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Researchers Uncover Potential Mechanisms to Protect Against Genetic Alterations, Diseases

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Peering into the DNA of tiny yeast, researchers at the Moores Cancer Center at the University of California, San Diego and the San Diego Branch of the Ludwig Institute for Cancer Research have pinpointed a large number of genes that can prevent a type of genetic rearrangement that may lead to cancer and other diseases.

The presence of these genes and their accompanying pathways, many of which are involved in repairing mistakes in DNA replication, may help explain how the body fends off so many potentially damaging genetic alterations while maintaining its stability.

"We've begun to identify the pathways that are very specific for preventing those types of rearrangements that involve DNA with duplications," said Richard Kolodner, PhD, professor of medicine and cellular and molecular medicine at the UC San Diego School of Medicine and the Moores UCSD Cancer Center, and a member of the San Diego Branch of the Ludwig Institute for Cancer Research (LICR).

Reporting online in advance of publication in the August 20, 2009 issue of the journal *Nature*, Kolodner and his team focused on a particular type of genetic change called a Gross Chromosomal Rearrangement (GCR), a large-scale change in the structures of chromosomes, which house genes. Such changes might entail a sequence of genes being deleted or genetic material exchanging positions on chromosomes. According to Kolodner, while the human genome contains many regions where rearrangements, genetic duplications and other aberrations are more likely to occur - increasing the likelihood for chromosomal mistakes and genetic mutations - the genome is surprisingly stable.

To try to better understand why, the researchers examined GCR formation in chromosome regions in yeast (*Saccharomyces cerevisiae*). Using a modified version of a previously developed test, they compared the rate and features of GCR formation in a chromosome region lacking "at-risk" DNA sequences with that of a region containing DNA duplications, which are more likely to drive rearrangements. These latter regions were much more like human chromosomes.

More importantly, they also looked at the effects of various genes and pathways on the development of GCRs. The research team found that many genes and genetic pathways that failed to block GCR formation in "lower-risk" regions actually played a large role in suppressing GCRs in "at-risk" areas.

"This work points out that there are many different and unexpected pathways that specifically prevent duplication-mediated rearrangements," said Christopher Putnam, PhD, adjunct assistant professor of medicine at the UC San Diego School of Medicine and assistant investigator at the LICR San Diego Branch. "All of these new pathways are important candidates for novel tumor suppressor genes and could be involved in cancer progression. They might also suggest novel therapeutic treatments."

"Because of the wide range of ways for an individual's genome to become unstable and for genetic mutations to occur, it has always been somewhat of a mystery why genetic mutations and genomic instability don't happen

more frequently," Kolodner said. "This is the first time we've identified pathways that can prevent GCRs mediated by at-risk sequences from happening."

Kolodner added that - if it can be shown that these genes are mutated in cancer - it gives reasons to target them, since genetic defects are most often found in repair pathways. "But we need to find out which are the right genes."

The list of genes and pathways is extensive, and will likely be much longer, Kolodner said, predicting that the list in humans will be 500 to 1,000 genes, and in yeast, closer to 500.

The Moores UCSD Cancer Center is one of the nation's 40 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer. For more information, visit http://health.ucsd.edu/cancer

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