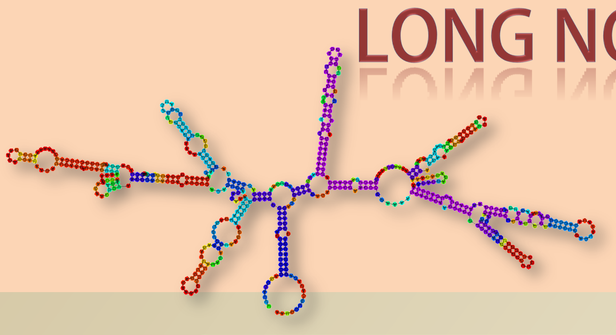

LONG NON-CODING RNAS IN CELL DEVELOPMENT AND CELL DIFFERENTIATION

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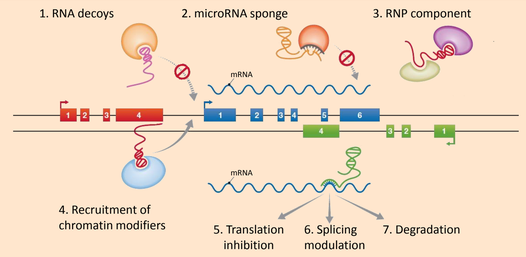
1. INTRODUCTION

OBJECTIVES

- To describe the current knowledge about long non-coding RNAs (lncRNAs) and their role in cell development and cell differentiation.
- To classify different kinds of lncRNAs and their mechanism of action.
- To define the most representative examples to deepen the issue and to understand the importance of this molecules.
- To explain the most relevant results of the research with lncRNAs which were carried out in recent decades.
- To analyze the possible applications of lncRNAs of interest in biomedicine.

MECHANISMS OF ACTION OF lncRNAs

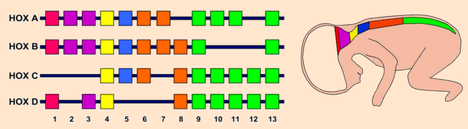
LncRNAs are capable of regulate gene expression by very different mechanisms.



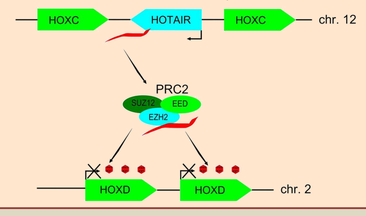
2. EPIGENETICS

HOX GENES

HOX genes are a set of *loci* crucial for cellular differentiation during embrionary development in animals. They encode for transcription factors which coordinate spatiotemporal gene expression and regulate different ways along the anterior-posterior axis of the body by lncRNAs.

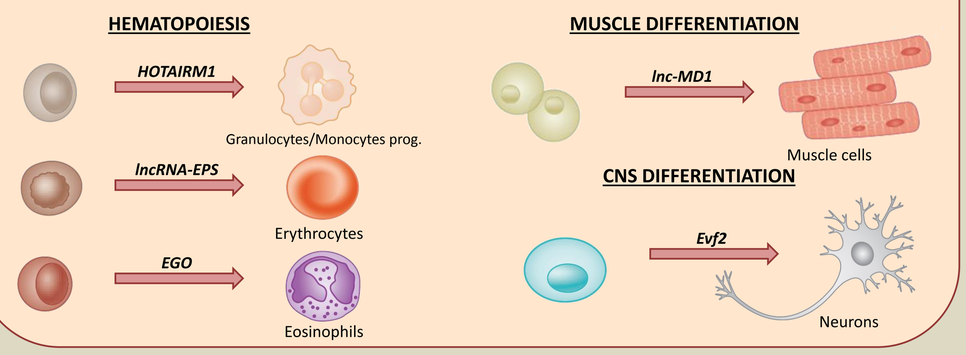


One representative example of a lncRNA encoded in Hox genes is HOTAIR. It acts as an *scaffold*, recruiting modifying chromatin complexes, like PCR2, to inhibit HoxD transcription.



ORGAN DIFFERENTIATION

Stem cells are differentiated in each tissue in a different cell type. Depending on the tissue, they are expressed one lncRNAs or another ones, mediating in the process of cellular differentiation. Here can be seen some examples of lncRNAs expressed in several tissues.



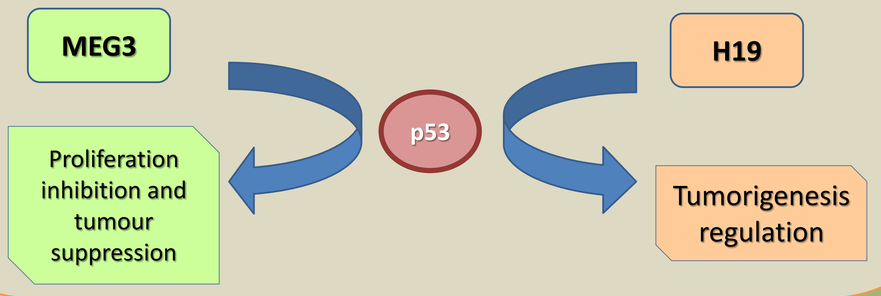
3. LncRNAs AND CANCER

Recent advances have determined that many lncRNAs have oncogenic functions and play an essential role in tumorigenesis. Furthermore, it has been found in cancer patients there is a deregulation in expression levels of lncRNAs.

Between lncRNAs associated with cancer, ***H19*** is one of the most studied. His transcription is activated by a protooncogen called *cMYC* and inactivated by p53 and by prolonged cell proliferation processes. His *knockdown* in model animals prevent cellular growth and clonogenicity in lung cancer cells *in vitro.*

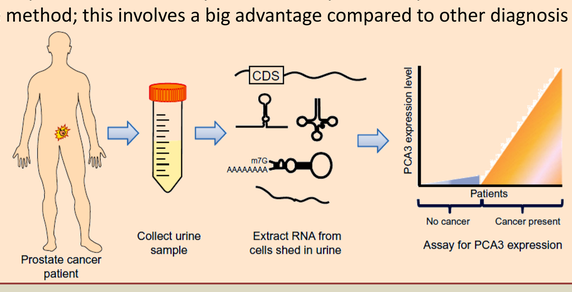
TUMOR SUPRESSOR ACTIVITY

It is known that several lncRNAs play an important role in regulating signaling through the known ***p53***. A clear example is ***MEG3***. It activates p53 and facilitates its signaling and its binding to the promoters of its target genes. *MEG3* overexpression produce suppression of proliferation.
Furthermore, hypermethylation of MEG3 and, consequently, a reduction in expression, has been observed in several types of cancer.



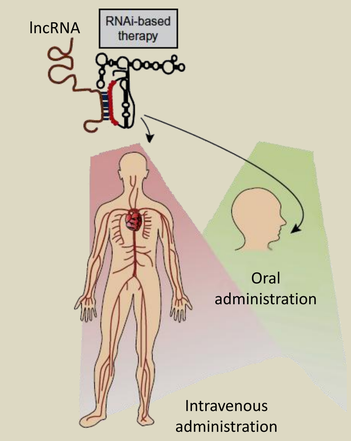
4. LncRNAs AS BIOMARKERS

Once the properties of lncRNAs and their different levels of expression in cancerous tissues compared with normal tissues are known, is easy to think about their application as biomarkers for cancer diagnosis.
Nowadays, there is a test for diagnose prostate cancer based in the level expression of ***PCA3***, a lncRNA. *PCA3* is a prostate specific gene that is overexpressed in prostate cancer. The detection of the transcript of PCA3 is made by an urine analysis of the patient. It does not require any invasive method; this involves a big advantage compared to other diagnosis methods.



5. THERAPIES WITH lncRNAs

In recent decades it is starting to be considered using lncRNAs as a therapy for various cancer diseases, but they are still only research long way to go. However, although their therapeutic use is still remote, there are clinical studies in Phase I that are employing interfering RNAs (RNAi) binding mRNAs. These were tested in both mice and humans with advanced stages of cancer.
The evidences confirm that RNAi-based therapies for human tumors effectively localized and reduced gene expression of target proteins and their mRNAs.
Currently, these trials are testing the safety and efficacy of these RNAi in patients with various diseases, including cancer.



6. CONCLUSIONS

The latest research about lncRNAs and their differential expression between normal tissues and cancerous tissues involve a big progress for the current biomedicine. They help us to understand molecular mechanisms implicated in complex multifactorial diseases, like cancer.

The rise of integrating such knowledge beside its application make us think of the possible use of lncRNAs as biomarkers in cancer diseases and as therapeutic molecules. This is a necessary contribution to scientific knowledge and it could, even, save lifes.

7. RELLEVANT REFERENCES

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