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Cultured CTCs reveal genetic profile, potential drug susceptibility of breast cancer cells

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Circulating tumor cells captured with a microchip-based device developed at the Massachusetts General Hospital (MGH) Center for Engineering in Medicine and the MGH Cancer Center can be cultured to establish cell lines for genetic analysis and drug testing. In the July 11 issue of *Science*, an MGH research team reports that the cultured cells accurately reflect a tumor's genetic mutation over time and changing susceptibility to therapeutic drugs.

"We now can culture cells from the blood that represent those present in metastatic deposits, which allows testing for drug susceptibility as the tumor evolves and acquires new mutations," says Shyamala Maheswaran, PhD, of the MGH Cancer Center, co-senior author of the Science paper. "We need to improve culture techniques before this is ready for clinical use, and we are working on doing that right now."

Circulating tumor cells (CTCs) are living solid-tumor cells that break off from either a primary or metastatic tumor and are carried through the bloodstream in extremely small quantities. The current version of the MGH-developed device, called the CTC-iChip, does not rely on prior identification of marker proteins on the surface of tumor cells, a limitation of previous versions of the MGH device and of the only commercially available device for capturing CTCs. Cell-surface proteins can change as tumors mutate during metastasis or in response to treatment, raising the possibility that methods targeting specific proteins

may not reveal the full spectrum of CTCs.

The current study was designed to verify the ability of the CTC-iChip – first described in an April 2013 *Science Translational Medicine* report – to capture viable CTCs in a way that enables the establishment of cell lines that accurately represent the genetic status of all existing tumor sites and can be used for the testing of therapeutic drugs. The researchers first isolated CTCs from the blood of 36 patients with metastatic, estrogen-receptor-positive breast cancer. Long-lived cell lines were successfully established from CTCs of six patients, all of whom previously had received several courses of hormonal and other therapies. Subsequent samples taken from three of those patients were used to establish additional cell lines to track how the tumors changed during subsequent treatment.

While the MGH Cancer Center currently tests biopsy samples of nearly all solid tumors for mutations that may reveal therapeutic targets, the current technology only analyzes a limited number of genes for known mutations. Since CTC-derived cell lines allow a much more comprehensive genetic analysis, the investigators were able to screen for mutations in 1,000 known cancer-associated genes.

In addition to confirming mutations identified in biopsy samples of the patients' primary tumors, genetic analysis of CTC cell lines revealed several additional mutations, some not present in the primary. For example, one cell line showed the development of a new PI3 kinase mutation known to be a therapeutic target. In addition, a usually rare estrogen-receptor mutation, known to develop in patients treated with estrogen-blocking aromatase inhibitors (AIs), was found in CTC cell lines from three patients, all of whom had received extensive AI treatment.

Testing these CTC cell lines for drug sensitivity identified potential

combinations – some involving drugs still at the investigational stage – that inhibited growth in cell lines and in mouse tumors developed from the injection of CTCs from specific patients. Some of these combinations included drugs known to inhibit proteins that were not mutated in the CTC cell lines but may otherwise contribute to tumor growth.

"This approach of culturing circulating cancer cells in the blood, analyzing them for new mutations that have developed during therapy, and testing the utility of drugs targeting those mutations could become the essence of individually adjusted cancer therapy in the future," says Daniel Haber, MD, PhD, director of the MGH Cancer Center, Isselbacher/Schwartz Professor of Oncology at Harvard Medical School (HMS) and co-senior author of the *Science* paper.

Adds Maheswaran, an associate professor of Surgery at HMS, "The ability to culture circulating tumor cells, do a comprehensive genetic analysis for new mutations, determine which ones are targetable and identify the most effective drug combinations could help us develop truly individualized therapeutic strategies. But this is still investigational. We hope that with further refinements it will become clinically available in the future."

In 2011 the MGH entered a collaborative agreement with Johnson & Johnson to establish a center of excellence in CTC research. Additional support for the current study includes a "dream team" grant from Stand Up to Cancer, and grants from the Breast Cancer Research Foundation, the National Institutes of Health, and the Howard Hughes Medical Institute. Patent applications have been filed for the CTC-iChip, which Johnson & Johnson will develop for commercialization.

More information: "Ex vivo culture of circulating breast tumor cells for individualized testing of drug susceptibility," by M. Yu; A. Bardia et

al. www.sciencemag.org/lookup/doi/ … 1126/science.1253533