

The DNA repair team

Researchers examine body's natural fix-it mechanisms

BY NATALIE OSBORNE

Baker and his team, including graduate students Maureen Mundia, Iulia Cealic, Vatsal Desai and head research assistant Alissa Magwood, have received a major renewal grant from the Canadian Institutes of Health Research for their work on a DNA repair mechanism called homologous recombination.

Baker and his colleagues developed a novel test that can detect homologous recombination's early steps. The assay gives researchers an unprecedented look at the beginning steps of the long and complicated repair mechanism.

"There are so many intermediate steps and products involved in the process, and

Prof. Mark Baker, head research assistant Alissa Magwood and graduate students Maureen Mundia and Sal Desai (from left to right) developed a test that allows them to examine the early steps of homologous recombination, an important mechanism of genetic repair.



DNA holds the life plan for every cell in the human body. And that's why protecting these molecules and the information they contain is vital to all living organisms. What's more, damaged DNA can lead to cell death or life-threatening diseases, such as cancer.

University of Guelph researchers are studying how cells naturally repair and maintain genetic material.

Molecular and cellular biology Prof. Mark

usually all you can see is the end result," says Baker. "But if you have a test that allows you to look right at the beginning of the repair process, then you can have a glimpse at how the proteins involved are working, and also determine how and why things go wrong."

During cell division, nuclear DNA, in the form of chromosomes, is duplicated. Roughly "X" shaped, each chromosome is made up of two chromatids, forming each side of the "X". These two structures, known

as sister chromatids, contain exactly the same genetic information.

When a strand of DNA is broken, the molecule can be degraded around the break site resulting in a loss of genetic information. Homologous recombination uses an undamaged strand, usually found on the sister chromatid, as a "template" or set of instructions, to rebuild the damaged strand. It adds components in the order specified by the template, and "synthesizes" a new DNA segment to match the sister chromatid.

Baker's new test can detect an early intermediate product of the repair mechanism, namely the new DNA synthesis that occurs at the break site. The intermediate's formation requires the participation of many proteins.

Researchers found that when a break occurs in a double-stranded DNA molecule, some of the loose ends are coated with a protein called RAD51. This protein allows the broken end to search out a comparable or "homologous" template that can be used to rebuild the strand.

RAD51 is loaded onto the loose DNA ends by another protein called BRCA2. BRCA2 stands for the breast cancer susceptibility 2 protein. Individuals carrying a mutant allele of BRCA2 (or a related protein called BRCA1), are genetically predisposed to the development of breast, ovarian and other cancers. About 80 per cent of these individuals will develop cancers during their lifetime, and their tumours are characterized by the loss of both normal *BRCA2* (or *BRCA1*) genes. Researchers believe that mutated *BRCA2* genes produce malfunctioning BRCA2 proteins that are unable to perform their loading job. As a result, the cell can't repair damaged DNA, and this may lead to genetic instability that can result in cancer.

However, the *BRCA2* gene can be mutated in hundreds of different ways and doctors don't necessarily know if and how the mutation will affect DNA repair or lead to cancer.

"We're hoping that our test might be used for detecting mutations in breast cancer, because there are over 1,800 catalogued mutations in the *BRCA2* gene, and the vast majority of them are not understood," says Baker. "We need to know exactly what these mutations do in order to provide predictive power for doctors diagnosing cases of breast cancer."

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