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INSTITUT LADY DAVIS DE RECHERCHES MÉDICALES | LADY DAVIS INSTITUTE FOR MEDICAL RESEARCH

PAPER OF THE MONTH • SEPTEMBER 2022

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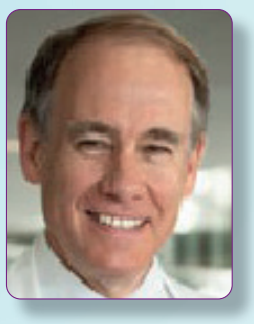

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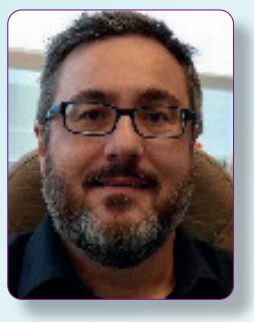

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PNAS

3D chromatin remodeling potentiates transcriptional programs driving cell invasion

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During cancer progression, cells must adapt to facilitate invasion through stroma and subsequent metastatic growth in a distal niche. This adaption necessitates a great deal of plasticity, and there is evidence that epigenetic mechanisms govern these processes. While long-range chromatin interactions are key for proper genome organization and control of transcription, it is unclear whether reprogramming of three-dimensional chromatin architecture is important for mediating tumor progression.

Here, we reveal that a common chromosomal aberration across cancers, CCCTC-binding factor (CTCF) copy number loss, potentiates cell invasion by reorganizing chromatin contacts at the level of sub–topologically associated domain (subTAD) interactions. We observe that subTAD reprogramming drives changes in gene expression that promote specific oncogenic pathways and predicts sensitivity to targeted therapy.

In this study, we further demonstrated that a global loss of insulation of subTAD domains, caused by reduced pools of CTCF, may promote breast cancer progression. This loss of insulation leads to shifts in subTAD boundaries, which are strongly associated with increased deposition of the activating histone marks H3K27ac and H3K4me3 and transcriptional up-regulation of oncogenes of the PI3K pathway and SNAI1. Based on the pathway's deregulated and invasive phenotype, we posit that CTCF CNL plays a more important role in tumor progression within breast tissue than tumor initiation.

Overall, our study highlights the interplay between long-range chromatin contacts and epigenetic remodeling and underscores the importance of defining epigenetic reprogramming in cancer as a means to uncover new therapeutic avenues.

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