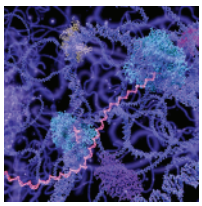
Transcription

Major finding: Intrinsically disordered regions of MED1 and BRD4 promote formation of phase-separated condensates.

Concept: Liquid-like condensates concentrate components of the transcriptional machinery at superenhancers.

Impact: Phase transitions mediated by intrinsically disordered regions may facilitate superenhancer activation.

PHASE SEPARATION CONCENTRATES TRANSCRIPTION PROTEINS AT SUPERENHANCERS



Superenhancers are characterized by dense assembly of transcriptional machinery, leading to the hypothesis that phase separation may allow for the required high-density assembly. In this process, molecules in fluids separate into a dense phase and a dilute phase, allowing for phase-separated biomolecular condensates that compartmentalize and concentrate biochemical reactions within cells. Sabari, Dall'Agnese, and colleagues demonstrated that the transcriptional coactivators BRD4 and MED1, which are enriched at superenhancers, undergo phase separation to form condensates at superenhancers. Immunofluorescence imaging showed that BRD4 and MED1 formed nuclear puncta at superenhancers, and, after photobleaching, the rate of fluorescence recovery suggested a liquid-like state, consistent with a phase-separated condensate. These coactivator puncta were sensitive to 1,6-hexanediol, a compound known to disrupt liquid-like condensates, resulting in a reduction in the number of BRD4 and MED1 puncta, and loss of RNA polymerase II occupancy at superenhancers, suggesting a reduction in transcriptional activity. Both BRD4 and MED1 contain large intrinsically disordered regions (IDR), and these IDRs formed reversible phase-separated condensates (in contrast to irreversible aggregates) *in vitro* and in cells. MED1 contains an enrichment of serine residues that were required for phase separation, and MED1-mediated phase separation was abrogated when the serines were mutated to alanines. *In vitro*, the MED1–IDR condensate droplets compartmentalized MED1 and other proteins required for transcription into concentrated droplets. Taken together, these findings provide a mechanism by which transcriptional machinery can be compartmentalized at superenhancers to promote gene transcription via phase separation induced by the IDRs of coactivator proteins. These findings may have implications for the expression of superenhancer-driven oncogenes in cancer. ■

Sabari BR, Dall'Agnese A, Boija A, Klein IA, Coffey EL, Shrinivas K, et al. Coactivator condensation at super-enhancers links phase separation and gene control. Science 2018 Jun 21 [Epub ahead of print].

Immunology

Major finding: Loss of LSD1 enhances tumor immunogenicity and sensitizes refractory mouse melanoma to anti–PD-1 therapy.

Mechanism: LSD1 blocks repetitive element expression and drives AGO2 stabilization to decrease dsRNA and TIL levels.

Impact: Therapeutic targeting of LSD1 may enhance the antitumor efficacy of immune checkpoint blockade.

THE HISTONE DEMETHYLASE LSD1 INHIBITS TUMOR CELL IMMUNOGENICITY

DNA methyltransferase inhibitors have been shown to activate the cytosolic antiviral double-stranded RNA (dsRNA) sensing pathway to promote type I IFN activation, associated with increased tumor response to anti-CTLA4 therapy, but how chromatin regulators modulate tumor immunity and immunotherapy has not been fully ascertained. Sheng, LaFleur, and colleagues screened compounds to identify chromatin regulators that promote the upregulation of endogenous retroviral elements (ERV) and activate type I IFNs and identified the histone demethylase LSD1, which was found to be often overexpressed in patient tumors. LSD1 repressed the expression of ERVs, and LSD1 ablation promoted intracellular dsRNA accumulation and the upregulation of type I IFN–related genes. Knockdown of individual dsRNA sensors in LSD1-ablated cells identified TLR3 and MDA5 as critical for LSD1 loss–mediated IFN signaling. Further, LSD1 knockdown resulted in the decreased expression of DICER, AGO2, and TRBP2, all of which are components of the RNA-induced silencing complex, which mediates gene silencing by processing dsRNA. AGO2 knockdown resulted in dsRNA accumulation, and knockdown of AGO2, DICER, or TRBP2 resulted in activated IFN signalling; additionally, LSD1-mediated demethylation of AGO2 promoted AGO2 stabilization. LSD1 ablation resulted in decreased proliferation *in vitro*, which was partially rescued by inhibition of IFN pathway genes. LSD1 ablation in mouse melanoma cells resulted in decreased tumor growth and dsRNA stress–dependent antitumor T-cell immunity only in immunocompetent, but not immunodeficient, mice. LSD1-depleted tumors exhibited increased numbers of $CD8^+$ tumor-infiltrating lymphocytes, elevated expression of MHC class I antigens, and the immune checkpoint PD-L1; similarly, LSD1 expression levels were inversely correlated with T-cell infiltration in patient tumors. Treatment with anti–PD-1 antibody resulted in greater tumor suppression and increased survival in mice with LSD1-depleted tumors compared to mice with LSD1-replete tumors. Thus, LSD1 is a negative regulator of antitumor immunity and responsiveness to immunotherapy, and inhibition of LSD1 potentially turns "cold" tumors "hot." ■

Sheng W, LaFleur MW, Nguyen TH, Chen S, Chakravarthy A, Conway JR, et al. LSD1 ablation stimulates anti-tumor immunity and enables checkpoint blockade. Cell 2018 Jun 21 [Epub ahead of print].