The occurrence of characteristic p53 mutation spectra upon exposure to a particular carcinogen can add to the 'weight of the evidence' implicating an environmental pollutant contaminant in the etiology of human cancer (190).

8.3. Virus infections

The study and use of DNA virus proteins that inactivate p53 have provided fundamental insights into tumorigenesis. Several tumor-inducing human viruses, including certain small DNA viruses (adenoviruses, polyomaviruses, papillomaviruses 16 and 18, and the viruses hepatitis B and C), large DNA viruses (cytomegalovirus, herpes virus 6 and 8, Epstein-bar virus) (197) and human retroviruses (HTLV-1 and HTLV-2) (198) adopt various mechanisms for p53 down-regulation. The tumor viruses such as adenovirus, SV40, and human papillomaviruses encode proteins which affect p53 stabilization and activity at multiple levels to facilitate viral replication and preventing premature death of infected cells. Although the Adenovirus E1B-19K protein can block apoptosis downstream of p53 (199), most of the small DNA tumor viruses encode proteins that target p53 directly. SV40 LT binds and inactivates p53 directly (200-201), and p53 was first identified as a cellular protein that interacts with SV40 LT (202-203). Adenovirus encodes two viral proteins, EIB-55K and E4-ORF 6 that form a complex, and together with cellular proteins are involved in ubiquitination (cullin 5, RBC, Elongin), and the binding and degradation of p53 (204-205). The HPV E6 protein also degrades p53 by binding to both p53 and the cellular E3 ubiquitin ligase, while E6AP does not normally function to degrade p53, and HPVE6 recruits and redirects its ubiquitin ligase activity to degrade p53 (206-207). Thus, disparate DNA viruses functionally converge to encode proteins that bind and inactivate p53, underscoring the importance of the p53 tumor suppressor pathway in monitoring normal cell growth and DNA replication (208-210). Further, Ferbeyre *et al* (211) found that adenovirus E1A protein circumvents Ras-induced senescence by interfering not only with p53 and Rb but also with promyelocytic leukemia protein (PML bodies). In particular, these authors found that PML upregulation is abolished and the shape and number of nuclear bodies (NBs) are changed into E1A-expressing cells. Moreover, in some cells, a fraction of the PML protein is relocalized into the cytoplasm. Regulation of p53 and PML by viruses might not be exclusive to adenoviruses. Interestingly, the SV40 large tumor antigen has been reported to relocalize p53 to structures that are juxtaposed with PML-containing bodies (212) and viral proteins, such as IE1 and IE2 from hCMV, or E4 or F3 of adenovirus, and disrupt NBs (213-214). In addition, relocalization of PML into the cytoplasm after infection by other viruses has been documented (215-216). Polyomavirus and SV40 are both closely related members of the Polyomaviridae family. In contrast to SV40, polyomavirus is unusual among the small DNA tumor viruses because none of its three early region proteins (PyLT, PyMT, PyST) directly binds and inactivates p53 (217). Nevertheless, PyMT induces ARF and consequently activates a p53 dependent checkpoint that prevents PyMT-mediated transformation of primary mouse cells, and also of rat REF52 cells (218). A recent study resolves the disparity and singularity of polyoma viral proteins that apparently fail to directly bind and inactivate p53 or disrupt the p53 downstream pathway. This study shows that PyST prevents the activation of p53 through its key upstream regulator, ARF. The PyST PP2A interacting domain plays a critical role in preventing ARF mediated activation of p53, implicating a previously unrecognized role for PP2A in the modulation of the ARF-p53 tumor suppressor pathway (219).

8.4. p53 family isoforms

The identification of the two p53-related genes, p63 and p73, initially provoked speculation that all three

genes might play an analogous role in human tumors (220-222). In particular, the striking homology among the family members within both their DNA binding domain (DBD) and oligomerization domain (OD) suggests that these genes might regulate transcription of a common subset of target genes by binding to common promoters as either homo- or heterotetrameric complexes. However, work in the ensuing years has revealed a much more complex picture of the contribution of p63 and p73 to human cancer. A major part of this complexity stems from the expression of both DN and TA isoforms of p63 and p73 in many human tumors. Such studies support the view that TAp63/TAp73 isoforms, like p53, exhibit tumor suppressive properties, and that upregulation of DNp63/ DNp73 isoforms is a common mechanism of their inactivation during tumorigenesis. Indeed, important physical and functional interactions among family members have now been demonstrated in tumor-specific contexts (223-226). In ectopic expression studies, heteromeric complexes have been demonstrated between different isoforms of the same gene, TAp63 / DNp73 and TAp73 / DNp63 isoforms (224, 226). In each case, the respective DN isoforms function as potent inhibitors of transactivation by the respective TA isoforms, and consistent with these findings, endogenous complexes have also been demonstrated between different p73 isoforms, and between DNp63 and TAp73 (227-228). Wild-type p53 binds to p63 and p73 with much lower affinity than p63 and p73 bind one to the other (229). However, despite the absence of strong physical interaction, it seems highly plausible that in some tumor contexts both DNp63 and DNp73 serve to inhibit the function of p53 through promoter competition or other indirect mechanisms (4, 5, 230).

7. SUMMARY AND PERSPECTIVE

A great deal has been learned about p53 protein and its participation in different cell signaling pathways. It is likely that p53 protein can cause virtually all cells, including normal to cancer cells, to adopt different cell fates. In general, p53 has been considered to be a tumor suppressor due to its ability to induce cell cycle inhibition and/or apoptosis. However, this may not be necessarily the case because p53 deficient cells can also execute cell cycle inhibition and/or apoptosis. Moreover, p53 knock-out mice develop normally with minor malfunctions but are prone to cancer. Insights from emerging data indicate that, in addition to tumor suppression p53 protein induces apoptosis and/or cell cycle inhibition. It is also possible that p53 deficiency can have secondary effects on metabolism and/or other effects in predisposition to cancer. Majority of cancers arise in the presence of an inactive p53 (mainly by mutation) and consequently, introduction of wild-type p53 into those cells can induce apoptosis and/or senescence depending on the cellular system.

Therapeutic strategies which result in the activation of p53 would benefit from an ability to modulate or at least take advantage of the differential responses to p53 activation. The availability of small molecule modulators of p53 activity will allow the planning of more sophisticated treatment options, involving the temporal manipulation of p53 activity, avoiding therapy-induced toxicity and retaining p53-dependent protection from tumor development (321). It is hoped that understanding of how p53 activation can be controlled will help in designing more effective and less toxic treatment options.

On the basis of available data, it can be concluded that p53 is acting as a main traffic controller in a network of cell signaling pathways. Corruption of these signaling pathways leads to immortalization and consequently to death of the host.

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Send correspondence to: Amalia Azzariti, Clinical Experimental Oncology Laboratory, National Cancer Institute, Via Hahnemann, 10, 70126 Bari , Italy, Tel: 39-080-5555556, Fax: 39-080-5555561, E-mail: a.azzariti@oncologico.bari.it

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