DNA Repair Teams' Motto: 'To Protect and Serve'

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When you dial 911 you expect rescuers to pull up at your front door, unload and get busy—not park the truck down the street and eat donuts.

It's the same for a cell—just before it divides, it recruits protein complexes that repair breakage that may have occurred along the linear DNA chains making up your 46 chromosomes. Without repair, damage caused by smoking, chemical mutagens, or radiation might be passed on to the next generation.

However, in 2005, investigators at the Salk Institute for Biological Studies observed that before cell division some of these cellular paramedics inexplicably idle at undamaged chromosome ends, known as telomeres. Apparently the telomeres' disheveled appearance —resembling that of broken DNA strands—raises a red flag.

Now, in a study published in the Nov. 17 issue of *Cell*, that same team led by Jan Karlseder, Ph.D, Hearst Endowment Assistant Professor in the Molecular and Cell Biology Laboratory, reveals why those repair crews are parked at the ends of chromosomes and in doing so answer fundamental questions about how chromosomal stability is maintained.

After the 2005 study, says Karlseder, "We formed a hypothesis that after telomeres replicate they need to be detected by the internal DNA damage machinery—otherwise they cannot form a protective structure, or chromosomal cap."

And that's exactly what the new study shows. Examining activity of telomeric and DNA repair proteins in cultured human cells, the investigators found that right before cell division cellular repair proteins (including one actually called the 9-1-1 complex) are recruited to exposed DNA ends. But rather than fixing what resembles a break, the repair crew, which first arrived at the scene, calls in a second conglomeration of repair proteins. This one, called the homologous recombination (HR) machinery, creates the protective structure.

"The HR machinery fixes any break in the genome that occurs during replication of DNA," explains post-doctoral researcher Ramiro Verdun, Ph.D., lead author of the 2005 and the current study. However, at telomeres, just before they unload their cellular repair truck, HR crews apparently realize where they are—at the end and not the middle of the DNA strand— and reconfigure. "At telomeres, they invade and then stop," says Verdun. "They adopt a different strategy."

That strategy is to tuck in the ragged chromosomal tips and form the cap, thereby hiding those tips from enzymes whose job it is to reattach errant DNA strands. "Again it was surprising," says Karlseder of the versatile HR team. "The cell is very clever. It takes advantage of a machinery that's already there and whose job it is to repair damage, but at telomeres this machinery fulfills a very special 'repair' function."

Be thankful your cells are so clever. Erroneous fusion of chromosome ends would be disastrous, leading to cell death or worse. "When DNA at telomeres is repaired chromosomes fuse together. If these cells then divide you could get chromosome breakage and genome instability, which leads to cancer," explains Karlseder.

In fact, the reason that telomeres, which are synthesized by an enzyme known as telomerase, exist is to assure that chromosome ends remain intact through a lifetime of cell divisions. When asked if there are

cancers in which telomerase activity goes awry, Karlseder answers with no hesitation: “Almost all of them.”

In fact, many proteins contained in DNA repair complexes are defective in cancer. “Proteins that play an important role in the model we propose are mutated in several diseases,” says Verdun. “In cells with those mutations, the telomeres are not normal—they are fused, broken, shorter, or longer—but they are not normal.”

For Verdun one goal of basic science is to understand how normal cells behave with the goal of fixing them if something goes wrong. “We are working on normal human cells—not cancer cells,” he explains. “But we cannot understand how badly behaved cancer cells work if we don’t know how a normal cell functions.”

Source: Salk Institute for Biological Studies