MedicalXpress

Breast cancer genome shows evolution, instability of cancer

December 15 2008

A newly published genome sequence of a breast cancer cell line reveals a heavily rearranged genetic blueprint involving breaks and fusions of genes and a broken DNA repair machinery, said researchers at Baylor College of Medicine in a report that appears online in the journal *Genome Research*.

"It's like a computer program that has become buggy and transcends into something dangerous," said Dr. Aleksandar Milosavljevic, associate professor in the BCM Human Genome Sequencing Center. "It makes the cell escape normal controls on cell proliferation. Experimentally, some of the rearrangements in the genome that we found produce fusion genes that confer uncontrolled cell growth and prevent tumor cells from dying, allowing them to grow outside their normal tissue environment. These are all essential attributes of cancer."

"From our standpoint, we are pretty convinced that these genomic translocations may turn out to be prognostic markers and also potential therapeutic targets," said Dr. Adrian Lee, associate professor in the Lester and Sue Smith Breast Center at BCM and a collaborator on the project. Both researchers are investigators in the National Cancer Institute-designated Dan L. Duncan Cancer Center at BCM.

"This is the first study to comprehensively map these genomic translocations to base pair resolution," Lee said. "I think it's pretty clear that the technology Milosavljevic is working with is probably going to change our understanding of breast cancer – particularly the genetics of

breast cancer."

"Using this new technology developed at Baylor College of Medicine it is clear that breast cancers have more damage to their chromosomes than we imagined before. Understanding which genes are malfunctioning to cause the cancer in the first place will tell us how to best treat that cancer," said Dr. C. Kent Osborne, director of the Smith Breast Center and the Duncan Cancer Center.

The researchers sequenced the MCF-7 breast cancer cell line, which is commonly used in studies of the disease. This study of the genome sequence refined the understanding of aberrant genomic rearrangements to the base pair level of resolution, said Milosavljevic.

"It was like working with a microscope and for the first time looking at the ultimate level of resolution. We found a number of genes that were rearranged that were known to be involved in cancer-related phenotypes or properties. We found that genes responsible for DNA repair are broken, explaining why the genome may be unstable," he said.

They identified two types of genomic instability. One type occurs at the point where the cancer becomes invasive, leaving the milk duct system and going into surrounding tissues. The other is associated with repetitive structures called low copy repeats found in the genome itself, a finding not associated with genomic instability before, he said.

The low copy number repeats expose a particular defect in the repair mechanism for double stranded DNA. When that does not work, the genome can break apart and fuse again, this type aberrantly.

Even though the study deals with only one cell line, it has proved valuable, said Lee.

"It has raised some novel ideas about how these rearrangements can affect the DNA repair pathways of the cell. We have a conundrum. You have these breaks in the DNA that affect the DNA repair proteins that are supposed to repair the breaks.

He said plans are already underway to study more cell lines along with individual breast tumors to obtain a more complete picture of the DNA changes that are involved.

Milosavljevic points out that this study is one of several that have appeared this year. For example, the BCM Human Genome Sequencing Center also took part in determining the sequences of glioblastoma (a brain cancer) and lung adenocarcinoma. All occurred under the umbrella of the Cancer Genome Atlas Project funded by the National Institutes of Health. These studies, along with others, prove the value of that more global project, he said.

"Our aim with this work is to establish a bench mark to validate the next generation of sequencing technologies and the whole method that will lead to new biologically significant discoveries," Milosavljevic said.

The full report is available at genome.cshlp.org/content/early … 59.108.full.pdf+html

Source: Baylor College of Medicine