

## Removing Radiation Roadblock

RESEARCHERS HAVE FOUND THE PROTEIN THAT MAKES SOME TUMORS UNRESPONSIVE TO RADIATION.

Almost half of all cancer patients receive radiation treatment. When it works, the high-energy rays damage genetic material inside tumor cells, causing them to self-destruct. But some tumors are resistant to the radiation. HHMI investigator M. Celeste Simon at the University of Pennsylvania School of Medicine has uncovered one protein responsible for radiation resistance in some renal cancers and likely implicated in other cancers as well.

Simon's lab studies proteins involved in maintaining normal oxygen levels throughout the body. Called hypoxia inducible factors (HIFs), these proteins usually signal cells to conserve energy when oxygen is depleted, promoting survival. But some types of cells, like those that form new blood vessels, need to grow more aggressively when they sense an oxygen shortage. This is the job, Simon's lab has shown, of HIF2—it encourages oxygen-depleted cells to grow by activating growth factors and inhibiting p53, a protein that normally induces cell death in the presence of DNA damage.

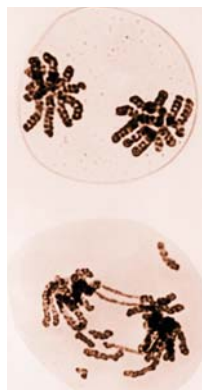
It has long been known that p53 is a tumor suppressor. When it's turned off, tumors can grow more aggressively. p53 inhibition also leads to radiation resistance as it is responsible for telling cells with radiation damage to die.

Knowing this, as well as the fact that radiation-resistant tumors

often show signs of oxygen depletion, Simon hypothesized that HIF2 was inhibiting p53 in these cancers. So she tested cell lines from renal cancers for HIF2 and p53 activity. She showed that when a tumor cell has increased HIF2, it has low p53 activity and is therefore resistant to radiation. Moreover, when the lab decreased the

amount of HIF2 in a cell, it had increased p53 activity and increased response to radiation. The results appear in the August 25, 2009, issue of *Proceedings of the National Academy of Sciences*.

If researchers can find a way to block HIF2, Simon says, p53 would once more do its job of directing radiation-damaged cells to die. HIF2 is not the only protein that inhibits p53 in cancers, so while Simon's approach would work for renal cancers with active HIF2, there are likely multiple forms of radiation resistance. Simon does, however, have evidence that HIF2 is linked to some forms of radiation-resistant lung cancer. ■ -SARAH C.P. WILLIAMS



Radiation damages the chromosomes inside cells (lower panel), normally causing the cells to die.

### IN BRIEF

#### CUTTING BACTERIAL CHATTER

It's a lesson learned by army generals throughout history: cut off communication among soldiers, and their attack strategy goes haywire. It's as true for bacteria as it is for human armies—bacteria rely on chemical signals to coordinate their activities. HHMI investigator Bonnie Bassler, at Princeton University, has used her work on bacterial communication to develop chemicals that can stop a bacterial infection in its tracks.

The bacteria in growing colonies produce chemical signals called autoinducers. When the amount of autoinducer reaches a threshold, the individual bacteria simultaneously change their behavior—by releasing a toxin when there are enough bacteria to have an impact on a host, for example. Bassler's lab group focused on *Chromobacterium violaceum*, a bacterium that rarely infects humans but can be lethal to other organisms. When *C. violaceum* reaches a certain growth level, the colony produces an easily detectable purple dye. The bacteria rely on an autoinducer called acyl-homoserine lactone (AHL) to communicate their population density.

Previously, Bassler had screened thousands of chemicals to find one that would

interfere with the bacteria's AHL receptors. In her latest work, which appears in the July 31, 2009, issue of *Molecular Cell*, she took a promising chemical from this screen and tweaked its structure to yield related chemicals. The most potent version, chlorolactone, protected roundworms from death due to *C. violaceum*, without any side effects. This inhibitor could lead to drugs that stop bacterial infections without relying on traditional antibiotics.

#### DAMAGE REPAIR IN MULTIPLE SCLEROSIS

Damaged nerve cells cause the tingling, paralysis, and numbness in multiple sclerosis (MS) patients. In the early stages of the disease, immune cells attack myelin—the protective coating surrounding nerve cells—which begins to erode. An analogous situation resulting from lack of myelin is seen in the major form of cerebral palsy that affects premature infants with brain injury. Eventually, unprotected nerve cells die. New evidence from HHMI investigator David H. Rowitch suggests that progression of multiple sclerosis involves not only initial myelin damage but also inhibition of the body's normal myelin repair mechanism.

Oligodendrocytes, the brain's fix-it cells, normally can rebuild myelin. Rowitch and his lab group at the University of California, San Francisco, set out to understand why this didn't happen effectively in MS patients. The researchers destroyed a bit of myelin in the spinal cords of healthy mice, and monitored the activity of more than a thousand genes during the repair process.

The team showed that 50 genes encoding transcription factors, which control the activity of other genes, were active during myelin repair. They focused on one, *Tcf4*, a member of the Wnt signaling pathway, which showed a localized increase in expression in white matter during myelin repair. They found that hyperactivation of the Wnt pathway in the oligodendrocytes of mice resulted in significantly delayed myelin repair compared with that in normal mice. Testing also showed that, in humans, *Tcf4* protein is found in areas damaged by MS but not in healthy myelin. Furthermore, the researchers discovered that many Wnt pathway signaling molecules are overactive in patients with MS. The results appear in the July 1, 2009, issue of *Genes & Development*.