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Reduction of global 5-hydroxymethylcytosine is a poor prognostic factor in breast cancer patients, especially for an ER/PR-negative subtype.

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Abstract

DNA methylation at the 5 position of cytosine (5 mC) is an epigenetic hallmark in **cancer**. The 5 mC can be converted to **5-hydroxymethylcytosine** (5 hmC) through a ten-eleven-translocation (TET). We investigated the impact of 5 mC, 5 hmC, TET1, and TET2 on tumorigenesis and prognosis of **breast cancer**. Immunohistochemistry was used to assess the levels of 5 mC, 5 hmC, TET1, and TET2 in the corresponding tumor adjacent normal (n = 309), ductal carcinoma in situ (DCIS, n = 120), and invasive ductal carcinoma (IDC, n = 309) tissues for 309 **breast** ductal carcinoma **patients**. 5 mC, 5 hmC, TET1-n, and TET2-n were significantly decreased during DCIS and IDC progression. In IDC, the decrease of 5 hmC was correlated with the cytoplasmic mislocalization of TET1 ($p < 0.001$) as well as **poor** disease-specific survival (DSS) (adjusted hazard ratio [AHR] 1.95, $p = 0.003$) and disease-free survival (DFS) (AHR 1.91, $p = 0.006$). The combined decrease of 5 mC and 5 hmC was correlated with worse DSS (AHR 2.19, $p = 0.008$) and DFS (AHR 1.99, $p = 0.036$). Stratification analysis revealed that the low level of 5 mC was associated with **poor** DSS (AHR 1.89, $p = 0.044$) and DFS (AHR 2.02, $p = 0.035$) for the **ER**/PR-positive **subtype**. Conversely, the low level of 5 hmC was associated with worse DSS (AHR 2.77, $p = 0.002$) and DFS (AHR 2.69, $p = 0.006$) for the **ER**/**PR-negative subtype**. The decreases of 5 mC, 5 hmC, TET1-n, and TET2-n were biomarkers of tumor development. The **global reduction** of 5 hmC was a **poor prognostic factor** for IDC, especially for **ER**/**PR-negative subtype**.

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