Long noncoding RNA as modular scaffold of histone modification complexes.

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Public Summary:
All the cells in the human body carry the same genetic information in the form of DNA. The process of choosing which genes are stably switched ON or OFF, termed epigenetics, determines whether a cell will become a brain cell, heart cell, or skin cells. This work seeks to understand the epigenetic control when stem cells become differentiated cells. We discovered that a new type of genes, termed long noncoding RNAs, are the key guiding mechanisms for controlling the ON and OFF state of genes. The long RNA acts like a train--organizing and carrying specific cargoes of enzymes--and deliver the entire package to specific locations on DNA. The cargo of enzymes can then carry out a series of reactions to turn previous active genes off in a permanent manner. These results explain how cell fates can become restricted as stem cells differentiate, as well as suggest mechanisms to control cell fate choices and reprogramming.

Scientific Abstract:
Long intergenic noncoding RNAs (lincRNAs) regulate chromatin states and epigenetic inheritance. Here, we show that the lincRNA HOTAIR serves as a scaffold for at least two distinct histone modification complexes. A 5' domain of HOTAIR binds polycomb repressive complex 2 (PRC2), whereas a 3' domain of HOTAIR binds the LSD1/CoREST/REST complex. The ability to tether two distinct complexes enables RNA-mediated assembly of PRC2 and LSD1 and coordinates targeting of PRC2 and LSD1 to chromatin for coupled histone H3 lysine 27 methylation and lysine 4 demethylation. Our results suggest that lincRNAs may serve as scaffolds by providing binding surfaces to assemble select histone modification enzymes, thereby specifying the pattern of histone modifications on target genes.