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Characterization of an epigenetic regulatory network on basal-like breast cancer subtype and its impact on signaling pathways and biological processes

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Objective: The main objective of this study was to identify DNA methylation at the distal cis-regulatory genomic regions associated with the basal-like breast cancer (BLBC) subtype, construct an epigenetic regulatory network, and determine its impact on cancer-associated signaling pathways and biological processes. **Methodology:** BLBC (n=134) and non-tumoral breast (n=84) samples with DNA methylation, mRNA, and miRNA expression data were downloaded from The Cancer Genome Atlas (TCGA) database using a pipeline of computational tools. DNA methylation patterns on cancer-specific enhancers enriched for transcription factor (TF) binding sites and potential master regulators TFs were identified. An epigenetic network among these elements and miRNA expression was constructed and analyzed in relation to the involved signaling pathways, biological processes, and potential interaction with druggable targets. **Results:** The analysis revealed 152 differentially methylated genes (99 hypomethylated and 53 hypermethylated) between BLBC and non-tumoral breast samples, with alterations negatively correlated with gene expression. Additionally, 500 miRNAs (317 upregulated and 183 upregulated) were observed differentially expressed between these groups. The regulatory network constructed from these elements implicated major regulators of cancer-associated signaling pathways, including AR, ErbB, KRAS, mTORC1, NOTCH, PI3K, TGF-β, NF-κB, WNT-β, and P53. Based on the DNA methylation status, the biological processes involved were primarily related to the cell cycle, cell binding activities, and transcription signaling pathways. Finally, drug–target analysis interactions of the regulatory pairs revealed 24 drugs commonly used in cancer treatment, such as 5-fluorouracil, methotrexate, cisplatin, and tamoxifen. **Conclusion:** In summary, this study demonstrated the impact of DNA methylation on distal genomic regions of transcription sites, revealing a complex and intricate epigenetic regulatory network involving genes, miRNAs, and TFs, highlighting the molecular heterogeneity of the BLBC. Additionally, the identification of critical signaling pathways and the potential druggable targets and pharmacological compounds found to interact with this epigenetic network indicate their potential role as therapeutic targets for BLBC.

Keywords: breast cancer; basal-like; epigenetics; DNA methylation; microRNA; transcription factor; regulatory network.