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Same cancer, different time zone

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Just as no two people possess the same genetic makeup, a recent study has shown that no two single tumor cells in breast cancer patients have an identical genome.

In fact, depending on the tumor cell, they grow at dramatically different speeds, according to a study led by Nicholas Navin, Ph.D., assistant professor in the Department of Genetics at The University of Texas M.D. Anderson Cancer Center in Houston. The study findings may have important implications for the diagnosis and treatment of breast cancer. The research may also assist in efforts to combat the development of chemotherapy resistant in breast cancer patients.

Navin's study results appeared in this week's issue of *Nature* and added to the understanding of "genomic diversity" within tumors. Large-group sequencing studies of breast tumors have identified many prevalent mutations, but have provided limited insight to diversity. Navin's team developed a new sequencing approach called Nuc-Seq, revealing that different subtypes of breast cancer displayed varied tumor diversity.

"We found that two distinct 'molecular clocks' were operating at different stages of tumor growth, said Navin. "Tumor cells from triple-negative breast cancer had an increased mutation rate, while tumor cells from estrogen receptor positive (ER+) breast cancer did not."

About 75 percent of breast cancers are ER+ and grow in response to the hormone estrogen. They are often treated with hormone therapy. Triple-negative breast cancers account for 15 to 25 percent of all breast cancers

and generally do not respond well to hormone therapy or standard chemotherapy.

Navin's team developed Nuc-Sec as a single-cell genome sequencing method and applied it to study how cell mutations occur in both types of breast cancer. Combined with single-cell molecule sequencing, they were able to profile thousands of cells.

"A common problem in the field of single cell genomics is the inability to validate mutations that are detected in individual cells," said Yong Wang, Ph.D., a postdoctoral fellow in the Department of Genetics and first author on the study. "To address this problem we combined single-cell sequencing with targeted single-molecule deep sequencing. This approach not only validates mutations, but also measures the precise mutation frequencies of thousands of cells."

An important question in the field of chemotherapy is whether resistance mutations pre-exist in rare cells in the tumor, or if they emerge spontaneously in response to therapy.

"While this question has been studied for decades in bacteria, it remains poorly understood in most human cancers," said Navin. "Our data suggests that a large number of diverse mutations are likely to be pre-existing in the tumor prior to chemotherapy. Therefore, we expect that measuring genomic diversity will have prognostic value in identifying which patient will develop resistance to chemotherapy."

The study also indicated that genomic diversity may also have useful clinical applications for predicting tumor invasion, metastasis and poor survival in patients.

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