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Measuring risk of disease recurrence in breast cancer with a DNA methylation liquid biopsy

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A number of clinico-pathological criteria and molecular profiles have been used to stratify patients into high and low risk groups. Currently, there are still no effective methods to determine which patients harbor micrometastatic disease after standard breast cancer therapy and who will eventually develop local or distant recurrence. In the last few years, circulating cell-free (cf) DNA has attracted attention for clinical use in the context of risk prediction, prognostication and prediction of response to chemotherapy in human cancer. Various types of DNA alterations have been reported in cfDNA including, point mutations, microsatellite instabilities, loss of heterozygosity and DNA methylation. Specifically, aberrant DNA methylation is among the earliest and most chemically stable molecular alterations in cancer, making it a potentially useful biomarker for early detection or risk prediction. The purpose of our study was to identify circulating DNA methylation changes that can be used for prediction of metastatic breast cancer (MBC). Plasma cell-free (cf) DNA from 40 MBC patients, 40 disease free survivors (DFS), and 40 healthy individuals (H) was analyzed by whole-genome bisulfite sequencing (WGBS) and differential analysis performed between groups. Targeted bisulfite amplicon sequencing was used as a validation strategy. Differential methylation analysis revealed ~5.0x10^6 differentially methylated CpG loci in MBC compared with H or DFS. In contrast, there was a strong degree of similarity between H and DFS. Overall, MBC demonstrated global hypomethylation and focal CpG island hypermethylation. Data analysis identified 21 novel hotspots, within CpG islands, that differed most dramatically in MBC compared with H or DFS. This first unbiased analysis of cfDNA identified 21 DNA hypermethylation hotspots associated with MBC, and demonstrated the ability to distinguish tumor-specific changes from normal-derived signals at the whole genome level. This signature is a potential blood-based biomarker that could be advantageous at the time of surgery and/or after the completion of chemotherapy to indicate patients with residual micrometastatic disease at high-risk of recurrence, and who could benefit from additional therapy.

Biography

Bodour Salhia received her Honors Bachelor of Science Degree (1998) in Biological Sciences from the University of Toronto. She earned Master of Health Sciences (2001) and a PhD (2006) in Cellular and Molecular Biology from the Arthur and Sonia Labatt Brain Tumor Research Center, Department of Laboratory Medicine and Pathobiology, University of Toronto. She completed a Post-doctoral fellowship from 2006-2011 at the Translational Genomics Research Institute (Phoenix, Arizona) in Cancer Genetics and Epigenetics. Currently she is an Assistant Professor in the Integrated Cancer Genomics Division at the Translational Genomics Research Institute.

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