LONG NON-CODING RNAs AND ITS RELATIONSHIP WITH CANCER

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Introduction

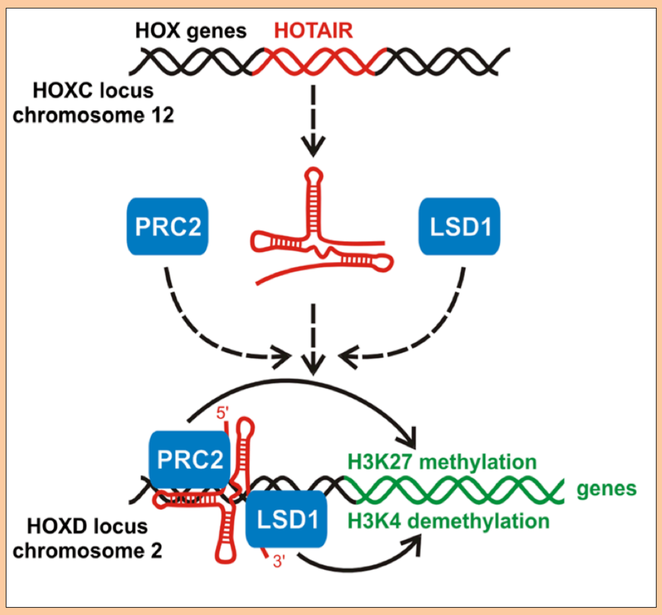
Long non-coding RNAs (lncRNAs) are non-protein coding transcripts larger than 200 nucleotides. Firstly seen as transcriptional noise, lncRNAs are now reported to regulate multiple key biologic processes including nuclear transport, epigenetic regulation and miRNAs activity. Recently, lncRNAs are emerging as a new factor to consider while studying mechanisms such as carcinogenesis, tumor progression or metastasis.

Objectives

The aim of this poster is to introduce two well-known lncRNAs, *HOTAIR* and *MEG3*, and review its relationship with cancer. *HOTAIR* is an oncogenic lncRNA primary related to breast cancer, while *MEG3* is the product of an imprinted gene and has an anti-proliferative role in multiple cancers.

HOTAIR – HOX transcript antisense RNA

Mechanism of action



HOTAIR serves as a scaffold for two distinct histone modification complexes:

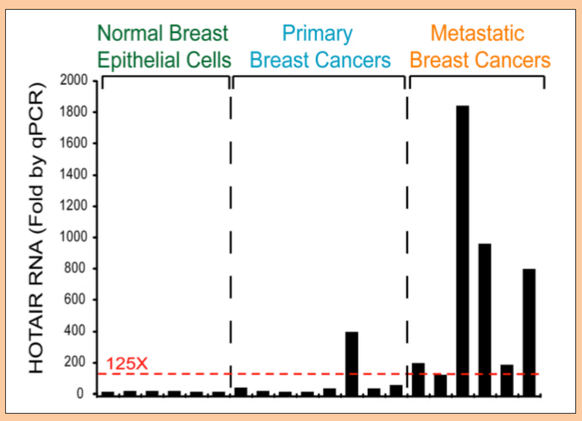
- 5' domain of *HOTAIR* binds to Polycomb repressive complex 2 (PRC2).
- 3' domain of *HOTAIR* binds to a lysine-specific histone demethylase (LSD1).

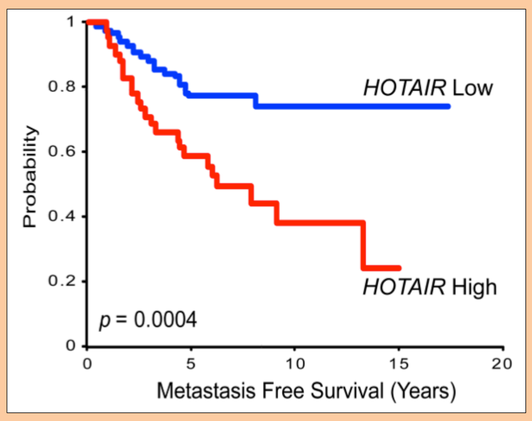
The ability of *HOTAIR* to tether two distinct complexes enables RNA-mediated assembly of PRC2 and LSD1, and coordinates targeting of both complexes to chromatin for coupled histone H3 Lys27 methylation and Lys4 demethylation, resulting in epigenetic repression of the genomic region.

Relationship with breast cancer

HOTAIR is overexpressed in one third of primary breast cancers over normal breast epithelia. In metastatic breast cancer this overexpression is much more clear, as seen in the graphic below.

Apparently there are differences in metastasis-free survival between primary breast cancers expressing high levels of *HOTAIR* and low-expressing primary breast cancers.





Relationship with other cancers

- Overexpression of *HOTAIR* has been described in multiple cancers apart from breast cancer.
- This upregulation of *HOTAIR* is associated with cancer progression and thus worse prognosis.

Cancer	Comments
Hepatocellular carcinoma	Overexpression of *HOTAIR* is related to recurrence risk of HCC after liver transplant
Non-small cells lung cancer	Tumor promoter type-1 collagen is described as a factor that upregulates *HOTAIR*
Colorectal cancer	Overexpression of *HOTAIR* is related to higher risk of metastasis
Pancreatic cancer	Genome-wide retargeting of PRC2 genes mediated by *HOTAIR* overexpression
Nasopharyngeal cancer	Knockdown studies of *HOTAIR* reveal decreasing malignancy of the tumor
Stromal GI cancer	Genome-wide retargeting of PRC2 genes mediated by *HOTAIR* overexpression

Concluding remarks regarding *HOTAIR*

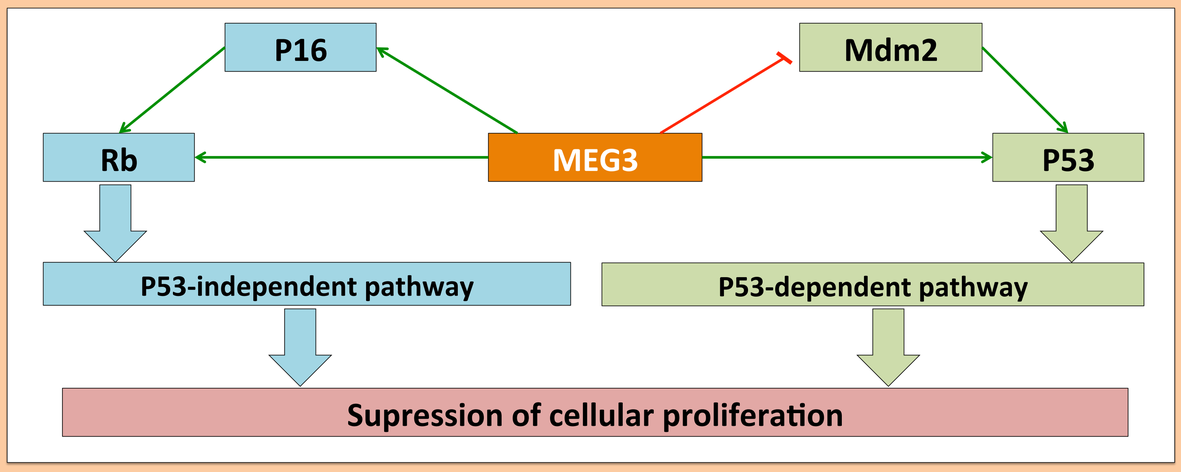
- The association between *HOTAIR* overexpression and cancer progression has been confirmed in multiple cancers, revealing the oncogenic role of *HOTAIR*.
- The oncogenic mechanism of *HOTAIR* has not been studied yet. However, the most discussed hypothesis is based on the repression of tumor suppression and anti-metastasis genes through the action of PRC2 and LSD1 complexes.
- Unfortunately, even the oncogenic role of *HOTAIR* is well-known, there are not enough studies about its viability as a prognosis biomarker.

MEG3 – Maternally expressed gene 3

Mechanism of action

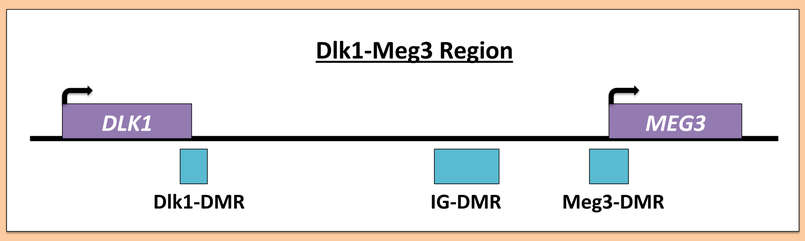
MEG3 has anti-proliferative effects acting directly on *P53* or on one of its regulators. However *MEG3* can also reduce cellular proliferation through a P53-independent pathway.

MEG3 also activates Notch signaling and inhibits VEGF pathway.



Imprinting and expression

MEG3 gene is a paternally imprinted gene that, in conjunction with the maternally imprinted gene *DLK1*, comprises the Dlk1-Meg3 region.



MEG3 is expressed in multiple tissues, showing the highest levels of expression in the pituitary gland and brain

DLK1 is a paternally expressed gene encoding a membrane protein involved in the differentiation of several cell types

The Dlk1-Meg3 region contains three known differentially methylated regions (DMRs):

Name	Paternal chr.	Maternal chr.	Classification	Comments
Dlk1-DMR	Methylated	Demethylated	Secondary DMR	Its methylation state is variable
IG-DMR	Methylated	Demethylated	Primary DMR	Acts as an imprinting center in maternal chr.
Meg3-DMR	Methylated	Demethylated	Secondary DMR	If methylated, *MEG3* expression is repressed

Relationship with cancer

- *MEG3* is underexpressed in multiple cancers such as pituitary adenomas or meningiomas.
- The table below summarizes the main discoveries of each cancer associated with *MEG3* downregulation.

Cancer	Comments
Pituitary adenomas	Underexpression of *MEG3* is described only in non-functioning adenomas and it is related to hypermethylation of IG-DMR
Meningiomas	Underexpression of *MEG3* in meningiomas is related to IG-DMR methylation and tumor progression
Multiple myelomas	Underexpression of *MEG3* in multiple myelomas is related to Meg3-DMR methylation and tumor progression
Non-small cell lung cancer	Tobacco smoke condensate represses *MEG3* expression through hypermethylation of its promoter in bronchial epithelia in vitro
Hepatocellular carcinomas	Underexpression of *MEG3* is described in cells presenting Mallory-Denk bodies, condition related to hepatocellular carcinomas

Concluding remarks regarding *MEG3*

- Underexpression of *MEG3* is clearly associated with multiple cancer tissues.
- The relationship between *MEG3* underexpression and tumor progression confirms its anti-proliferative role.
- Methylation studies have demonstrated that hypermethylation of IG-DMR induces hypermethylation of Meg3-DMR, which represses the expression of *MEG3*.
- Although treatment with hypomethylation agents *in vitro* induces re-expression of *MEG3* in cancer cells, there are no further studies regarding its use in therapy against cancer.

References

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4. Benetatos, L., Vartholomatos, G. & Hatzimichael, E. MEG3 imprinted gene contribution in tumorigenesis. *Int. J. Cancer* **129,** 773–9 (2011).