## Inflammation-sensitive super enhancers form domains of coordinately regulated enhancer RNAs.

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**Public Summary:**
Enhancers are critical genomic elements that define cellular and functional identity through the spatial and temporal regulation of gene expression. Recent studies suggest that key genes regulating cell type-specific functions reside in enhancer-dense genomic regions (i.e., super enhancers, stretch enhancers). Here we report that enhancer RNAs (eRNAs) identified by global nuclear run-on sequencing are extensively transcribed within super enhancers and are dynamically regulated in response to cellular signaling. Using Toll-like receptor 4 (TLR4) signaling in macrophages as a model system, we find that transcription of super enhancer-associated eRNAs is dynamically induced at most of the key genes driving innate immunity and inflammation. Unexpectedly, genes repressed by TLR4 signaling are also associated with super enhancer domains and accompanied by massive repression of eRNA transcription. Furthermore, we find each super enhancer acts as a single regulatory unit within which eRNA and genic transcripts are coordinately regulated. The key regulatory activity of these domains is further supported by the finding that super enhancer-associated transcription factor binding is twice as likely to be conserved between human and mouse than typical enhancer sites. Our study suggests that transcriptional activities at super enhancers are critical components to understand the dynamic gene regulatory network.

**Scientific Abstract:**
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