COMMENTARY

p53 Tumor suppressor gene: from the basic research laboratory to the clinic—an abridged historical perspective

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Introduction

Tumor suppressor genes maintain tissue homeostasis by controlling cellular proliferation, terminal differentiation and programmed cell death (1,2). The p53 tumor suppressor gene has come to the forefront of cancer research because it is commonly mutated in human cancer and the spectrum of p53 mutations in these cancers is providing clues to the etiology and molecular pathogenesis of cancer (3-8). Of the ~6.5 million cancer cases worldwide each year, 2.4 million tumors are estimated to contain a p53 mutation (examples shown in Figure 1). In the most common lethal types of cancers found in the US population, the estimate is over 300,000 cancers (Table I). These are necessarily crude estimates, because the mutation frequency differs among populations due to dissimilar exposures to environmental carcinogens (and perhaps other reasons such as genetic variation among ethnic groups of genes involved in critical biologic pathways), and selection bias might confound figures derived from early studies. Nevertheless, the high frequency of p53 mutations attests to their potential importance in the pathogenesis, diagnosis and treatment of human cancer.

The 16 year history of p53 investigations is a paradigm in cancer research, illustrating the convergence of previously parallel lines of basic, clinical, and epidemiologic investigation and the rapid transfer of research findings from the laboratory to the clinic. This rich history of scientific accomplishment is briefly reviewed in Table II. The initial observations in 1979 of a cellular protein of ~53 kDa complexing with the large T antigen of SV-40 DNA virus, and of accumulation of p53 protein in the nuclei of neoplastic rodent cells stimulated several researchers to investigate the presence of p53 in tumors and its potential role in carcinogenesis. The p53 gene cloned from neoplastic rodent and human cells was then shown to have weak oncogenic activity. In the late 1980s, researchers discovered that they were studying p53 mutants instead of the wild-type gene; thus the first decade of p53 history can be confusing to the novice reader. Whereas many p53 mutants acted as a dominant-acting oncogene, the wild-type gene suppressed both the neoplastic transformation of rodent fibroblasts in vivo and the growth of rodent and human cancer cells in vitro and in vivo. To the surprise of cancer researchers in 1989, p53 was found to be mutated frequently in human cancers, and the search for p53 functions intensified which has resulted in an explosion of reports in the literature (Figure 2). Recent studies indicate that the p53 protein is involved in gene transcription, DNA synthesis and repair, senescence, genomic plasticity, and in programmed cell death (2-5,9-13). These complex biochemical processes are performed by multicomponent protein machines, so it is not surprising that the p53 protein forms complexes with other cellular proteins, and that oncoviral proteins of certain DNA viruses alter the functions of these protein machines by binding to p53 and perturbing its interaction with other cellular protein components (Figure 3). Ongoing studies are both defining the threedimensional structure of these p53-containing protein complexes and uncovering the regulation of their precise functions.

p53 is clearly a component in a biochemical pathway(s) (5) central to human carcinogenesis; p53 protein alterations due to missense mutations and loss of p53 protein by nonsense or frameshift mutations provide a selective advantage for clonal...
### Table I. Incidence of some common cancers in the USA: estimated number of cases with p53 mutations

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<tr>
<th>Cancer</th>
<th>New cases</th>
<th>Estimated cases with p53 mutations (%)</th>
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<tbody>
<tr>
<td>Lung</td>
<td>169,900</td>
<td>95,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>244,000</td>
<td>73,000</td>
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<tr>
<td>Colorectal</td>
<td>138,000</td>
<td>68,000</td>
</tr>
<tr>
<td>Breast</td>
<td>183,400</td>
<td>44,000</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>24,000</td>
<td>10,400</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>24,000</td>
<td>10,400</td>
</tr>
<tr>
<td>Stomach</td>
<td>22,800</td>
<td>9,500</td>
</tr>
<tr>
<td>Melanoma</td>
<td>34,000</td>
<td>3,000</td>
</tr>
</tbody>
</table>


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### Acknowledgements

I appreciate the comments of Drs E. Appella, D. Lane, E. Mercer, M. Oren, C. Prives, V. Rotter and B. Vogelstein. Any errors of omission are the responsibility of the author and suggested revisions from the readers are most welcome. The editorial and graphic assistance of Dorothea Dudek is appreciated.
Table II. Examples of advances in the 16 year study of the p53 tumor suppressor gene

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<tbody>
<tr>
<td>1</td>
<td>Discovery of the cellular p53 protein in SV-40 transformed and neoplastic cells</td>
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<tr>
<td>2</td>
<td>Anti-p53 antibodies are found in sera of tumor-bearing mice and certain patients with cancer</td>
</tr>
<tr>
<td>3</td>
<td>Other viral oncoproteins (adenovirus E1B, papillomavirus E6, Epstein-Barr virus EBNA-5, Epstein-Barr virus BZLF1, cytomegalovirus-IE84, hepatitis B virus X protein) bind to and inactivate p53 protein</td>
</tr>
<tr>
<td>4</td>
<td>Certain human cancers and cell lines contain increased amounts of p53 protein as detected by immunohistochemistry and enzyme immunoassay</td>
</tr>
<tr>
<td>5</td>
<td>p53 protein expressed in nontransformed cells is associated with growth response</td>
</tr>
<tr>
<td>6</td>
<td>Molecular cloning of murine and human p53; later discovered to be mutant (see advance 18)</td>
</tr>
<tr>
<td>7</td>
<td>Neoplastic transformation of rat cells by transfected p53 (mutant) cooperating with a ras oncogene</td>
</tr>
<tr>
<td>8</td>
<td>p53 (mutant) immortalizes rat chondrocytes and rat embryonic fibroblasts</td>
</tr>
<tr>
<td>9</td>
<td>p53 (mutant) increases the tumorigenicity and metastatic potential of p53 null murine cells indicating gain of oncogenic function</td>
</tr>
<tr>
<td>10</td>
<td>Insertional mutation and rearrangement of the p53 gene by Moloney leukemia virus or Friend leukemia virus</td>
</tr>
<tr>
<td>11</td>
<td>DNA damage leads to 'accumulation' of p53 (wild-type) protein and cell cycle arrest</td>
</tr>
<tr>
<td>12</td>
<td>Chromosomal mapping of p53 to the chromosome 11 in murine and chromosome 17 in human cells</td>
</tr>
<tr>
<td>13</td>
<td>p53 gene arrangements in human cancers are observed</td>
</tr>
<tr>
<td>14</td>
<td>p53 mRNA is alternatively spliced in normal and malignant mouse cells</td>
</tr>
<tr>
<td>15</td>
<td>p53 protein is post-translationally modified by serine phosphorylation (serine kinase, casein kinase II, DNA-dependent protein kinase, casein kinase 1-like kinase, protein kinase C, p34&lt;sup&gt;cdc2&lt;/sup&gt;, MAP kinase, c-jun kinase, raf) and covalent binding to ribosomal RNA</td>
</tr>
</tbody>
</table>

Selected references:

Lane and Crawford, 1979 (15)  
Linzer and Levine, 1979 (16)  
DeLeo et al., 1979 (17)  
Chang et al., 1979 (18)  
Kress et al., 1979 (19)  
Melerio et al., 1980 (20)  
Rottet et al., 1981 (21)  
Rottet et al., 1980 (22)  
Crawford et al., 1982 (23)  
Carro and DeMentia et al., 1987 (24)  
Sarnow et al., 1979 (17)  
Zantema et al., 1985 (26)  
Werness et al., 1990 (27)  
Crook et al., 1991 (28)  
Crook et al., 1991 (29)  
Feinberg et al., 1993 (30)  
Szarka et al., 1993 (31)  
Wang et al., 1994 (32)  
Speir et al., 1994 (33)  
Ueda et al., 1995 (34)  
Truant et al., 1995 (35)  
Benchimol et al., 1982 (36)  
Crawford et al., 1982 (23)  
Mercer et al., 1982 (37)  
Reich and Levine, 1984 (38)  
Mercer and Baserga, 1985 (39)  
Oren and Levine, 1983 (40)  
Zakus-Hoorn et al., 1983 (41)  
Matlashewski et al., 1984 (42)  
Harlow et al., 1985 (43)  
Bienz-Tadmor et al., 1985 (44)  
Eliyahu et al., 1984 (45)  
Parada et al., 1984 (46)  
Jenkins et al., 1984 (47)  
Rovinski and Benchimol, 1988 (48)  
Wolf et al., 1984 (49)  
Eliyahu et al., 1985 (50)  
Pohl et al., 1988 (51)  
Dettner et al., 1993 (52)  
Hsiao et al., 1994 (53)  
Wolf and Rotter, 1984 (54)  
Mowat et al., 1985 (55)  
Maltzman and Czyzik, 1984 (56)  
Kastan et al., 1991 (57)  
Kastan et al., 1992 (58)  
Lu and Lane, 1993 (59)  
Khanna and Lavin, 1993 (60)  
Rottet et al., 1984 (61)  
Czosnek et al., 1984 (62)  
Miller et al., 1986 (63)  
Isobe et al., 1986 (64)  
Wolf et al., 1985 (65)  
Masuda et al., 1987 (66)  
Kelman et al., 1989 (67)  
Wolf et al., 1985 (68)  
Arai et al., 1986 (69)  
Han and Kulesza-Martin, 1992 (70)  
Anderson et al., 1986 (71)  
Samad et al., 1986 (72)  
Meek and Eckhart, 1988 (73)  
Van Roy et al., 1990 (74)  
Bischoff et al., 1990 (75)  
Snurzchek et al., 1990 (76)  
Lees-Miller et al., 1990 (77)  
Tach and Wright, 1992 (78)  
Baudier et al., 1992 (79)  
Delphin and Baudier, 1994 (80)  
Milne et al., 1994 (81)  
Milne et al., 1995 (82)  
Jamal and Ziff, 1995 (83)  
Takenaka et al., 1995 (84)
| 16. | p53 protein binds to other cellular proteins (heat shock 70, Mdm2, WT1, E6-AP, TBP, RPA, SP1, CBF, XPB, XPD, CSB, TAF40, TAF60, TAF31, p62, abl, spot-1) |
| 17. | p53 gene is evolutionarily conserved |
| 18. | p53 (mutant) protein binds to SV-40T antigen less efficiently than wild type p53 and does not inhibit replication of SV-40 virus, whereas, p53 (wild-type) protein inhibits DNA polymerase alpha binding to SV-40T antigen and its ATP-dependent helicase activity |
| 19. | Loss of heterozygosity of chromosome 17p is frequently found in human cancers |
| 20. | p53 (wild-type) fails to cooperate with ras oncogene in the neoplastic transformation of rat embryonic fibroblasts; clarification that previous studies utilized mutant p53 |
| 21. | p53 (mutant) protein can have dominant negative properties on cell growth |
| 22. | p53 (mutant) transgene increases frequency of tumors in transgenic mice |
| 23. | Point mutations in p53 are associated with chromosome 17p deletions in human tumors; providing genetic evidence that p53 is a tumor suppressor gene |
| 24. | p53 is frequently mutated in diverse types of human cancers |
| 25. | p53 functions as a tumor suppressor gene by inhibiting rodent and human cancer cell growth in vitro and/or tumorigenicity in vivo. |
| 26. | Germline p53 mutations are found in certain cancer-prone families |
| 27. | p53 (wild-type) protein contains a transcription activation domain |
| 28. | Human cells with p53 heterozygote mutations can spontaneously immortalize in vitro |
| 29. | p53 can regulate the G1-S and G2-M checkpoints of the cell cycle |

Table II. continued

*Pinhasi-Kinhi et al., 1986 (85)*
*Sturzbecher et al., 1987 (86)*
*Hinds et al., 1987 (87)*
*Huibregtse et al., 1991 (88)*
*Nomand et al., 1992 (89)*
*Baudier et al., 1992 (79)*
*Oliner et al., 1992 (90)*
*Borellini and Glazer, 1992 (91)*
*Seto et al., 1992 (92)*
*Lin et al., 1993 (93)*
*Truant et al., 1993 (94)*
*Chen et al., 1993 (95)*
*Dutta et al., 1993 (96)*
*Li and Botchen, 1993 (97)*
*Agoff et al., 1993 (99)*
*Wang et al., 1994 (100)*
*Wang et al., 1995 (101)*
*Thut et al., 1995 (102)*
*Lu and Levine, 1995 (103)*
*Goga et al., 1995 (103)*
*Olin et al., 1995 (104)*
*Thut et al., 1995 (105)*
*Soussi et al., 1987 (106)*
*Braithwaite et al., 1987 (107)*
*Vogelstein et al., 1988 (108)*
*Mackay et al., 1988 (109)*
*Baker et al., 1989 (110)*
*Weston et al., 1989 (110)*
*Ahuja et al., 1989 (117)*
*Finlay et al., 1988 (118)*
*Eliyahu et al., 1988 (119)*
*Hinds et al., 1989 (120)*
*Rovinski et al., 1988 (121)*
*Eliyahu et al., 1988 (122)*
*Finlay et al., 1989 (121)*
*Gannon and Lane, 1990 (122)*
*Yokota et al., 1987 (111)*
*Lavigueur et al., 1989 (123)*
*Takahashi et al., 1989 (124)*
*Baker et al., 1990 (125)*
*Wang et al., 1990 (126)*
*Wang et al., 1991 (127)*
*Michalovitz et al., 1990 (128)*
*Chen et al., 1990 (129)*
*Malkin et al., 1990 (140)*
*Martinez et al., 1991 (141)*
*Martinez et al., 1991 (142)*
*Cross et al., 1991 (143)*
*Michalovitz et al., 1991 (144)*
*Paules et al., 1991 (145)*
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<tr>
<td>30. Accumulation of p53 protein and/or p53 mutations are found in preinvasive epithelium</td>
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<tr>
<td>31. p53 (wild-type) protein displays sequence specific DNA binding</td>
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<td>32. p53 protein can transcriptionally transactivate genes (muscle creatinine kinase, GADD45, Mdm2, p21\textsuperscript{WAF1}, cyclin G, Bax, Fas, TFG-\alpha and IGF-binding protein 3)</td>
</tr>
<tr>
<td>33. p53 protein can transcriptionally transrepress genes (IL6, Rb, MDRI, p53, c-fos, bcl-2, thrombospondin-1, Tat and NOS-2)</td>
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<td>34. Environmental chemical (aflatoxin B\textsubscript{1}) and physical (ultraviolet light) carcinogens are linked with specific mutation spectra in the p53 tumor suppressor gene in human carcinogenesis</td>
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<td>35. p53 mutant cells can be detected in exfoliated human cells from the bladder</td>
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<td>36. Latent p53 activity (DNA binding and transcription transactivation) can be activated by carboxy-terminal deletions and posttranslational mechanisms</td>
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<tr>
<td>37. Accumulation of p53 (wild-type) protein in tumor cells can cause programmed cell death</td>
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<td>38. p53 can modulate cellular differentiation</td>
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<tr>
<td>39. Conformation of the p53 protein (mutant and wild-type) correlates with its modulation of cell proliferation</td>
</tr>
<tr>
<td>40. p53 missense mutation and/or overexpression in human cancer generally indicates poor prognosis</td>
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<tr>
<td>41. p53 mutation can be associated with tumour progression or metastatic conversion</td>
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<tr>
<td>42. p53 (wild-type) can transcriptionally activate genes adjacent to its sequence-specific DNA binding site</td>
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Baker et al., 1990 (146)
Purdie et al., 1991 (147)
Gusterson et al., 1991 (148)
Bartkova et al., 1991 (149)
Vahakangas et al., 1992 (150)
Bennett et al., 1992 (151)
Kern et al., 1991 (152)
Bargonetti et al., 1991 (153)
Farmer et al., 1992 (154)
Weintraub et al., 1991 (155)
Kastan et al., 1992 (156)
Momand et al., 1992 (157)
Barak et al., 1993 (158)
Wu et al., 1993 (159)
Harper et al., 1993 (160)
El-Diery et al., 1993 (161)
Xiong et al., 1993 (162)
Baker et al., 1994 (163)
Purdie et al., 1994 (164)
Gusterson et al., 1994 (165)
Bartkova et al., 1994 (166)
Vahakangas et al., 1994 (167)
Bennett et al., 1994 (168)
Kern et al., 1994 (169)
Bargonetti et al., 1994 (170)
Farmer et al., 1994 (171)
Weintraub et al., 1994 (172)
Kastan et al., 1994 (173)
Momand et al., 1994 (174)
Barak et al., 1995 (175)
Wu et al., 1995 (176)
Harper et al., 1995 (177)
El-Diery et al., 1995 (178)
Purdie et al., 1995 (179)
Gusterson et al., 1995 (180)
Bartkova et al., 1995 (181)
Vahakangas et al., 1995 (182)
Bennett et al., 1995 (183)
Kern et al., 1995 (184)
Bargonetti et al., 1995 (185)
Farmer et al., 1995 (186)
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Harper et al., 1996 (192)
El-Diery et al., 1996 (193)
Purdie et al., 1996 (194)
Gusterson et al., 1996 (195)
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Vahakangas et al., 1996 (197)
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Kern et al., 1996 (199)
Bargonetti et al., 1996 (200)
Farmer et al., 1996 (201)
Weintraub et al., 1996 (202)
Kastan et al., 1996 (203)
Momand et al., 1996 (204)
Barak et al., 1997 (205)
Wu et al., 1997 (206)
Harper et al., 1997 (207)
El-Diery et al., 1997 (208)
Purdie et al., 1997 (209)
Gusterson et al., 1997 (210)
Bartkova et al., 1997 (211)
Vahakangas et al., 1997 (212)
Bennett et al., 1997 (213)
Kern et al., 1997 (214)
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Harper et al., 1998 (222)
El-Diery et al., 1998 (223)
Purdie et al., 1998 (224)
Gusterson et al., 1998 (225)
Bartkova et al., 1998 (226)
43. p53 (mutant) can cause neoplastic transformation of a human epithelial cell line
44. p53 (mutant) or lack of wild-type p53 enhances frequency of gene amplification
45. p53 (homozygous and hemizygous knockout) mice are cancer prone
46. p53 mutants can have a dominant negative effect on the function of wild-type p53
47. A pathway of programmed cell death initiated by DNA damage is p53 (wild type) dependent and p53 inactivation can lead to resistance to DNA damaging radio- or chemotherapeutic agents
48. p53 (mutant) elicits a cytotoxic T lymphocytic response in mice
49. Tobacco smoking is associated with a dose–response increase in p53 mutations (G→T and G→A)
50. The transcribed strand and specific codons of the p53 gene are preferentially repaired
51. Mice with homozygous or heterozygous deficient p53 alleles can have an increased sensitivity to carcinogen-induced tumorigenicity or tumor progression
52. p53 binds to proteins, e.g., XPB and XPD, in the TFIIH transcription repair complex and modulates nucleotide excision repair
53. p53 can modulate homologous DNA recombination
54. Crystal structure of p53 sequence-specific DNA binding and tetramerization domains are determined
55. Transcriptional activation by p53 results in growth, but not transformation suppression
56. p53 activates a G1 arrest through the pRB family
57. p53-dependent apoptosis can regulate carcinogenesis
58. p53-dependent apoptosis can occur by a transcription transactivator independent pathway
59. p53 recognizes primary DNA damage in the form of insertion/deletion mismatches
60. Serum anti-p53 antibodies can predate clinical evidence of human cancer
61. p53 null mice have a developmental neural tube defect, exencephaly
62. Inactivation of p53 can lead to increased frequency of chromosomal rearrangements and mutations
63. Hypoxia can increase p53-dependent apoptosis and select p53 mutant cells
64. p53 can be posttranslationally modified by O-glycosylation
65. Inactivation of p53 can deregulate centrosomal replication and lead to abnormal chromosomal segregation

The list of advances are examples listed in chronological order and are not all inclusive. The number of references following each example is generally limited to a 3 year period following the initial report. General reviews with more comprehensive lists include (10, 13, 263-266).
References

35. Sarnow,P., Ho,Y.S., Williams,J. and Levine,A.J. (1982) Adenovirus E1b-S8kd tumor antigen and SV40 large tumor antigen are physically associated with the same 54 kDa cellular protein in transformed cells. EMBO J., 28, 387-393.

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