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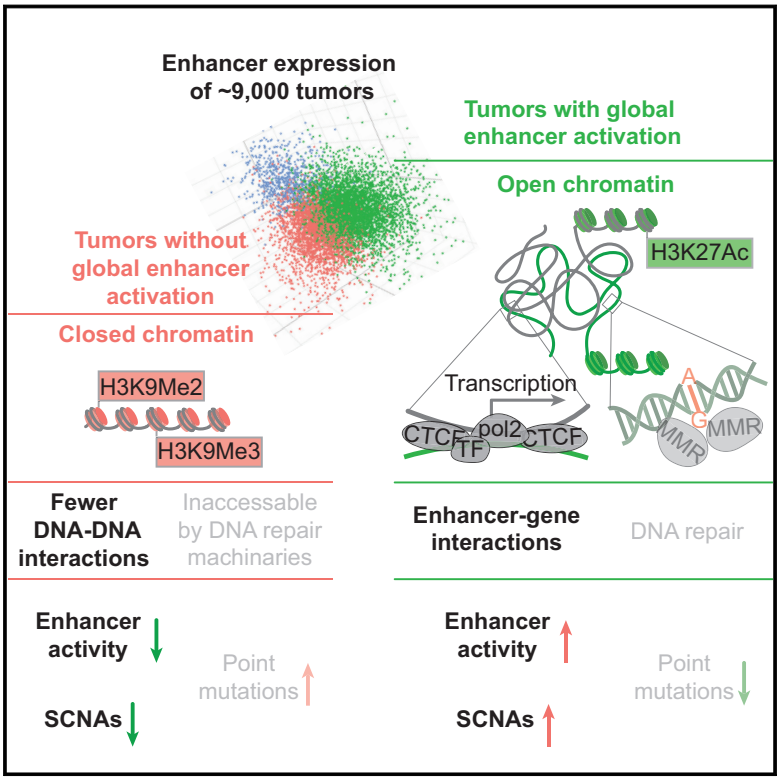
A Pan-Cancer Analysis of Enhancer Expression in Nearly 9000 Patient Samples

Graphical Abstract



Highlights

- Systematic analysis of enhancer expression across ~9,000 samples of 33 cancer types
- Global enhancer activation positively correlates with aneuploidy but not mutations
- A computational method that infers causal enhancer-target-gene relationships
- Enhancers as key regulators of therapeutic targets, including PD-L1

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In Brief

Causal enhancer-target-gene relationships are inferred from a systematic analysis of 33 cancer types.

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A Pan-Cancer Analysis of Enhancer Expression in Nearly 9000 Patient Samples

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SUMMARY

The role of enhancers, a key class of non-coding regulatory DNA elements, in cancer development has increasingly been appreciated. Here, we present the detection and characterization of a large number of expressed enhancers in a genome-wide analysis of 8928 tumor samples across 33 cancer types using TCGA RNA-seq data. Compared with matched normal tissues, global enhancer activation was observed in most cancers. Across cancer types, global enhancer activity was positively associated with aneuploidy, but not mutation load, suggesting a hypothesis centered on "chromatin-state" to explain their interplay. Integrating eQTL, mRNA co-expression, and Hi-C data analysis, we developed a computational method to infer causal enhancer-gene interactions, revealing enhancers of clinically actionable genes. Having identified an enhancer ~140 kb downstream of PD-L1, a major immunotherapy target, we validated it experimentally. This study provides a systematic view of enhancer activity in diverse tumor contexts and suggests the clinical implications of enhancers.

INTRODUCTION

The biological functions of each cell component are controlled by a Russian-nesting-doll-like multi-level gene-regulatory hierarchy that includes transcription-factor-promoter interaction, enhancer activation, DNA methylation, microRNA-mediated regulation, translation, and post-translational modification (He and Hannon, 2004; Jaenisch and Bird, 2003; Murakawa et al., 2016). In cancer cells, such regulatory networks are often rewired by molecular aberrations that collectively lead to the cancer phenotype (Chen et al., 2015; Kolch et al., 2015). For example, somatic mutations can modify the functions of both *trans* and *cis* elements in a regulatory network, thereby conferring cell behaviors related to tumorigenesis (Garraway and Lander, 2013; Hanahan and Weinberg, 2011). Using high-throughput molecular profiling techniques over large patient cohorts, The Cancer Genome Atlas (TCGA) (Cancer Genome Atlas Research Network et al., 2013) has systematically characterized key molecular alterations at different levels in a broad range of cancer types, providing unprecedented insight into oncogenic mechanisms and potential therapeutic approaches.

However, our information on the rewiring of gene regulatory networks in cancer is far from complete, and enhancers represent a missing piece of the jigsaw puzzle (Aran and Hellman, 2013). Enhancers are important non-coding DNA elements that interact spatially with their target promoters to regulate downstream genes (Schmitt et al., 2016). As a major category of regulatory elements in cell development, enhancers also play critical roles in the oncogenic process (Murakawa et al., 2016). Despite recent systematic efforts, including genome-wide profiling of tissue and cell line collections (ENCODE Project Consortium, 2012; Hnisz et al., 2013; Roadmap Epigenomics Consortium et al., 2015) and a pan-cancer analysis of some super-enhancers (Zhang et al., 2016), a global view of enhancer activity in cancer is still lacking. That hole in our understanding is due in part to the technical difficulty of applying high-throughput techniques (e.g., ChIP-seq) to investigate enhancer activity using large patient sample cohorts.

The Functional Annotation of the Mammalian Genome (FANTOM) Project has generated large-scale, high-quality annotation of ~65,000 enhancers expressed in the human genome across multiple tissues (Andersson et al., 2014). FANTOM thus provides an alternative solution for studying enhancer activities in cancer. An inactive enhancer is usually well organized by unmodified nucleosomes, so it cannot be accessed by either transcription factors or polymerase. When an enhancer is primed for activation in response to signaling, its local chromatin is first modified (often by H3K4Me1) and becomes loose, rendering the motifs on the enhancer available to transcription factors and RNA polymerase. When the bound transcription factors fully activate the enhancer, usually with re-marked by H3K27Ac, the local chromatin is completely open, recruiting RNA polymerase to initiate transcription in both directions (Figure 1A) (Heinz et al., 2015; Li et al., 2016; Murakawa et al., 2016). Thus, the expression level of enhancer RNA molecules represents an

