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## Molecular Circuit Breaker Can Prevent Runaway Cell Growth

A long-standing mystery about how cells resist the powerful effects of cancer-causing genes has been solved by researchers studying a genetic check-and-balance system that prevents cells in the body from multiplying chaotically.

Drugs that activate this system, says Charles J. Sherr, an HHMI investigator at St. Jude Children's Research Hospital in Memphis, Tennessee, could increase the effectiveness of conventional anti-cancer therapy.

Cells are equipped with several systems for controlling their multiplication, but when these cease to work properly, uncontrolled cell growth can lead to tumor formation. Sherr and St. Jude colleague Martine F. Roussel have been studying how some of these systems work at the molecular level.

In 1995, the HHMI team discovered an unusual example of such a "checkpoint" whose key component is a protein they named ARF. Now they have learned that this protein "monitors the system carefully and works like a fuse or circuit breaker," Sherr says. "The gene for ARF is not activated until signals that stimulate cell growth exceed a critical threshold. It's as if too much current runs through the circuit and the breaker trips."

Although it is generally thought that one gene encodes one protein, the gene encoding the ARF protein initially escaped attention because it lies embedded within another gene called *INK4a*. Sherr's group realized that, like the protein specified by the *INK4a* gene, ARF also inhibits cell growth. The intimate physical relationship between two overlapping genes that ordinarily restrain cell multiplication explains why the *INK4a-ARF* gene pair is missing in many human cancers. Without the growth inhibitory effects of this gene pair, cells are more likely to grow uncontrollably.

Now, the investigators are refining their understanding of how ARF works. ARF's major role is to monitor various kinds of signals that stimulate cells to proliferate. When the strength of these signals rises to dangerous levels, ARF relays this information to another growth inhibitory protein, p53, that in turn prevents the over-stimulated cells from growing and can even induce them to commit suicide. One protein whose levels are carefully monitored by this ARF-p53 "fail-safe" mechanism is Myc, a protein that is required for normal cell growth but whose unregulated overexpression can lead to cancer.

"The ARF protein controls a p53-dependent process that helps to safeguard cells against runaway growth promoting signals," Sherr says. "ARF and p53 act together to limit Myc's stimulatory potential, but in cases where ARF is damaged and can no longer function, unchecked Myc activity can cause havoc."

Sherr and Roussel collaborated with Scott W. Lowe and his colleagues at Cold Spring Harbor Laboratory, and Carol Prives at Columbia University in an attempt to further generalize these findings. The Cold Spring Harbor researchers have been studying another tumor-inducing viral gene, called E1A. They had previously found that p53 suppresses the tumor-generating activity of E1A. The new findings reveal that this ability of cells to resist E1A also depends strongly upon ARF.

Understanding how ARF works has helped to interpret the actions of what Robert Weinberg [of the Whitehead Institute for Biomedical Research at MIT] calls 'collaborating oncogenes.' This theory posits that truly normal cells resist certain oncogenes and refuse to be transformed into cancer cells.

"We have known for 15 years that genes like *Myc* and *E1A* help to overcome this resistance. *Myc* and *E1A* kill normal cells by activating the ARF-p53 checkpoint," says Sherr, "but they also select for the emergence of rare tumor cells that have lost the ARF-p53 checkpoint and no longer die." The studies on ARF's ability to counteract the effects of *Myc* and *E1A* were published in two articles in the August 7, 1998, issue of *Genes and Development*.

While it has been known for several years that damage to a cell's DNA can signal a p53 response that induces cell suicide, these researchers have concluded that ARF sends an alternative signal that does not rely upon DNA damage. However, the ARF pathway can also act hand in hand with the DNA damage pathway in triggering p53-induced cell suicide. According to both Sherr and Lowe, drugs designed to emulate ARF or stimulate ARF production might make cells more sensitive to the many conventional forms of anti-cancer therapy that act by damaging the DNA of tumor cells.