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Chromatin Looping Shapes KLF5-Dependent Transcriptional Programs in Human Epithelial Cancers

Yanli Liu, Bingqian Guo, Estrella Aguilera-Jimenez, Vivian S Chu, Jin Zhou, Zhong Wu, Joshua M Francis, Xiaojun Yang, Peter S Choi, Swneke D Bailey, Xiaoyang Zhang

Abstract

Activation of transcription factors is a key driver event in cancer. We and others have recently reported that the Krüppel-like transcription factor KLF5 is activated in multiple epithelial cancer types including squamous cancer and gastrointestinal adenocarcinoma, yet the functional consequences and the underlying mechanisms of this activation remain largely unknown. Here we demonstrate that activation of KLF5 results in strongly selective KLF5 dependency for these cancer types. KLF5 bound lineage-specific regulatory elements and activated gene expression programs essential to cancer cells. HiChIP analysis revealed that multiple distal KLF5 binding events cluster and synergize to activate individual target genes. Immunoprecipitation-mass spectrometry assays showed that KLF5 interacts with other transcription factors such as TP63 and YAP1, as well as the CBP/EP300 acetyltransferase complex. Furthermore, KLF5 guided the CBP/EP300 complex to increase acetylation of H3K27, which in turn enhanced recruitment of the bromodomain protein BRD4 to chromatin. The 3D chromatin architecture aggregated KLF5-dependent BRD4 binding to activate polymerase II elongation at KLF5 target genes, which conferred a transcriptional vulnerability to proteolysis-targeting chimera-induced degradation of BRD4. Our study demonstrates that KLF5 plays an essential role in multiple epithelial cancers by activating cancer-related genes through 3D chromatin loops, providing an evidence-based rationale for targeting the KLF5 pathway. SIGNIFICANCE: An integrative 3D genomics methodology delineates mechanisms underlying the function of KLF5 in multiple epithelial cancers and suggests potential strategies to target cancers with aberrantly activated KLF5.