sexual selection among many theoretical biologists (*2*).

Kodric-Brown and Brown clearly favor Zahavi's position more than Fisher's. They stress the point that sexually selected characteristics should be only weakly heritable, so that their elaboration in any particular individual will reflect overall phenotypic vigor, in gaining access to resources for instance. The development of big antlers in red deer, for example, depends in large part on the animal's age and on superior nutrition. Similarly, the bright blue coloration required by pupfish males in order successfully to attract gravid females to their territory depends on their access to good quality food and on fighting displays. Large antlers in red deer and bright nuptial coloration in pupfish are examples of an interaction between genes and environment and as such represent truth in advertising, say the Tucson researchers.

Where Kodric-Brown and Brown depart from the handicap model is in saying that the elaborated sexual trait need not necessarily be a handicap. In focusing too narrowly on the reproductive function of sexually selected traits biologists too often overlook their potential contribution to improved survival, they argue. "Many male traits, such as large body size and weapons, may confer an advantage in intraspecific competition for resources as well as for mates, and hence may enhance both survivorship and reproductive success."

The Tucson researchers' definition of cost is therefore best seen as being broader than Zahavi's. Zahavi says that advertising must be costly to be honest, which is true. But Kodric-Brown and Brown believe that cost does not inescapably have to imply potentially reduced survival. They agree that some sexually selected traits, such as long plumes and bright nuptial plumes, may increase the risk of predation while enhancing attractiveness to females. But they insist that there is no "necessary trade-off between the expression of male sexual traits and survivorship."

Central to the Kodric-Brown/Brown argument is a considerable plasticity in development of sexually selected characteristics. The existence of some apparently invariant sexual traits, such as the bright color patterns of many male passerine birds, such as manakins, might therefore seem to challenge their hypothesis. Here, once again, they suggest that too narrow a vision has been used in assessing the factors involved in attracting females. The plumage should be regarded as a basic entry fee in the courtship game, after which other features in the overall display become crucial.

Kodric-Brown and Brown contend that biologists too often concentrate on just one or two obvious traits in mating behavior and overlook the real degree of complexity, including the manner in which it might be integrated with the animals' survivorship needs. The theoreticians point out that, so far at least, mathematical models have failed to substantiate the premises of the honesty in advertising hypotheses. "This short-circuits theoretical work on the topic," says Stevan Arnold of the University of Chicago. Kodric-Brown and Brown reply that this reflects an inadequacy of the inevitably simplified mathematical models, not that the proponents of the honesty in advertising position are misinterpreting the natural history observations they make.—**ROGER LEWIN**

References

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Oncogene Linked to Cell Regulatory System

Analysis in yeast of the activity of the ras *oncogene suggests that it works through adenylate cyclase, a major cell regulatory enzyme*

The transforming protein produced by the *ras* gene, one of the two dozen or so oncogenes that have been implicated as possible contributors to cancer development, is an activator of the enzyme adenylate cyclase, at least in yeast. This result, which was presented by Michael Wigler of Cold Spring Harbor Laboratory at the Seventh Annual Bristol-Myers Symposium on Cancer Research, links the *ras* product to what may be the best studied of the cell's regulatory systems. Adenylate cyclase, which catalyzes the formation of cyclic AMP (cyclic adenosine monophosphate) from ATP (adenosine triphosphate), is activated when any of several hormones or neurotransmitters binds to specific receptors on the cell surface. The enzyme is an integral component of the system that transmits the hormonal signals from the membrane to the cell interior.

Robert Weinberg of the Massachusetts Institute of Technology characterized the work, an early example of the way in which the function of a potential cancer gene can be dissected in a simple eukaryotic organism, as "one of the milestones of cancer research." It grew out of last year's discovery by Deborah DeFeo-Jones and Edward Scolnick of Merck Sharp & Dohme Research Laboratories in West Point, Pennsylvania, and then by the Wigler group that yeast contains its own *ras* gene counterparts.

Many living species, including humans, rodents, and fruit flies, also carry *ras* genes. These genes are thought to be required in normal cells for the regulation of growth and differentiation, a hypothesis that is supported by their presence in such evolutionarily diverse species. However, the genes were first identified in animal cancer viruses that had picked up the genes during the course of infection. In contrast to the normal genes, those of the cancer viruses can cause the malignant transformation of cells. Identification of *ras* genes with the ability to transform in several types of human cancer cells has lent credence to the view that the genes may contribute to cancer development.

The activation of the transforming potential of the *ras* genes in cancer cells and the viruses has been linked to small structural changes in their protein-coding sequences. Analyzing the biochemical functions of the normal and transforming *ras* products, although a matter of intense interest, has proved difficult in the higher organisms. Identification of the genes in yeast cells opened the door to studies of *ras* functions by methods that are simply not applicable to mammalian cells. "Yeast has clearly emerged as one of the best systems for studying the mechanism of the oncogene's action because you can combine genetic and biochemical studies," Scolnick notes.

The Wigler and Scolnick groups have found that yeast contains two *ras* genes,

designated yeast *Ras*1 and yeast *Ras*2. The proteins encoded by the yeast genes are about 90 percent homologous to the mammalian proteins for the first 80 amino acids and about 50 percent homologous for the next 80. Then all the proteins have variable regions and finally terminate in short conserved sequences. The yeast *Ras* products contain more than 300 amino acids, whereas the mammalian *ras* proteins have either 188 or 189. Most of the difference is accounted for by longer variable segments in the yeast proteins.

One manipulation that can be performed with yeast, but so far does not work with mammalian cells, is the replacement of specific genes with altered forms. Replacement of either *Ras*1 or *Ras*2 with a nonfunctional version did not affect the ability of yeast spores to germinate, according to Wigler and his Cold Spring Harbor colleagues Tohru Kataoka and Scott Powers. Kelly Tatchell of the University of Pennsylvania and Scolnick have similar results, although they also found that yeast cells in which *Ras*2 alone is inactivated are not completely normal. For example, the cells can multiply with glucose as an energy source but not with certain other nutrients, including ethanol and glycerol.

Although yeast cells can grow with only one *Ras* gene, both groups of investigators find that inactivation of the two genes simultaneously produces a different result. "The yeast cell has an absolute requirement for at least one intact *Ras* gene for spores to germinate," as Wigler puts it. This finding is consistent with proposals that the cellular oncogene counterparts normally act to regulate cell division or differentiation.

The Wigler group has also shown that a human *ras* gene can substitute for the inactivated endogenous yeast genes. "These genes were so tightly conserved in evolution that the human gene will function in yeast cells," Wigler told the symposium participants.

Activation of the transforming potential of the mammalian *ras* genes is brought about by a simple structural change that causes one amino acid to replace another in either of two critical locations in the *ras* proteins. Wigler and his colleagues then constructed a mutant yeast *Ras* gene with an alteration analogous to one known to activate the mammalian genes. When the mutant gene was introduced into yeast cells, they lost the ability to form spores in response to nutrient deprivation. "The yeast cells' physiological response to starvation is clearly upset," Wigler observes.

The alterations conferred by the mutant gene closely parallel those produced by another yeast mutation that was identified by Kunichiro Matsumoto of Tottori (Japan) University and Isao Uno and Tatsuo Ishikawa of the University of Tokyo. Cells with this mutation, which is designated *bcy1*, have a biochemical defect resulting in the continuous activation of the enzyme protein kinase A. Normally this enzyme, which attaches phosphate groups to proteins, is maintained in the inactive state. It is turned on in response to stimuli that act through adenylate cyclase to increase cyclic AMP concentrations in the cell. The cyclic AMP then activates the kinase. By attaching phosphate groups to its target proteins the kinase can modify their activities, thus effecting the cell's responses to the original stimulus.

"The yeast cell has an absolute requirement for at least one intact *Ras* gene for spores to germinate."

The resemblance between the effects of the mutant *Ras* gene and the *bcy1* mutation led Wigler and his colleagues to ask whether the *Ras* protein might also interact with the adenylate cyclase–protein kinase system. In collaboration with the Japanese workers, they found that the mutant protein continuously activated adenylate cyclase, whereas the normal protein did not have this effect.

Other observations also suggest that *ras* proteins might interact with adenylate cyclase. This important enzyme is subject to complex control mechanisms, which involve, among other things, two more regulatory proteins, one ultimately working to stimulate and the other to inhibit adenylate cyclase when the appropriate receptor is activated.

The two proteins, which are sometimes called G proteins because they bind GTP (guanosine triphosphate), are located with adenylate cyclase on the inner surface of the cell membrane. Receptor activation causes the G proteins to bind GTP, leading either to adenylate cyclase stimulation or inhibition.

There are a number of points of resemblance between the G and *ras* proteins. For example, the *ras* proteins also bind GTP and are located mainly on the inner cell membrane.

Recently, at least three groups,* Scolnick's, Arthur Levinson's at Genentech, Inc., in San Francisco, and the third, including investigators from James Feramisco's laboratory at Cold Spring Harbor and from Smith Kline & French Laboratories in Philadelphia, have found that normal *ras* proteins are enzymes that split GTP to GDP and inorganic phosphate, a property also shared by G proteins, which may be inactivated by loss of the GTP. Transforming *ras* proteins have a greatly reduced GTP-splitting ability.

Taken in conjunction with the results of the Wigler group, all this implies that the *ras* proteins may activate adenylate cyclase as the G protein does. Although the normal *ras* protein apparently must itself be turned on in some fashion to achieve this, the transforming protein, perhaps because it has lost the ability to split GTP, may be constantly "on," even when it should be "off." Findings by Melvin Simon of the California Institute of Technology and Alfred Gilman of the University of Texas Health Science Center at Dallas that G proteins share regions of amino acid homology with *ras* proteins also buttress the view that they all have similar functions.†

An effect of *ras* proteins on adenylate cyclase in mammalian cells has yet to be demonstrated directly. Nor is it clear how even the yeast *Ras* protein activates adenylate cyclase. It might directly replace the G protein or work indirectly through some alternative path. Wigler notes, however, that the yeast *Ras* product is of comparable size to the stimulatory G protein. Mammalian *ras* proteins are smaller, although the human *ras* gene was capable of replacing the yeast genes.

Linking *ras* to the adenylate cyclase system by no means solves the problem of how either the transforming or normal gene works. Many problems remain to be solved. The nature of the biochemical changes that ultimately bring about normal cell division or transformation is one. Another concerns whether growth factors might be involved in some way. Among the known effects of growth factors are activation of protein kinases in the cell membrane. Although these are distinct from protein kinase A, the various systems may intersect at some point to produce a common result.

Two other oncogenes, namely, *sis* and *erbB*, have already been connected to well-studied growth factors. Now, *ras* has been tied to a possibly related system that has already been the subject of voluminous research. The molecular biology of oncogenes and cellular biology seem to be merging.—**JEAN L. MARX**

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