Network integration of epigenomic data: Leveraging the concept of master regulators in ER negative breast cancer

There has been relatively little advancement in changing the management of women with estrogen receptor (ER) negative breast cancer (BC), mainly due to a dearth of actionable therapeutic targets. The majority of published studies investigating driver genes have focused primarily on genomic mutations which have led to novel study designs (basket trials) where patients with a rare mutation, regardless of tumor histology, are matched to a drug expected to work through the mutated pathway. This study illustrates network integration of epigenomic data to prioritize ER negative specific methylated genes as potential epigenetic drivers of aggressive disease. A master regulator is a gene or drug positioned as the central or master hub that has the ability to command or influence downstream events. Causal network analysis (CNA) was used to find networks with directionality that connect upstream master regulators with a 16 candidate methylation gene signature differentiating ER negative from ER positive BC. CNA software identified four hierarchical networks and their corresponding master regulatory molecules, diethylstilbestrol, transcription regulator SP1, MSH2, and 15-ketoprostaglandin E2. Diethylstilbestrol and SP1 had direct regulatory influence (depth level 1) to the candidate molecules ALPL, CCND1, EGFR, ESR1 and CCND1, CIRBP, EGFR, ESR1, respectively. In this study, direct regulatory influence, noted for 5/16 candidate genes indicates additional rationale for further consideration and validation of ALPL, CCND1, CIRBP, EGFR, ESR1 as potential epigenetic driver targets in ER negative BC. Currently epigenetic therapy exhibits clinical efficacy in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) including those patients not responding to cytotoxic therapy.

Biography

Maria J Worsham completed her PhD in 1993 from Wayne State School of Medicine, Detroit, Michigan, followed by a three year Medical Genetics Fellowship at Henry Ford Health System (HFHS). She is a Fellow of American College of Medical Genetics and Genomics with subspecialties in Clinical Cytogenetics and Clinical Molecular Genetics. As Senior Scientist and Professor of Pathology, she heads the HFHS Cancer Genetic Research Program. The multi-disciplinary program integrates genomics, epigenomics, next generation sequencing and immune checkpoint research strategies for tumor biomarkers of potential clinical benefit in the diagnosis, prognosis and treatment of cancer.

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