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The effect of chromatin states on cancer: big data lead the way

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Graphical Abstract

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A central question in the field of human cancer research, including that of blood malignancies, is how the chromatin state regulates the initiation and progression of disease.^{1–3} Chromatin state is controlled by a multilevel, genetic and epigenetic, regulatory hierarchy that includes DNA and histone modifications, as well as three-dimensional

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enhancer–promoter interactions. Accordingly, various mutations that perturb the functions of key epigenetic factors that determine chromatin states are oncogenic.^{2–4} Therefore, it is crucial to understand the mechanisms by which recurrent mutations in epigenetic regulators affect chromatin states (and enhancer activities) to facilitate cellular transformation. Fuelled by unprecedented progress in next-generation sequencing, studies^{5,6} from the past decade have improved our understanding of the epigenome, providing analyses of DNA and histone modifications, non-coding genomes, and three-dimensional chromosomal interactions. However, the technical and computational difficulties of applying such high-throughput techniques in large patient cohorts have hindered studies that can provide extensive maps of malignant transformation.

Several cancer resource articles published this year comprehensively characterised human cancers using different approaches—efforts that have provided an exciting new perspective on the mechanisms that might trigger malignant transformation and tumour maintenance. In one of these studies, Chen and colleagues⁷ identified 15 808 detectable enhancers (of about 65 000 enhancers annotated by the Functional Annotation of the Mammalian Genome project) using histone mark distribution and RNA-sequencing data from The Cancer Genome Atlas database, hypothesising that the expression of enhancer RNA represents activation of the enhancer itself. The authors successfully identified multiple interactions between enhancers and cancer-related genes, and correlated global enhancer activities with somatic copy-number alteration values, on the premise that chromatin state is a key contributor to genomic patterns.⁷ This study was the first to systematically analyse a large number of active enhancers across different cancer types and with large patient cohorts, and has created an invaluable dataset for further investigations into the mechanisms by which changes in chromatin state can drive cancer development. Furthermore, this study underscored the clinical relevance of two enhancer–gene interactions (enhancer 22 [chr22:50980817–50981280] with the spleen tyrosine kinase [*SYK*] gene, and enhancer 9 [chr9:5580709–5581016] with the programmed cell death 1 ligand 1 [*CD274*] gene) by confirming strong correlations among enhancer activities, oncogene expression, and clinical outcomes. These findings highlight the possibility that enhancer activities can serve as predictive markers for prognosis and therapeutic response.

This research has provided a global view of enhancer activity on a pan-cancer scale, and identified several novel interactions between enhancers and key oncogenes (including leukaemogenic genes, such as *NOTCH1*, *MYC*, *RARA*, *RUNX1*, and *CXCR4*), although these interactions were not experimentally validated in the study.⁷ Subsequent investigations aiming to characterise these interactions in the context of normal tissues and specific cancers will be important to reveal how key oncogenes are precisely controlled across normal cellular hierarchies and epigenetically hijacked in malignancies. Of relevance for haematologists, the authors identified more than 8000 active enhancers in samples from patients with acute myeloid leukaemia. However, because of the insufficient sample size and follow-up time, the study did not investigate the correlation between enhancer expression in acute myeloid leukaemia and patient response to treatment and overall survival, leaving open the question of which enhancers might be crucial for oncogenesis or prognosis in such patients. This question could be addressed by the use of CRISPR activation or interference

screening⁸ to systematically characterise putative enhancers in multiple models of acute myeloid leukaemia, followed by validation in patient-derived xenografts.

Although genomic instability is a hallmark of cancer,⁹ the correlations between key transforming events (eg, aneuploidy and point mutations) and global enhancer activities remain controversial. By integrating cancer mutational information (somatic copy-number alteration and mutational burden) with chromatin state parameters (DNA accessibility, three-dimensional chromatin architecture, and histone marks), the study by Chen and colleagues depicts a chromatin state-centred model, in which open chromatin facilitates long-range DNA interactions to increase DNA rearrangements (eg, somatic copy-number alterations), whereas closed chromatin blocks the entry of DNA repair machineries and leads to increased point mutations.⁷ This model is reasonable and simple, but preliminary because of several technical limitations, including the relatively low depth and poly(A) selection of The Cancer Genome Atlas RNA-sequencing data, as well as the low resolution of currently available high-chromosome conformation capture results.⁷ Further validation of this model in specific cancer types with available high-quality sequencing data could be promising.

An accompanying study¹⁰ attempted to systematically identify cancer driver genes in acute myeloid leukaemia samples, revealing a large number of recurrent genetic lesions (ie, mutations) in several epigenetic regulators (eg, *EZH2*, *KMT2D*, *DNMT3A*, *TET2*, *CTCF*, and *EP300*). On the basis of such studies, we can now use the knowledge of the ability of epigenetic regulators to alter chromatin states and enhancer activity to test whether somatically acquired mutations in these regulators are selected during tumour evolution. This information could explain why epigenetic and transcriptional regulators comprise a category of genes among the most frequently mutated in cancers.

Research efforts involving meta-analyses of large cohorts of patients and many different tumour types can transform the way we understand cancer. A key question is how researchers and oncologists will take advantage of such studies to identify the selective vulnerabilities of different cancer types.

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