Long Noncoding RNAs: Chromatin modification in Cancer

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Introduction

Genome research has been mainly focused on **protein coding genes** (**PCGs**).

- Advances in DNA sequencing and microarrays revealed a much more complex transcriptional landscape raising dramatically the interest in **noncoding RNAs.**
- **MicroRNAs** became the aim of exhaustive studies.

- Attention is now shifting towards **long noncoding RNAs** (**lncRNAs**).
- Central regulators of gene expression involved in several diseases, including **cancer.**

Aims

❖Review the main characteristics of lncRNAs as gene regulators.
❖Describe the mechanism underlying chromatin modification by four different lncRNAs.
❖Highlight the links between lncRNAs deregulation and cancer.

Materials and Methods

Initial search in PubMed (NCBI) for scientific reviews publicated within the last 5 years containing the keywords "long non-conding RNAs" OR "long noncoding RNAs" OR "lncRNAs" AND cancer. Knowledge acquired upon reading these reviews allowed further searches in PubMed and Web of Knowledge for original articles.

LncRNAs

Definition. LncRNAs are endogenous cellular RNAs of more than 200 nucleotides that lack an open reading frame of significant length (≥100 amino acids).

Classification. Generally according to their location with respect to PCGs:

❖Intergenic (**lincRNAs**) (Fig.1A), which do not intersect PCGs.

❖Genic, which are subclassified into:

- **Exonic** transcripts (Fig.1B)-intersect an exon of a PCG on the opposite strand.
- **Intronic** transcripts (Fig. 1C)-lie within introns of PCGs.
- **Overlapping** transcripts (Fig.1D)-contain a complete PCG within an intron on the same strand.

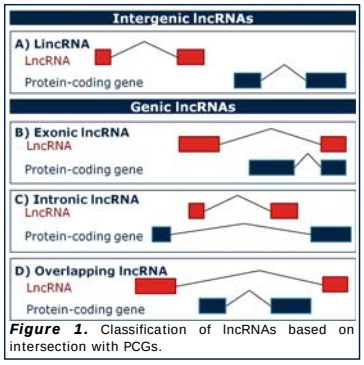

Figure 1. Classification of lncRNAs based on intersection with PCGs.

Characteristic features:

- Transcribed by RNA polymerase II
- Polyadenylated
- Spliced: 2.9 exons on average
- Lower expression than PCGs
- **High tissue-specificity**
- Enriched in the chromatin

Functions. LncRNAs accomplish their role as gene regulators through a wide range of mechanisms, as summarized in Fig 2, but the aim of this review is **chromatin modification**.

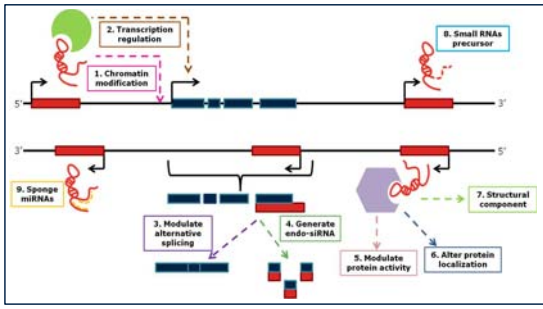

Figure 2. Functions of lncRNAs (red) within the cell. They can regulate the expression of PCGs (blue) through chromatin modification [1] or transcription regulation [2]. In addition, antisense lncRNAs can pair to specific sense RNAs to modulate alternative splicing [3] or to produce endo-siRNAs [4]. They can also form complexes with proteins (purple) [5-7] or function as small RNAs precursors [8] or miRNA sponges [9].

Different models have been proposed for chromatin modification mediated by lncRNAs (Fig.3) according to the effect they have upon chromatin modifiers. LncRNAs may function as **decoys** by sequestering chromatin modifiers, as **guides** by recruiting them to specific genome loci or as **scaffolds** by bringing together different protein complexes.

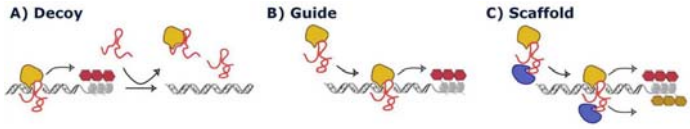

Figure 3. Models explaining lncRNA-mediated chromatin modification. Modified from (1).

Role of lncRNAs in cancer

Consisting with their essential role in gene control, some lncRNAs aberrations have been involved in the process of oncogenesis. Similarly to PCGs, these lncRNAs can be classified into **tumor-suppressor lncRNAs** or **oncogenic lncRNAs** according to their role in this process (2).

Oncogenic lncRNAs

❖**HOTAIR** (HOX Antisense Intergenic RNA)**:**

- Discovered as an antisense transcript in the HOXC locus (3).
- Represses transcription in ***trans*** in the HOXD locus.
- Functions as a **scaffold** recruiting the PRC2 complex through its 5' domain and the LSD1/CoREST/REST complex through its 3' domain.

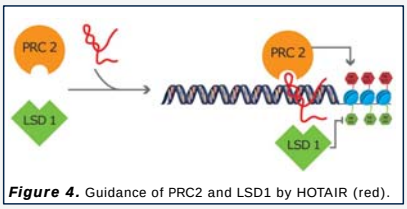

Figure 4. Guidance of PRC2 and LSD1 by HOTAIR (red).

- Overexpressed associated with agressive metastatic phenotypes and poor survival in **breast**, **colorectal** and **hepatocellular carcinomas**.

❖**ANRIL**(Antisense Noncoding RNA in the INK4 locus)**:**

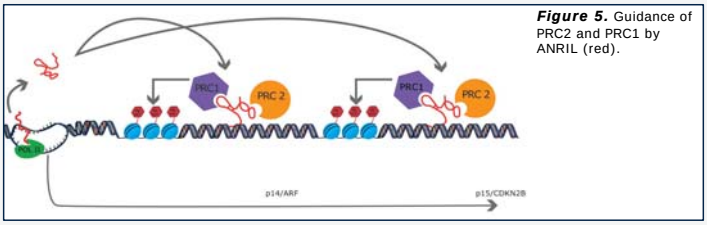

Figure 5. Guidance of PRC2 and PRC1 by ANRIL (red).

- Identified in a germ-line deletion predisposing to melanoma (4).
- Antisense to the tumor-suppressor gene *p15* overlapping its two exons.
- Gene silencing of p*15*, *p16* and *ARF.*
- Acts as a **scaffold** recruiting both PRC1 and PRC2.
- Associated with acute myeloid and lymphoblastic **leukemia**, prostate cancer, neural system tumors and **melanoma.**

Tumor-suppressor lncRNAs

❖**PINT** (P53-Induced Noncoding Transcript) (5)**:**

- Both the murine ortholog ***Pint*** and the human ***PINT*** are regulated by p53.
- While *Pint* promotes proliferation and survival, PINT inhibits them.
- *Pint* is a ***trans*-acting** lncRNA which regulates the expression of genes downstream p53, mainly regulators of **apoptosis** and **cell cycle**.
- *Pint* recruits PRC2 functioning as a **guide**.
- PINT is a tumor-suppressor lncRNA downregulated in **colorectal tumors.**

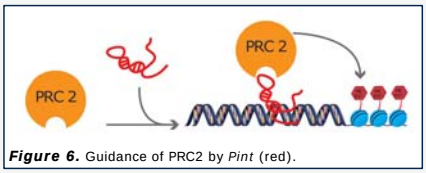

Figure 6. Guidance of PRC2 by *Pint* (red).

❖**CCND1 associated lncRNAs** (6)**:**

- Transcribed upstream the G1-phase cyclin D1 (CCND1) promoter.
- Function in ***cis*** repressing *CCND1* expression.
- Trigger a conformational change in the TLS protein which allows it to bind and repress the histone acetyl-transferases CBP/p300.
- Currently, CCND1 associated lncRNAs have **not** been **found** involved in any tumoral process.

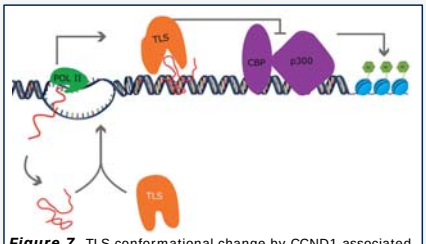

Figure 7. TLS conformational change by CCND1 associated lncRNAs (red).

Conclusions

●LncRNAs exert a major role in **gene regulation**, for instance, through chromatin modification. Thus, its deregulation can contribute to the development and progression of several diseases such as **cance**r.

●Taking advantage of their high tissue-specificty, lncRNAs could be used both as diagnostic and prognostic **cancer biomarkers**. Indeed, lncRNA prostate cancer gene 3 (PCA3) is already used for prostate cancer detection.

●LncRNAs can be regarded as **potential therapy targets** in cancer: oncogenic lncRNAs could be assessed with RNA-mediated gene silencing while loss of tumor-suppressor lncRNAs could be approached with gene therapy.

References

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