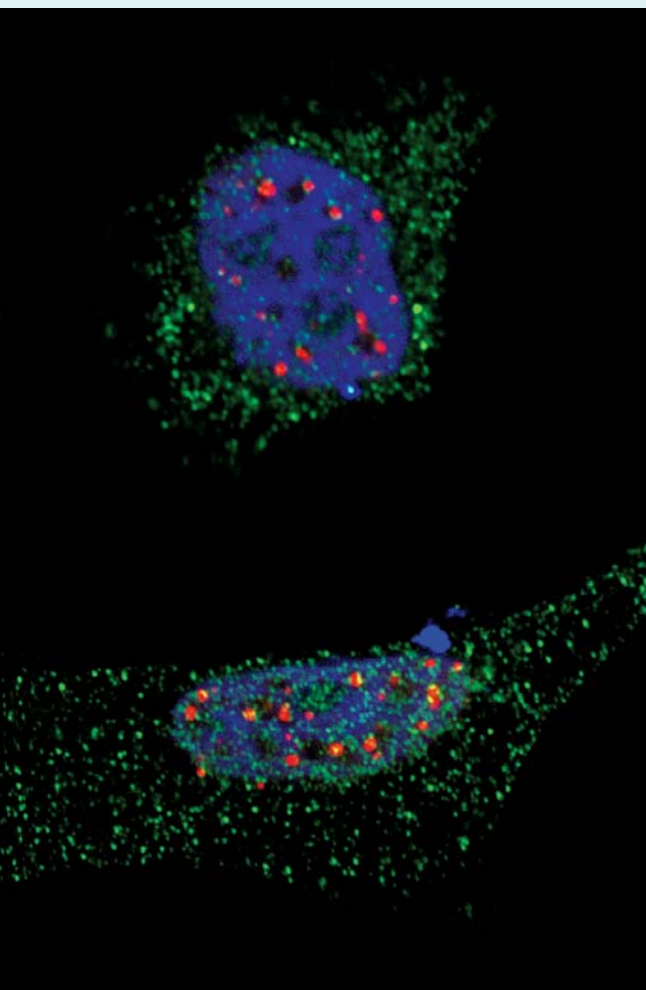


HOW CELLS FLAG DOWN THE BIG GUNS

AND WHY RADIATION ISN'T ALWAYS
AN EFFECTIVE CANCER THERAPY

BY LEAH KAUFFMAN



COURTESY: B. RAJASEKARAN

By revealing the secret lives of mismatch-repair proteins (shown here in intranuclear depots known as PML bodies), Rajasekaran has, among other things, told scientists why radiation and chemotherapy aren't effective against certain cancers.

Cells make mistakes. And who could blame them? According to the Human Genome Project, which mapped the minutiae of our DNA, there are perhaps 25,000 genes within each of our cells. As cells copy that huge volume of information in preparation for division, there's bound to be a clerical error or two.

Fortunately, there's a rigorous copy editor at work in most of us. As cells progress through the cycle of DNA replication and cell division, several checks assure that DNA is faithfully reproduced. Protein proofreaders scan lengths of DNA, checking for errors and omissions, alerting other proteins to drop in to make repairs. And if the DNA damage is too severe to be fixed, defective cells are discarded entirely.

"Proteins that are involved in these responses are actually genome protectors," says Pitt molecular biologist Baskaran Rajasekaran. So there's a lot of interest in how the process works—or doesn't. When these proteins stumble, cells with mutated DNA continue to replicate. By picking apart the subtleties of this protective process, Rajasekaran has revealed why radiation therapy is not always effective in warding off certain cancers.

For all our complexity, our 25,000 genes are made of just four molecules bound together in a specific way: adenine to thymine, cytosine to guanine. And for all the immutability of this pattern, sometimes

cells have been known to muddle things, say by joining an adenine to a guanine. Lucky for us, aptly named mismatch-repair proteins can catch these errors and correct them. Rajasekaran, who is an associate professor of molecular genetics and biochemistry in the School of Medicine, is interested in fully illuminating the function of these proteins.

Mismatch repair, though important, has been thought of as junior copy-editing stuff for proteins, like correcting punctuation. But in a 2003 *Nature Genetics* paper, Rajasekaran and colleagues described another, even more vital role for these proteins: They point out broken DNA to proteins equipped to bring cell replication to a halt and destroy the defective cell.

Those cell-killing heavies can't recognize DNA damage on their own. As Rajasekaran sees it, because the mismatch-repair protein has to look for damage anyway, it may as well hang out a flag to alert the big guns. (Although the current model of cell cycle proteins gives just one function to each kind of protein, "in reality this is not the case," Rajasekaran says. "It's much more complicated than that.") The newer model being built by him and others describes a myriad of functions for a protein, depending on which molecules it communicates with at which point in the cell cycle. These proteins are, in fact, jacks of many trades.)

Rajasekaran's findings explain why cell lines from certain inherited forms of cancer are resistant to radiation therapy. In garden-variety cancer cells, treatments like chemotherapy and radiation aim to jump-start DNA quality control, rendering cancer cells defective enough that they'll be marked for destruction. But in some forms of colorectal and endometrial cancer, the crucial mismatch-repair protein pennant is missing, so cells ravaged by radiation continue to chug through the cell cycle and divide: "They don't even know that they're damaged," says Rajasekaran. When the mismatch-repair protein is restored, news of damage is correctly communicated down the line, and the cell replication cycle functions as it should: Irradiated cancer cells cease to replicate, arrested just before their chromosomes separate. While this approach is still a long way off, Rajasekaran imagines one day dosing radiation-resistant cancer cells with the missing protein prior to therapy, so that chemo- and radiation therapies can do their work. ■