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DNA mutation rates raise curtain on cause of cancer

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What if we could understand why cancer develops? We know that certain risk factors, such as smoking or excessive sun exposure, can increase the chances of developing this terrible disease, but cancer can form in any tissue, and the cause is not always clear. One idea that has emerged is that for a cell to transform into a cancer cell it must suffer a large number of mutations affecting different genes needed to control cell growth. In a study published this week in *Science*, Brandeis University researchers have found that the process of repairing DNA damage also unexpectedly increases the rate of mutations and changes the kinds of mutations that arise.

Surprisingly, as cells progress toward full-blown cancer they begin to suffer alterations of the normal DNA replication process, leading to an increased amount of DNA damage, especially chromosome breaks. Thus there is an increased need for cells to accurately repair these breaks.

Biologist James Haber, graduate student Wade Hicks and undergraduate Minlee Kim report that the repair of damaged strands of DNA, specifically by a process known as gene conversion, can cause higher-than-normal levels of mutation; in fact, 1,400 times as high as spontaneous mutations in cells.

"It has been hard to imagine how cells could accumulate so many mutations in the few generations that they undergo cell division on the way to becoming cancerous," Haber said. "We think that the elevated rate of mutation at sites where DNA has been broken may be an

important source of these gene changes."

Most DNA damage takes the form of double-stranded DNA breaks (DSBs), for which the cell has multiple methods of self-repair. One method, gene conversion (GC), was originally believed to be relatively error-free, since it involves repairing the break by copying in DNA from a nearly identical sequence that serves as a library to restore the original DNA sequence.

"During repair, mutation rates increase, and the types of mutation during repair are different from normal mutagenesis, explained Hicks, the lead author. "It would be interesting to do an in depth analysis of the types of mutations in cancer cells and compare to those we observed in a repair event to see if they match up."

While other studies have looked at GCs and mutation rates in the past, this is the first study to look directly at the region where both DNA strands are replaced. The researchers used yeast cells, a simple organism in which it is possible to induce a single DSB at one location in all cells and then count the number of mutations that arise during the repair of the break. Through this simple system, Haber and his colleagues were able not only to measure the mutation rates, but also to determine which DNA repair enzymes are most important for GC, and to suggest a possible reason for the high number of mutations created.

They discovered that an innate repair system known as mismatch repair does not get recruited during GC; therefore mutations cannot be fixed. In addition, they discovered that many of the repair-associated mutations had a distinct "signature", which suggested that the copying of DNA that must occur during the repair of the break was frequently interrupted and required a way to "find the right place" to recommence copying. One striking consequence of the lack of straightforward copying was that some of the repair events involved "template switches," in which the

copying machinery jumped from the template it was supposed to use to another, distantly related DNA sequence on another chromosome.

"The next steps for this project will be to better characterize these template switches we observed," said Hicks. "What is the actual rate of these events? What proteins are required or not to do the template switches?"

It will now be important to see if there is an acceleration of mutagenesis in precancerous mammalian cells and to learn if there are ways to prevent it from occurring.

Provided by Brandeis University