wells created by the vacuum field. All these conditions were achieved in the experiment of Hood *et al.* (*1*), which obtained the values (g_0, κ, γ, $1/T$)/2π = (120, 40, 2.6, 0.002) MHz in the optical domain. The cavity requirements to get these values are rather extreme: The cavity length is 10 μm, and the cavity finesse is F = 180,000. Slow atoms are dropped into the cavity from a magneto-optical trap 5 mm above the cavity mirrors (see figure). In the strong coupling regime, the presence of one atom within the cavity mode completely changes its optical properties: The usual Fabry-Perot peak of the empty cavity turns into two peaks shifted by $\pm g_0$, which are direct evidence of the coherent atom-cavity coupling. Moreover, the value of g_0 depends on the atom's position with respect to the cavity mode and changes from zero, when the atom is outside the mode or at a node of the standing wave, to a maximum obtained when the atom is centered at an antinode. It is, therefore, possible to monitor in real time the motion of the atom as it goes through the cavity, just by looking at the transmission of a weak probe beam fed into the cavity mode. Depending on the precise tuning of the probe beam, the transmitted beam either turns on or off when an atom enters the cavity.

By following in real time a large number of such single-atom trajectories through the cavity mode, Hood *et al.* come to the following conclusions. First, the standard cavity quantum electrodynamics theory for the atom-cavity coupling gives a good qualitative and quantitative account of the observations. Second, when the probe is detuned to the longer wavelength side of the atomic transition, more atoms achieve a large value of g_0 than when the probe is detuned to the shorter wavelength side. This novel result is attributed to a light-induced force at the single-photon level, which "channels" the atoms into the antinodes and therefore increases the apparent value of g_0.

It can reasonably be expected that this experiment will open the way to many others, which have several different but complementary objectives. First, the light-induced forces can presumably be exploited further and may go from the channeling effect observed here to an actual one-photon, one-atom trapping effect. Second, the atom-light interaction in the strong coupling regime also modifies the light itself: In particular, one may expect to produce light beams that would appear as regular streams of individual photons (*1*). Another possible objective is to achieve an extremely efficient two-beam coupling, for performing quantum measurements (*3*) or for implementing quantum logical gates (*4*, *5*). The objective here is to manipulate information stored at the quantum level with single photons or single atoms, keeping an eye on the possible implementation of simple quantum computational algorithms (*5*). In a deliberately optimistic view about the future of such experiments, this is the concrete; soon will come the bricks and maybe one day the house.

References and Notes

1. C. J. Hood, M. S. Chapman, T. W. Lynn, H. J. Kimble, *Phys. Rev. Lett.* **80**, 4157 (1998), and references therein.
2. S. Haroche, M. Brune, J. M. Raimond, *Europhys. Lett.* **14**, 19 (1991); B.-G. Englert, J. Schwinger, A. O. Barut, M. O. Scully, *ibid.*, p. 25.
3. J. F. Roch *et al.*, *Phys. Rev. Lett.* **78**, 634 (1997).
4. Q. A. Turchette *et al.*, *ibid.* **75**, 4710 (1995).
5. See special issue on new forms of computation and communication, *Physics World* **11** (March 1998).

PERSPECTIVES: CARCINOGENESIS

Another p53 Doppelgänger?

William G. Kaelin Jr.

Nature is an efficient employer—if it needs to fill a new position, it retrains an employee already on the books. And so, many proteins have relatives, similar in sequence and structure, but slightly different in function. Recent work is now redefining the tumor suppressor p53's previously solo act to show that it too belongs to a larger group of related proteins.

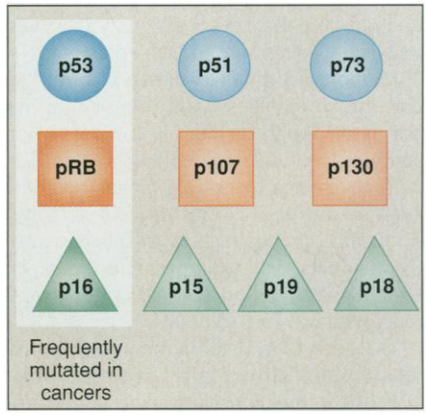
First detected in the 1970s, the p53 tumor suppressor protein is mutated in about 50% of human cancers. Even when the p53 allele is normal, the p53 protein can contribute to disease if it is inactivated through physical association with proteins such as MDM2 or sequestration within the cytoplasm. Thus, it is possible that p53 is absolutely crucial for cancer—that it is always inactivated, directly or indirectly, during all human carcinogenesis. Indeed, a variety of unrelated DNA tumor viruses, through convergent evolution, inactivate p53 during cellular transformation, and germ line *p53* mutations in humans predispose to cancer.

The author is at the Howard Hughes Medical Institute, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02115, USA. E-mail: William_Kaelin@dfci.harvard.edu

p53 is a sequence-specific DNA binding transcription factor. In model systems, reintroduction of wild-type p53 into p53-defective tumor cells leads to apoptosis or to blockade of the cell cycle, or it increases the cell's sensitivity to chemotherapeutic agents. If any of these outcomes could be triggered at will in actual tumors, the therapeutic benefit could be considerable. Thus, interest in p53 is intensive, particularly in restoring its function in human tumors.

Last summer, it became clear that there were other members of the p53 family when Caput and co-workers serendipitously identified a human p53 homolog called p73 (*1*). The primary sequence of p73 is very similar to that of p53, especially in the region corresponding to the p53 DNA binding domain. Indeed, p73 can bind to canonical p53 DNA binding sites in vitro (*2*). Furthermore, p73 can, like p53, activate p53-responsive promoters and induce apoptosis in tumor cells lacking p53 (*1*, *3*). In addition, *p73* maps to chromosome 1p36, a region that is deleted in a variety of human tumors. These findings suggest that *p73*, like *p53*, is a tumor suppressor gene.

To date, however, no mutations in the *p73* gene have been identified in human cancers. Thus *p73*, unlike *p53* and *RB-1*, does not conform to the classical "two-hit" model in which inactivation of both the maternal and paternal copies of a tumor suppressor gene are required for tumor development. It has been suggested, however, that *p73* is monoallelically expressed (*1*), that is, only one of its alleles is transcribed. If true, loss of the transcribed allele might contribute to carcinogenesis. Nonetheless, there are currently no genetic data that firmly establish *p73* as a bona fide tumor suppressor gene. The notion that *p73* is monoallelically expressed is currently being challenged (*4*), and mice lacking p73



Close cousins. Members of the p53 family, the pRB family, and the cdk4 inhibitor (INK4) family. p53, pRB, and p16 are frequently mutated in human cancers.

are viable and do not develop tumors (*5*).

By using degenerate polymerase chain reaction approaches, two groups have now identified two new proteins—p40 and p51—both encoded by an additional *p53* family member (*6, 7*). The new family members are the products of alternatively spliced mRNAs encoded by a single gene located on chromosome 3q. For simplicity, I refer to the gene as *p51*. Preliminary data suggest that p51, like p53 and p73, can activate transcription and induce apoptosis (*6*). The primary sequence of p51 and p73 resemble each other more closely than either resembles p53. Unlike p53, but in keeping with p73, p51 is rarely mutated in human cancers. p51 mutations were seen in only 3 of 101 evaluable primary tumors and tumor cell lines (*6*). All three of these mutations were in places that would be predicted to abrogate DNA binding. As it turns out, the rat *Ket* gene, initially thought to be the rat homolog of *p73*, is more closely related to *p51* (*8*).

Why is p53 recurrently mutated in human cancers, whereas the other members of this protein family—with similar functional abilities—are not? A similar conundrum exists with respect to two other proteins associated with human tumors. pRB and p16 (see the figure). Both p107 and p130 can, like their well-known family member pRB, interact with members of the E2F transcription factor family and induce a cell-cycle block. Yet pRB, but not p107 and p130, is recurrently mutated in human cancers. Likewise, all of the p16 family members can inhibit cdk4 kinase activity and block progress of the cell cycle; yet only p16 among these proteins is recurrently altered in human cancer. A simple explanation is that certain critical afferent or efferent functions are in fact not shared by these various family members. In this regard, p53 is induced by DNA damage, whereas p73 is not, and so it is possible that p53 is uniquely recruited to execute a response to DNA damage.

A more insidious explanation would be that the similarities within these families are more apparent than real. First, when studying proteins that belong to families, it is necessary to establish that reagents such as antibodies and nucleic acid hybridization probes react with specific family members. For example, it is unknown whether some antibodies to p53 will cross-react with p51 or p73.

Second, firm establishment of family relationships also requires critical evaluation of the procedures used to study protein function. For example, many of the functional studies of p73, p51, and even of p53 have relied on protein overproduction, in which high concentrations of the proteins may have obscured true physiological differences. High protein levels can also induce an apparent loss-of-function if the stoichiometry of a particular multiprotein complex is disturbed, for example, when overproduced protein causes transcriptional squelching by sequestration of transcriptional activators.

Finally, other family members can also complicate the selective inhibition of a particular protein's function. Certain dominant-negative p53 mutants used in past experiments might also interfere with the function of p51, or p73, either by occupying p53 DNA-binding sites or by inducing heteroligomer formation.

Even gene-knockout studies provide an imperfect solution to addressing function because they only reveal functions that are not shared among family members and because they can induce a potentially compensatory change in the expression of another family member. [For example, p107 is up-regulated in fibroblasts without *RB-1* (*9*).] Strain differences in the phenotype of genetically altered mice can complicate interpretation; knockout of *p130* causes no phenotype in one strain of mouse and yet is lethal in another (*10, 11*). In addition, some functions, such as that of pRB, cannot be extrapolated from mice to humans insofar as *RB-1* +/- mice do not develop retinoblastoma.

In conclusion, the normal functions of p73 and p51 remain to be elucidated, as do their potential roles in cancer. Paradoxically, their potential as therapeutic targets might be augmented if they prove to be largely vestigial copies of p53 that are rarely mutated or altered in human carcinogenesis. Because these p53 homologs can cause p53-defective tumor cells to undergo apoptosis, therapies that triggered the transcription of these genes might restore one measure of p53 function in tumor cells.

References

1. M. Kaghad *et al.*, *Cell* **90**, 809 (1997).
2. M. C. Marin, personal communication.
3. C. Jost, M. Marin, W. G. Kaelin, *Nature* **389**, 191 (1997).
4. S. Nomoto *et al.*, *Cancer Res.* **58**, 1380 (1998).
5. A. Yang and F. McKeon, personal communication.
6. M. Osada *et al.*, *Nat. Med.* **4**, 839 (1998).
7. B. Trink *et al.*, *ibid.*, p. 747.
8. H. Schmale and C. Bamberger, *Oncogene* **15**, 1363 (1997).
9. R. K. Hurford, D. Cobrinik, M.-H. Lee, N. Dyson, *Genes Dev.* **11**, 1447 (1997).
10. D. Colbrinik *et al.*, *ibid.* **10**, 1633 (1996).
11. J. E. LeCouter and M. A. Rudnicki, personal communication.

PERSPECTIVES: STRUCTURAL BIOLOGY

Secret Life of Cytochrome bc_1

Janet L. Smith

The inner membrane of the mitochondrion houses the power plant of the cell. Here, the fundamental chemistry of respiration takes place to generate energy for aerobic life. Together three large protein complexes in this membrane—NADH dehydrogenase, cytochrome bc_1, and cytochrome oxidase—transfer electrons to molecular oxygen from NADH produced by oxidation of food molecules. Cytochrome bc_1, the central electron-transfer complex, oxidizes the membrane-soluble electron carrier ubiquinol and reduces the water-soluble carrier cytochrome c.

This deceptively simple function belies the complexity of events that occur within the cytochrome bc_1 molecule, including a bifurcated electron transfer pathway and translocation of protons across the mitochondrial inner membrane. Although intensively studied, the respiratory complexes have been very difficult to isolate in pure form because of their size and complexity; for instance, cytochrome bc_1 is a dimer of 11-subunit monomers. But finally, a wealth of data from the crystal structures of cytochrome bc_1 and cytochrome oxidase is illuminating the extensive biochemical and spectroscopic data, repaying decades of crystallization effort.

Exactly 2 years from the day S. Yoshikawa and H. Michel announced structures of cytochrome oxidase to much fanfare at the Bioenergetics Gordon Conference on 4 July 1995, Xia *et al.* presented the first structure of cytochrome bc_1 (*1*). In the ensuing year, a more complete, detailed, and fascinating picture of cytochrome bc_1 has emerged. The latest installment, from Iwata *et al.* (*2*), appears on page 64 of this issue.

The initial report by Deisenhofer and co-workers of an 80% complete, 2.9-Å crystal structure of bovine cytochrome bc_1 established the organization of the complex and positions for the metal centers (*1*). Berry and co-workers have just published the structure of the chicken bc_1 complex, nominally at 3 Å, including 9 of 11 subunits and complete chain tracing for the functional extrinsic domains of the cy-

The author is in the Department of Biological Sciences, Purdue University, West Lafayette, IN 47907, USA. E-mail: smithj@bragg.bio.purdue.edu