Regulation of LINE-1 in human cancers

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1. Introduction

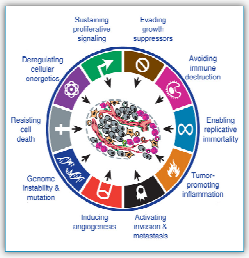
Nowadays there are many cancer studies in progress with the aim of finding better treatments, diagnostic markers and depth knowledge of the tumor progress. Considering factors involved in cancer regulation is also essential.
The role of transposable elements such as LINE-1 is gaining prominence. There has been an important step on the understanding: from being considered 'junk DNA' to find out about their involvement in cell regulation, in addition to realize the ectopic recombination and transposition effects.
The disruption of the tumor suppressor gene APC by a LINE-1 has been known since 1992, revealing their possible role in cancer.

Aims

For these reasons a literature review was made with the aim of learning the biology of LINE-1 and its involvement in cancer as a regulator, insights in different regulation levels.

Keywords: LINE-1 , cancer regulation, methylation, histone modification, iRNA, helicase.

2. Cancer and LINE-1

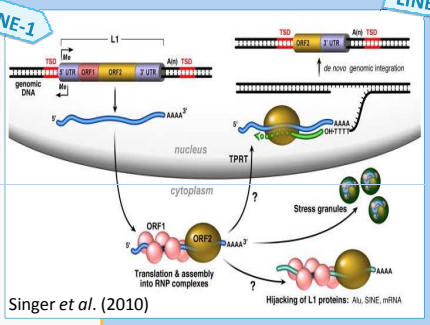


Hanahan *et al.* (2011)

Cancer is an uncontrolled cells proliferation.

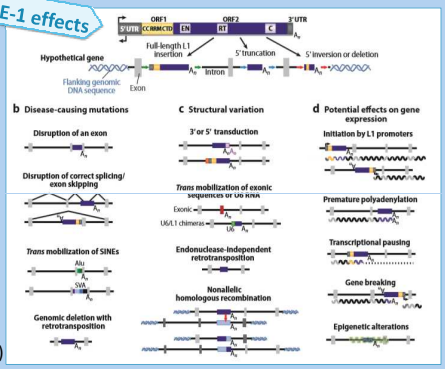
- **Oncogene**
  - Cell division
  - Cell growth
- **Tumor Supressor Gene**
  - DNA repair
  - Apoptosis

LINE-1



Singer *et al.* (2010)

LINE-1 effects



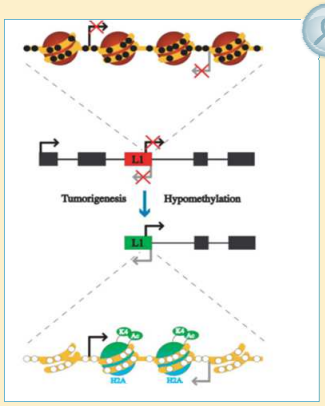
Beck *et al.* (2011)

3. Results

A) Methylation

DNA methylation leads to gene silencing. Cells control LINE-1 transposition by DNA hypermethylation. In cancer, this pattern is lost and it can be seen hypomethylated LINE-1. Hypomethylation of LINE-1 in cancer enables transposition and leads an increase on genomic instability.

Currently the level of LINE-1 methylation is used as a biomarker in cancer to determine the state of the cell global methylation, and as a diagnostic marker.
Association was found between the degree of LINE-1 methylation and factors such as tumor progression, poor prognosis, metastasis and low survival, even though this association is not the same for all types of cancers. The correlation was also studied with factors such as age of onset, sex, diet or alcohol intake, but the results are very different depending on the type of cancer studied.



Wolff *et al.* (2010)

B) Histone modifications

Histones are nucleosomes proteins that regulate gene expression due to its interaction with chromatin which modulates its compactness. Different modifications of histone tails lead to compaction changes, and therefore, expression changes.
The histones' repression as a regulation of LINE-1 is known as a genomic defence mechanism, although it has been observed a more relaxed repression in cancer, acting together with methylation. Even an upregulation has been observed in some LINE-1 which acts as oncogenes' regulators. Moreover, cell lineage-specific or tissue differences in histones repression have been seen.

C) iRNA

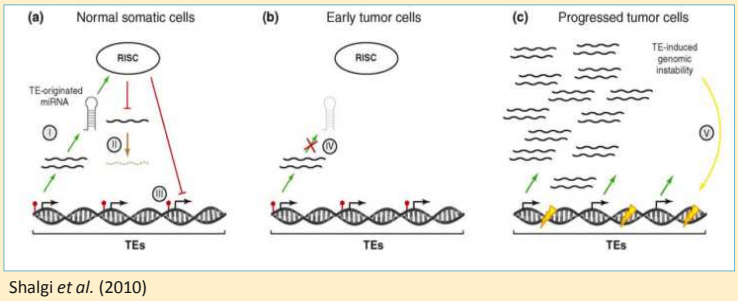
The iRNA are small interfering RNA that act on RNA - protein complexes. They can repress expression in the post transcriptional step by producing cuts in the mRNA or blocking at translational level.

23% of miRNA, a type of iRNA, were originated from transposable elements, so they share a high degree of complementarity with LINE- 1 and are their regulators.
In the tumor process a reduction of miRNA is observed, a fact that prevents them from regulating LINE-1. As a result there is an increase on transposition and ectopic recombination leading to deregulation of oncogenes and tumor suppressor genes, ending as genomic instability.

Besides, it has been shown a regulatory role of LINE-1 in mRNA transcription. Some LINE-1 are close to or within genes sequences and affect its regulation finding chimeric mRNA, splicing variants and premature polyA sites. Moreover a deregulation of cancer genes is caused by an antisense RNA that controls post transcriptional level. This antisense RNA is transcribed through the antisense promoter of a near LINE- 1 and has enough complementarity with the mRNA that cause gene silencing.

D) Helicase MOV10

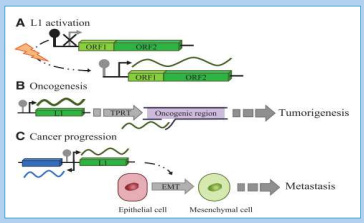
Recent studies point to MOV10 helicase as a LINE-1 regulator. It has been seen that the helicase reduces the average life of the LINE-1 transcript, thus being the regulator. Some studies are currently being carried out to find out the molecular mechanism and its possible application on cancer knowledge.



Shalgi *et al.* (2010)

4. Conclusions

All studies do not deepen because they observe a regulatory role of LINE-1 but the molecular mechanism is unknown. This leads to underestimate their participation in cancer. It should be taken into account that they are also the support for other types of transpositions.
It might be an issue of great concern in oncology to know the participation of LINE-1 in the regulation, because it is known its involvement in genomic instability, in regulation of oncogenes and tumor suppressor genes, and lately, participation with the immune system is intuited.
It has been observed, therefore, inconsistencies between studies, probably due to not taking into account the differences among types of cancers due to the origins of cell types or tumor heterogeneity.
Another important factor is the coordinated regulation, the participation of more than one type of regulation at the same time.



Carreira *et al.* (2014)

5. References

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