Role of transcriptional enhancers in gene regulation

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Genes are regulated by distal regulatory elements known as enhancers that exert their function on target genes by establishing looping with the promoter. ENCODE (ENCyclopedia of DNA Elements) has revealed thousands of enhancers populate mammalian genomes where they act in cell-type specific manner. Although discovered over thirty-five years ago, the molecular mechanisms underlying enhancer functions still remain poorly understood. Recently, another layer of complexity has been uncovered by the discovery that in addition to widespread transcription of long non-coding RNAs (lncRNAs) in mammalian cells, bidirectional ncRNAs are transcribed on enhancers, and are thus referred to as enhancer RNAs (eRNAs). However, it has remained unclear whether these eRNAs are functional or merely a reflection of enhancer activation. Different roles of eRNAs in gene regulation are just emerging.

Using genomic techniques that quantify the alterations in nascent transcription and three-dimensional architecture we have shown that these eRNAs are required for gene activation and establishing looping with the promoter. Further, they mostly are involved in cis-gene regulation and act in a sequence specific manner. Interestingly, high resolution chromatin structures reveal a complex pre-existing network of multiple enhancers, which mediate their effects on target genes in a hierarchical manner. This phenomenon warrants a new model of enhancer function that depends on the strength of other enhancers.