Scientists show how DNA repairs may reshape the genome

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Researchers at Duke University Medical Center and at the National Institute of Environmental Health Sciences (NIEHS) have shown how broken sections of chromosomes can recombine to change genomes and spawn new species.

"People have discovered high levels of repeated sequences in the genomes of most higher species and spun theories about why there are so many repeats," said Lucas Argueso, Ph.D., a research scholar in Duke's Department of Molecular Genetics and Microbiology. "We have been able to show with yeast that these repeated sequences allow the formation of new types of chromosomes (chromosome aberrations), and represent one important way of diversifying the genome."

The scientists used X-rays to break yeast chromosomes, and then studied how the damage was repaired. Most of the chromosome aberrations they identified resulted from interactions between repeated DNA sequences located on different chromosomes rather than from a simple re-joining of the broken ends on the same chromosome.

Chromosome aberrations are a change in the normal chromosome complement because of deletion, duplication, or rearrangement of genetic material. On rare occasions, the development of one of these new chromosome structures is beneficial, but more often DNA changes can be detrimental, leading to problems like tumors.

"Every so often the rearrangements may be advantageous," Argueso said.

"Those particular differences may prove to be more successful in natural selection and eventually you may get a new species."

The radiation-induced aberrations in yeast were initially detected by co-author Jim Westmoreland in the NIEHS Laboratory of Molecular Genetics and the molecular dissection was done by Duke's Argueso.

In the yeast used for this study, the repeated DNA sequences account for about 3 percent of the genome. In higher species, like humans, about half of the genome consists of these repeated sequences, "which makes for an Achilles heel among humans," Argueso said. "If you have a break in this repeated part, you can repair not only from the same chromosome, but also from a similar repeated sequence in many other places in the genome."

Sequencing the genomes of different humans has turned up a surprising amount of structural variation between individuals, said Thomas D. Petes, Ph.D., chair of Duke molecular genetics and microbiology and co-author of the yeast study. "We expected to see primarily single base pair changes or small deletions and insertions. No one expected to see that one person would have two copies of a gene, while others would have one or three copies of the same gene."

These human studies also showed that many of the rearrangements found in humans are at sites of repeated DNA, which may occur through a mechanism similar to what this study found in yeast.

Petes said this work with yeast also could prove relevant to cancer research. "Most solid tumors have a high level of these rearrangements, as well as a high level of extra chromosomes; recombination between repeated genes is clearly one way of generating rearrangements, although some rearrangements also occur by other pathways," he said. "It is an evolutionary battle between normal cells and tumor cells. One way that

tumor cells can break free of normal cell growth regulation is to rearrange their genomes."

Source: Duke University