

EPIGENETICS OF lncRNAs: HOTAIR AND ITS RELATIONSHIP WITH CANCER

Introduction

Epigenetics is the study of alterations in gene expression that are not caused by changes in the DNA sequence. The epigenetic that establish different patterns of gene expression includes: methylation of cytosine, posttranslational modification of histone proteins and chromatin remodeling proteins and RNA-based mechanisms. These processes that regulate gene expression patterns, are run by the non-coding material of the genome. Without being translated into protein can function as RNA. They are referred to, as non-coding RNAs (ncRNA) and are divided into several large groups. This work will focus on lncRNA. lncRNAs are transcripts produced by RNA polymerase II longer than 200 nucleotides. They are processed by splicing and may or may not be polyadenylated [1] [2].

Structure and function

lncRNAs are typically formed by random RNA sequences. They have structural motifs in triplet over the gene body critical for their función, evolutionarily conserved. However, the 5' and 3' are fully destructured.

Biological functions:

-Regulation of gene expression. lncRNA remodel chromatin to make genes more or less accessible. It aims to increase or decrease the expression of theme.

-Maintenance of pluripotency. lncRNA maintain the pluripotency of stem cells. They Suppress or activate cell differentiation related genes.

-Nuclear-organization. lncRNA organize the nucleus with the formation of paraspeckles. lncRNA retain the mature mRNA in paraspeckles and prevent translation.

-Alternative splicing. lncRNAs play a critical role in the alternative splicing of the mRNA maturation. [2]

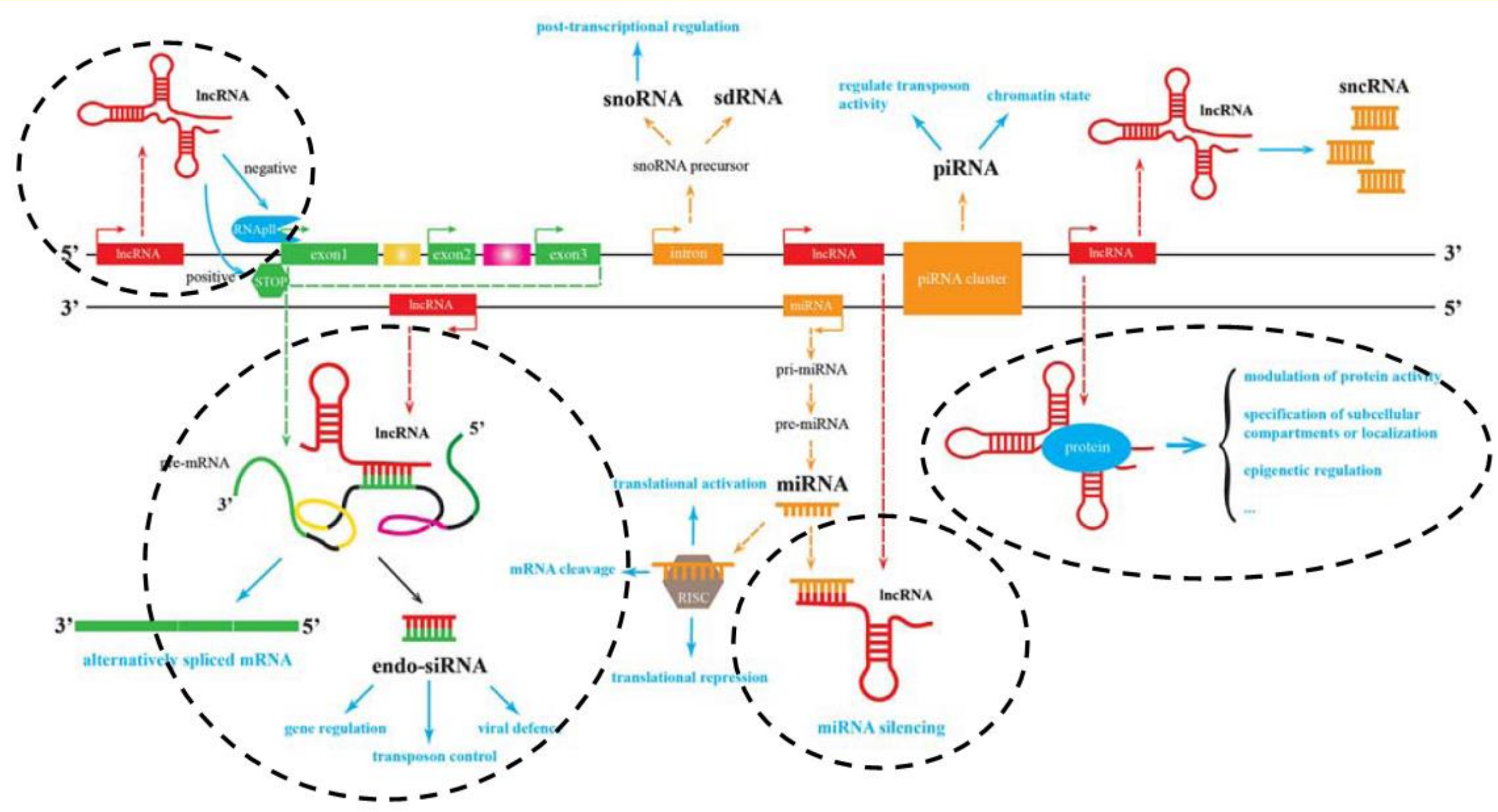


Figure 1: major ncRNA. Highlights lncRNAs where appears their structure and their most important functions. Figure comes from [3]

Classification of lncRNA15

Class

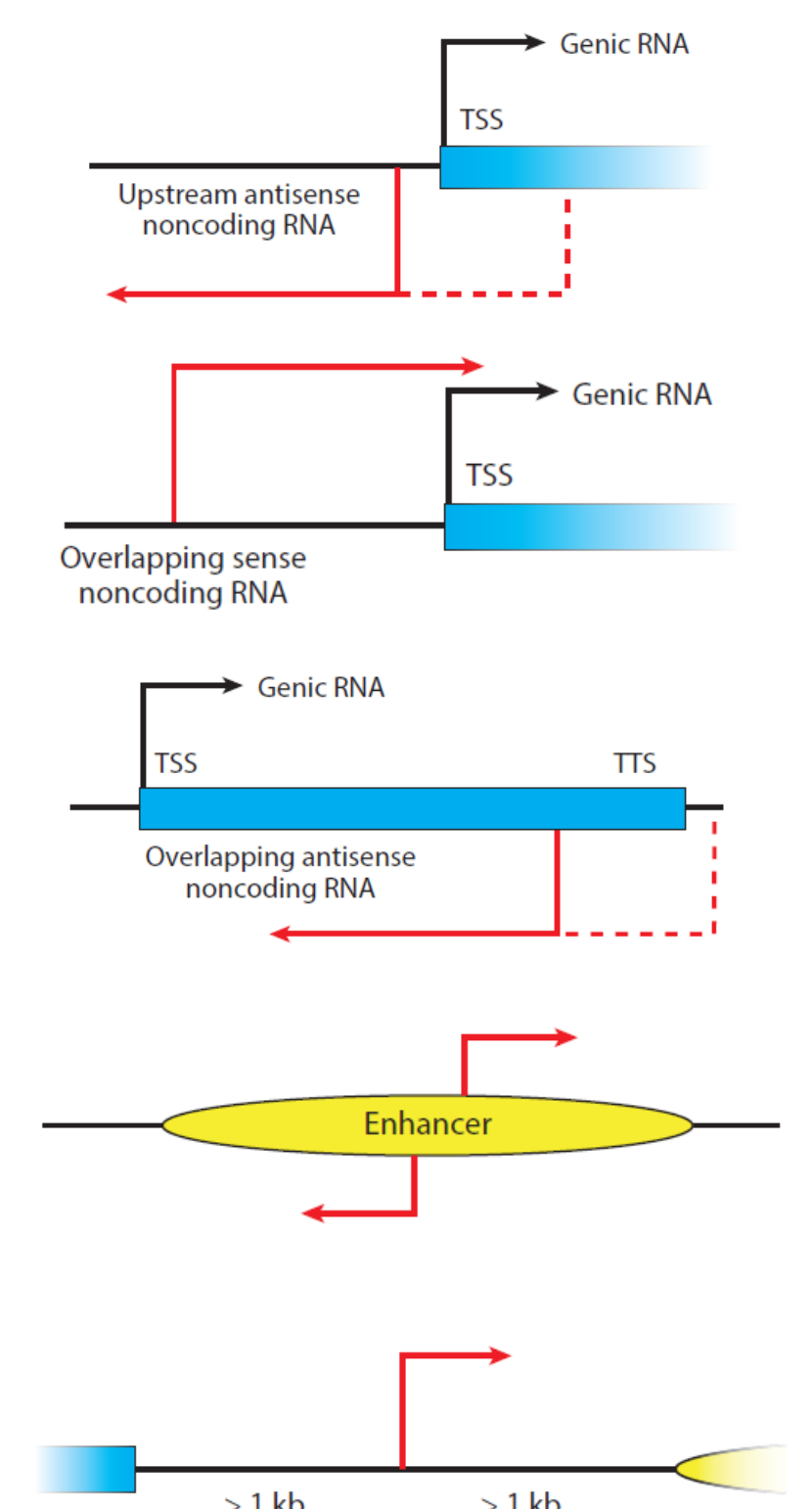
Promoter-associated (pRNA)

Gen body-associated (sense) (gsRNA)

Gen body-associated (antisense) (gaRNA)

Enhancer-associated (eRNA)

Intergenic (lincRNA)



[4]

Mechanisms of action

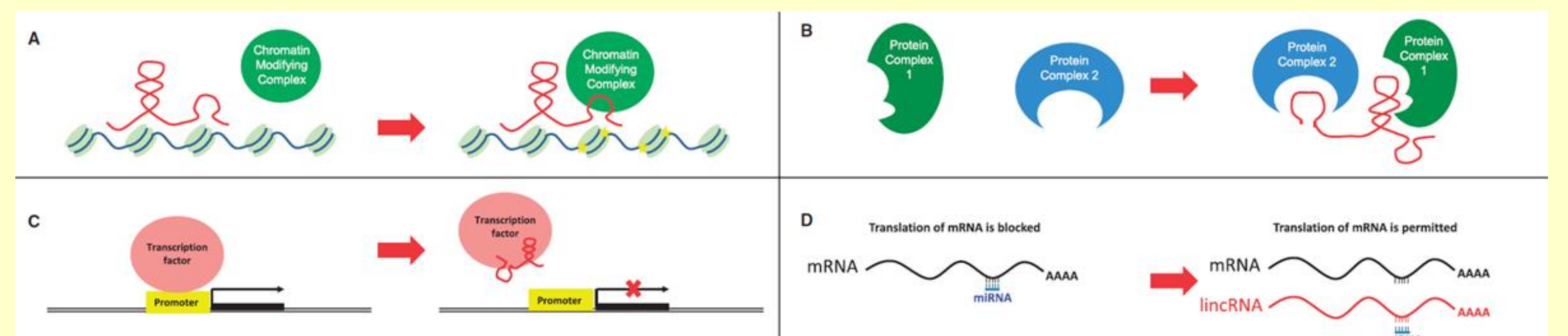


Figure 3: Mechanisms of action by which lncRNA can exert their function. A) lncRNAs can act as guides of chromatin-modifying complexes to regulate gene expression. B) lncRNAs can be scaffolds and bring two proteins in space to perform their role. C) lncRNAs can bind to transcription factors and prevent them of binding to their target genes. D) lncRNAs can inhibit the action of a miRNA joining them by homology. Figure comes from [2]

lncRNA in cancer: HOTAIR

lncRNAs are closely related to cancer. They regulate the expression of genes involved in cellular proliferation. When they are deregulated, the cell cycle is disturbed.

HOTAIR (HOXC Antisense Intergenic RNA) is a lncRNA found in the cluster HOXC, in the chromosome 12q13.13, it is transcribed in antisense and represses in trans the HOXC cluster of chromosome 2 along 40kb. HOTAIR recruits the protein complexes PRC2 and LSD1 so as to modify the chromatin and suppress the expression of their target genes. In cancer, HOTAIR is overexpressed and alters the expression pattern of genes involved in epithelial mesenchymal transition, which dedifferentiate the cell and promote cell proliferation, invasiveness and ability to metastasize [2].

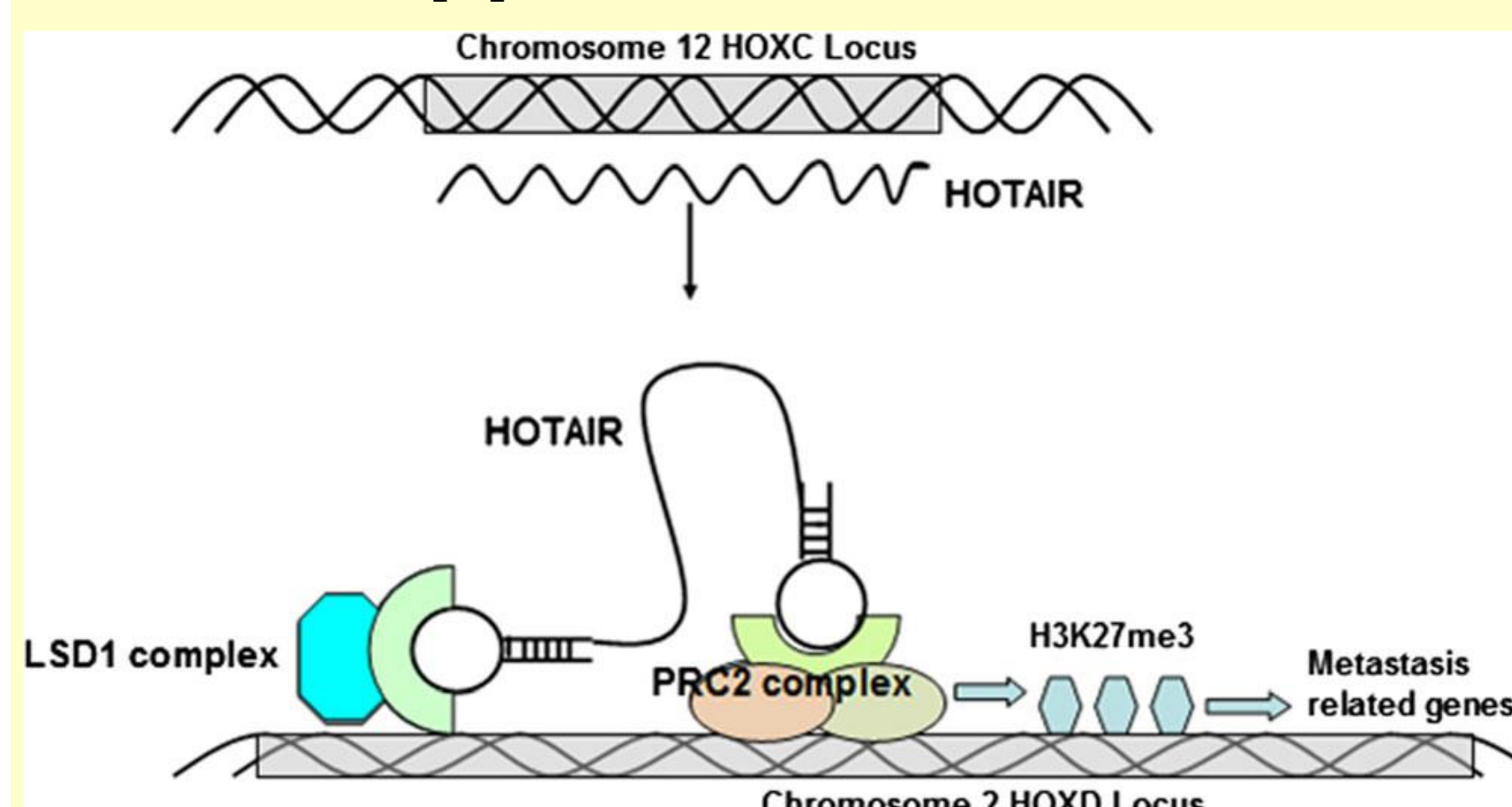


Figure 4. Figure comes from [5]

Regulation

- HOTAIR is induced by estradiol (E2) in a dose dependant manner, because of its estrogen response elements (EREs) [5].

Mechanisms of action

- HOTAIR recruits de chromatin modifying complexes PRC2 and LSD1. It brings them to the promoter of their target genes.
 - **PRC2** \Rightarrow H3K27me3 \Rightarrow gain of a repressive mark
 - **LSD1** \Rightarrow demethylation H3K4 \Rightarrow loss of an activating mark

Breast cancer

- HOTAIR increases its expression in primary breast cancer tissue 2000 folds, and metastasizes to the lung. The retargeting of PRC2 alters the expression of 854 genes, although, is not clearly if HOTAIR levels can serve as diagnostic or prognosis.

Biomarker and therapy

- HOTAIR can be a good biomarker because:
 - It has tissue specific expression
 - It's the effector molecule
 - Can be easily accessible (body fluids)
 - It is easily quantifiable [2]
- Possible therapy
 - Interference RNA
 - Inhibitors of lncRNA target proteins

Conclusions

- ✓ lncRNAs are very important in cell function, because of their role regulating gene expression.
- ✓ lncRNAs aberrant functions can cause diseases like cancer.
- ✓ In a high percentage of breast cancers, HOTAIR is overexpressed. Although its correlation with the severity and prognosis of the disease is unclear.
- ✓ Further studies are needed to better understand of the mechanism of action of lncRNA and to use them as therapy.