Abnormal DNA maintenance related to cancer

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DNA, like houses and cars, needs ongoing maintenance. Rays of ultraviolet sunlight, chemical pollutants and normal biochemical processes in the cell can damage it. Cells routinely repair this damage before making proteins or copying DNA for cell division. The repairs are remarkably accurate in normal cells but cancer cells make far more mistakes in fixing their DNA. Alan Tomkinson, PhD, University of New Mexico Professor of Internal Medicine and Associate Director of Basic Research at the UNM Cancer Center, wants to understand why and how these repair mechanisms go awry in cancer cells. This understanding could lead to new targets for cancer drugs. Dr. Tomkinson recently won a 4-year $1 million grant renewal to continue his 18-year research investigation on DNA ligases, the enzymes that repair DNA strands.

DNA ligases fuse the backbone of a DNA strand. The strand is a long string of nucleotides that structurally resembles one half of a ladder sliced lengthwise through the rungs. Each nucleotide consists of a deoxyribose molecule with a phosphate molecule on one side and a base molecule on another. The phosphate of one nucleotide attaches to the deoxyribose of the adjacent nucleotide, forming the alternating phosphate-deoxyribose DNA strand backbone—the side of the ladder. In a DNA molecule—a full ladder—each base attaches to a complementary base on the mirror strand to form the rung-like structures that encode genes.

Products of normal cellular chemical reactions and DNA repair proteins that replace damaged bases can break the phosphate-deoxyribose

backbone. If only one strand is broken, the overall DNA structure remains intact because the bases of the broken strand still attach to those of the second, unbroken strand. It is relatively simple for DNA ligases to fuse such single-strand breaks. The DNA molecule falls apart, however, if both strands are broken at the same time and in the same place. In this situation, the cell has several different options to repair these breaks, all of which end with a DNA ligase rejoining the DNA backbone. Dr. Tomkinson studies how DNA ligases work with other DNA repair proteins to repair damage to DNA.

These repair mechanisms are not perfect, though. "You can measure the frequency at which the cell will make a mistake," says Dr. Tomkinson. This error rate is very low in normal cells but the DNA of cancer cells has many changes. "The error rate is so low in normal cells that you would not expect to see cancer normally," says Dr. Tomkinson. "In the process of a normal cell turning into a cancer cell," he explains, "a certain number of changes must accumulate. So at some stage it appears that the mechanisms that normally repair DNA become abnormal."

In fact, these processes become so abnormal that DNA in cancer cells is vastly different from DNA in normal cells. Normal cells have 46 chromosomes; cancer cells frequently do not, a condition called aneuploidy. Normal cells have 23 pairs of chromosomes and the chromosomes of 22 of those pairs resemble each other. Cancer cells, in contrast, have many chromosomes that look vastly different and researchers can see these differences through modern staining techniques that allow them to stain each chromosome a different color. In normal cells, the chromosome pairs retain their color and stay monochromatic; cancer cells become multicolored because the cell links part of one chromosome to part of another. Called translocation, this shuffling of DNA pieces is common in some cancers. "A lot of leukemias have single translocations and they're stable events that you can see easily by cytogenetics," says Dr. Tomkinson. "In some breast

cancers you see almost a complete shuffling of the genetic information. The chromosomes look more like a rainbow than like a single color and the sizes are mismatched."

So, Dr. Tomkinson is studying the enzymes that complete the repair of DNA, the DNA ligases, to learn how the process becomes abnormal. Humans have three types of DNA ligases named ligase I, ligase III, and ligase IV. Dr. Tomkinson is able to measure each ligase's activities in a cell. He has found that the type of ligase that is most active differs between a normal cell and a cancer cell. Normal cells have more ligase IV activity while cancer cells have more ligase III activity. Dr. Tomkinson's grant renewal will further investigate what each of these ligases do and how their activity differs between normal and cancerous cells. "If you know that cancer cells have an abnormality in how they handle DNA damage," he says, "you can selectively target that abnormality so that you kill the cancer cell without harming normal cells."

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