

Blood cells of *BRCA1* mutation and epimutation carriers appear to acquire specific epigenetic signatures

Katarzyna Ewa Sokolowska (1), Jacek Antoniewski (1), Marta Sobalska-Kwapis (2), Dominik Strapagiel (2), Jan Lubiński (3), Tomasz Huzarski (3), Tomasz Kazimierz Wojdacz (1)

(1) Independent Clinical Epigenetics Laboratory, Pomeranian Medical University, Unii Lubelskiej 1, 71-252, Szczecin, Poland.

(2) Biobank Laboratory, Department of Oncobiology and Epigenetics, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 139 St., 90-235 Lodz, Poland

(3) Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, ul. Unii Lubelskiej 1, 71-252 Szczecin, Poland.

Introduction: In the population of Polish women, germline mutations in *BRCA1* gene are present in up to 5% of breast cancer cases and the contribution of these mutations to increased breast cancer risk has been extensively studied. Others and us have repeatedly shown, that detectable in blood *BRCA1* promoter methylation (epimutation) is also associated with elevated risk of breast cancer, especially triple-negative breast cancer (TNBC). However, whether these lesion impact genome-wide methylation patterns (methylomes) in the somatic cells of carriers has not been studied so far.

Methods: We compared methylomes (InfiniumMethylationEPIC microarray data) of blood cells from germline mutation and epimutation carriers and blood cells of individuals sampled 4.7 years prior breast cancer diagnosis, who neither carried the mutation nor the epimutation, to the methylomes of controls confirmed to be cancer-free during an over eight-year follow up period and did not carry either the mutation or the epimutation. We then performed Gene Set Enrichment Analysis (GSEA) to analyze physiological context of the identified methylation changes. As well as assessed the enrichment of histones with specific modifications at the genomic regions harboring *BRCA1* epimutation and germline mutations associated methylation changes. Additionally, we evaluated the presence of these methylation changes in methylomes of TNBC cases, both with and without *BRCA1* mutation and epimutation.

Results: Our analyses revealed specific methylation signatures in the blood cells of *BRCA1* mutation and epimutation carriers that were absent in the blood of cancer-free women and in the blood cells of women sampled years before diagnosis. The GSEA linked these identified methylation changes not only to the physiological processes but also to genomic regions that have been previously shown to be involved in breast cancer pathology. Most interestingly, an unsupervised clustering analysis confirmed the presence of these changes in methylomes of TNBC cases with somatic *BRCA1* mutation or epimutation.

Conclusions: Carriers of *BRCA1* mutation and epimutation exhibit distinct genome-wide methylation signatures, that impact specific regions of the genome and biological processes, disruption of which, has previously been shown to contribute to breast cancer pathology. Interestingly, these methylation signatures are absent in the blood cells of breast cancer patients before diagnosis but are detectable in methylomes of TNBC.

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