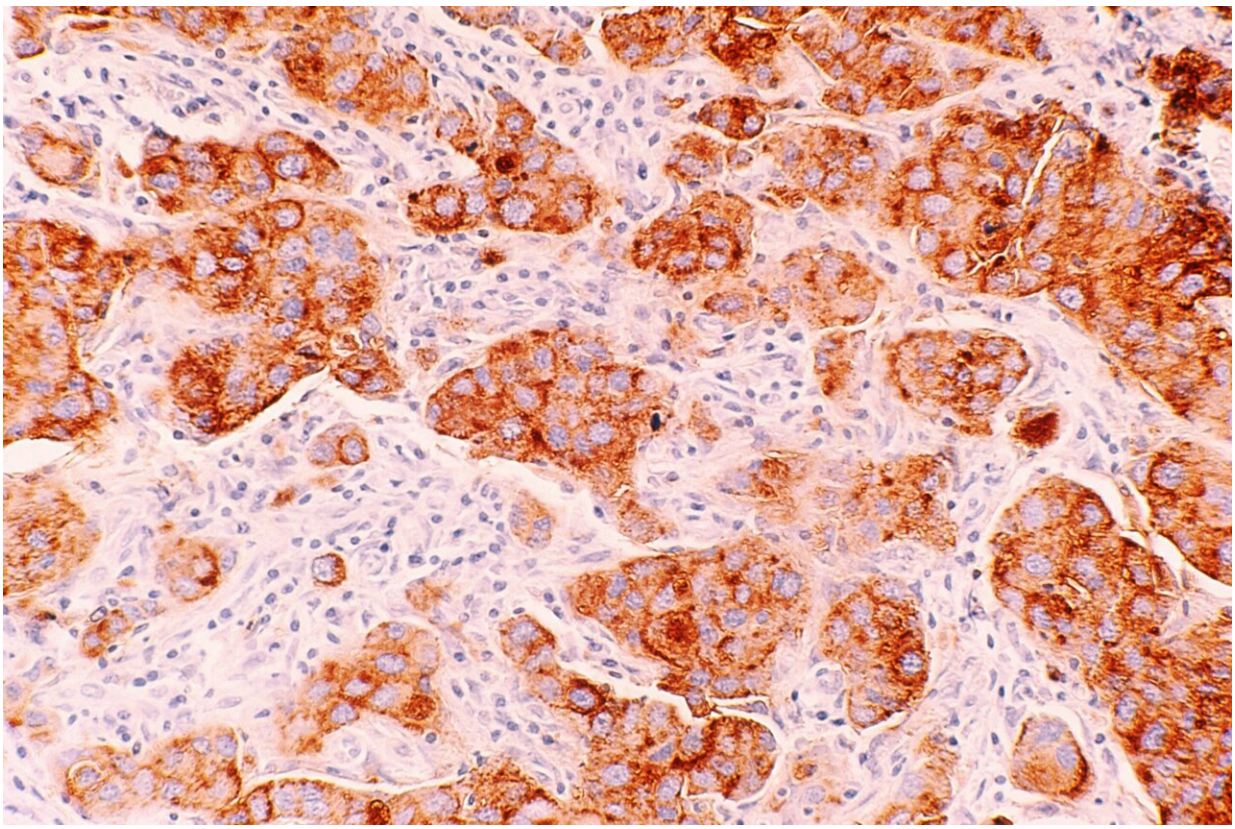
Impaired histone inheritance accelerates breast cancer growth and metastasis, study shows

June 16 2023, by Li Yuan



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Chromatin states and their associated epigenetic information play a crucial role in maintaining the identity of cells as they divide. Histone

post-translational modifications (PTMs) are important determinants of the cellular epigenetic state, carrying epigenetic information and regulating gene transcription.

Epigenetic aberrations are linked to various diseases, including cancer. However, the role of parental histone inheritance in tumorigenesis or tumor evolution has been unclear.

To explore the impact of impaired parental histone inheritance on histone modification profiles in MCM2 mutant cells, a team from the Shenzhen Institute of Advanced Technology (SIAT) of the Chinese Academy of Sciences developed a tumor model that introduces an MCM2-2A mutation, which is defective in parental histone binding, into breast cancer cell lines. The study was published in *Nature Communications* on June 10.

In this model, the researchers observed changes in the distribution of multiple PTMs, including both repressed and active histone marks. Impaired histone inheritance led to significant epigenetic reprogramming, particularly affecting the repressive histone mark H3K27me3.

"The loss of H3K27me3 at the promoters of development-related genes resulted in their activation in cancer cells, thereby promoting tumor growth and metastasis," said Prof. Gan Yunhai, corresponding author of the study.

Furthermore, cancer cells with impaired histone inheritance exhibited accelerated growth and a tendency towards increased aggressiveness after orthotopic transplantation.

Subsequent single-cell RNA sequencing analysis revealed that newly formed subclones in cancer cells with histone inheritance disorders

promoted tumor progression. These subclones acquired advantages in proliferation and fitness, evolving faster when faced with more complex environments.

This study confirms the crucial role of parental histone inheritance carrying H3K27me3 in maintaining specific regions of differentiated cells. Failure to restore H3K27me3 can reactivate mammary gland development processes that are often exploited by breast cancer cells as drivers of tumor progression.

"These findings provide valuable insights into how epigenetic instability contributes to tumor progression, suggesting that targeting abnormal epigenetic inheritance may improve patient outcomes by preserving epigenetic stability," said Prof. Gan.

More information: Congcong Tian et al, Impaired histone inheritance promotes tumor progression, *Nature Communications* (2023). DOI: 10.1038/s41467-023-39185-y

Provided by Chinese Academy of Sciences