

New Genes May Shed Light on Cell Growth Control

Two independent lines of work in molecular biology have now begun to converge: research on the cancer-causing oncogenes and research on the signaling pathways that carry messages telling cells to start—or stop—dividing. Cell biologists have found that the pathways that transmit growth signals into the cell contain the proteins made by several known oncogenes. However, the question has been what are the intermediaries between the growth factor receptors and the oncogenes that, when activated, signal the cell to divide and to keep dividing until the oncogene signal is turned off?

One of the most common oncogene proteins involved in this type of signaling is *ras*, which acts as a relay point to the nucleus for all

the growth factor receptors examined so far. When the *ras* protein is locked in a permanent “on” position by a mutation, various types of cancer may result. Researchers have begun to understand how *ras* works (Reddy BV, Khanna SN, Jena P. *Science* 1992;258:1640). They have found that *ras* is turned on only when it has bound to the nucleotide GTP (guanosine triphosphate). It is turned off again via reaction with another protein, called GAP (GTPase-activating protein), that stimulates the breakdown of GTP into GDP (guanosine diphosphate), which in turn inactivates *ras* and remains tightly bound to it.

It would be disastrous, however, if this inactivated form of *ras*

could not be reversibly reactivated. Thus, the need for exchange proteins has been postulated — proteins that would remove the GDP and free up the *ras* protein so that it could bind new, activating GTP molecules. Such “*ras* exchangers” have been known for some time in yeast and in the fruit fly, *Drosophila*. Recently, several groups have identified and cloned genes for exchange proteins in mammals. These have been shown to be highly specific, stimulating the release of GDP from *ras*, but not from 2 other members of the *ras* superfamily that have different functions and presumably their own exchangers. There is some evidence, however, that the *ras* exchangers also may serve as a link to exchangers for other oncogene proteins, such as *rho*.

Marx J. *Science* 1992;257:484-485.

Editor's comment: *Researchers are gradually beginning to unravel the nature and function of the genes that are essential to*

normal cell growth but that, when improperly regulated, lead to devastating disorders such as cancer and neurofibromatosis. The discovery of intermediate proteins in the signaling pathway between growth factor receptors, on the cell membrane, and growth effector proteins such as ras, provides a mechanism for the delicately balanced regulation of cell division and quiescence. In addition, the fact that these intermediary exchanger proteins may serve as links to yet other signaling pathways allows us to begin to see how the incredibly intricate cascade and feedback pathways of the cell work on molecular level. And, as ras scientist Frank McCormick of Onyx Pharmaceuticals observes in Marx's article, this new information “has all sorts of therapeutic possibilities.” Drugs that inhibit ras activation might be used, for example, to treat diseases such as cancer and neurofibromatosis, in which growth stimulatory pathways are excessively active.

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