Impact of microRNAs deregulation on the mobility of LINE-1 retrotransposons in colon cancer

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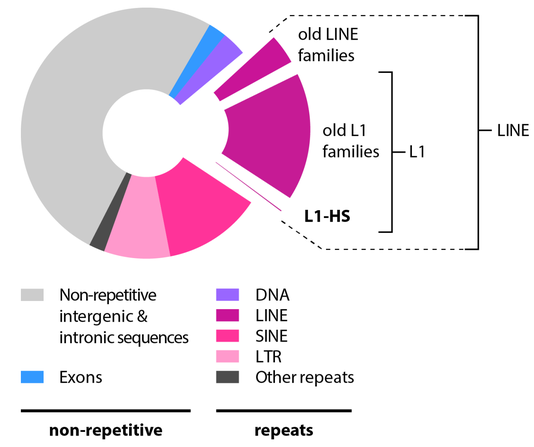
INTRODUCTION

Taken from euL1db



50% of the human genome is mobile DNA

Almost half of the human genome is comprised of **transposable elements** (TEs), whose ongoing activity continues to impact our genome. Among them, there are ~100 copies of a subfamily of Long INterspersed Element class 1 (**LINE-1**/L1) elements that can still retrotranspose: L1Hs (human-specific)

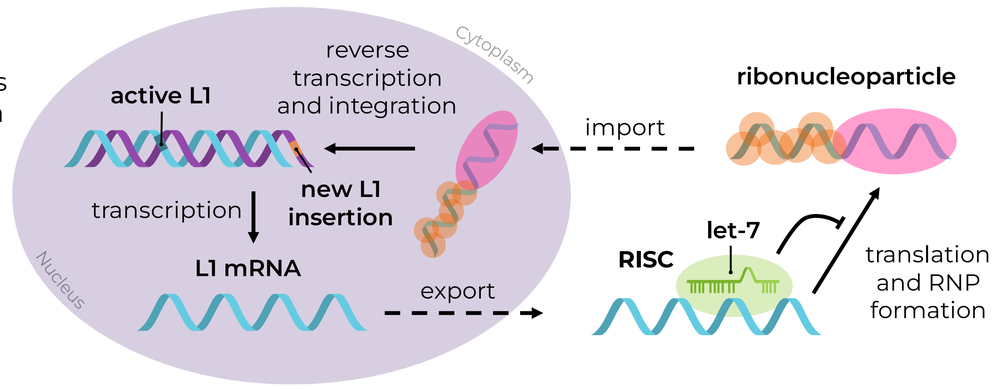
L1 is deregulated in cancer

In somatic cells, L1 expression is silenced by a variety of mechanisms. However, L1s are **expressed and mobilized** in many cancers, causing mutagenic insertions and genomic instability that can affect tumor malignancy

Let-7 can regulate L1 retrotransposition

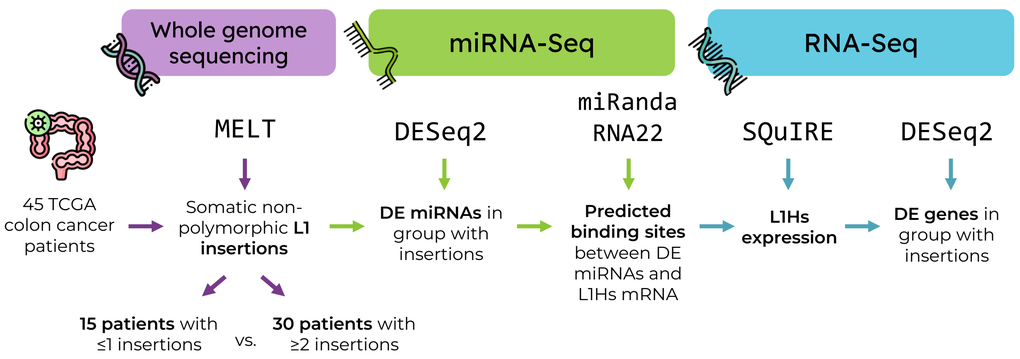
Our lab has recently described a **new mechanism** that represses L1 in normal cells and is deregulated in cancer

Adapted from Tristán-Ramos et al. (*Nat. Commun.*)

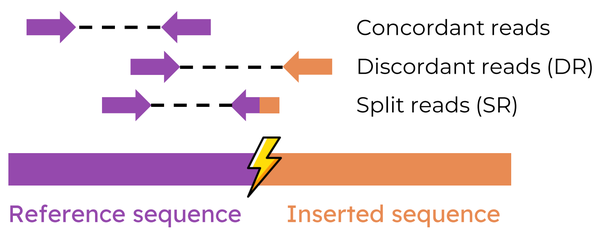


A tumor suppressor miRNA, let-7, can directly bind to the L1 mRNA and repress the translation of an L1 protein needed for L1 mobilization. In lung cancer, deregulation of this miRNA correlates with somatic L1 insertions. ***Could there be other miRNAs inhibiting LINE-1 as well?***

METHODS



MELT We specifically included **non-polymorphic** and **accurate** insertions (`SR≥8, ASSESS=5, FILTER=PASS`)

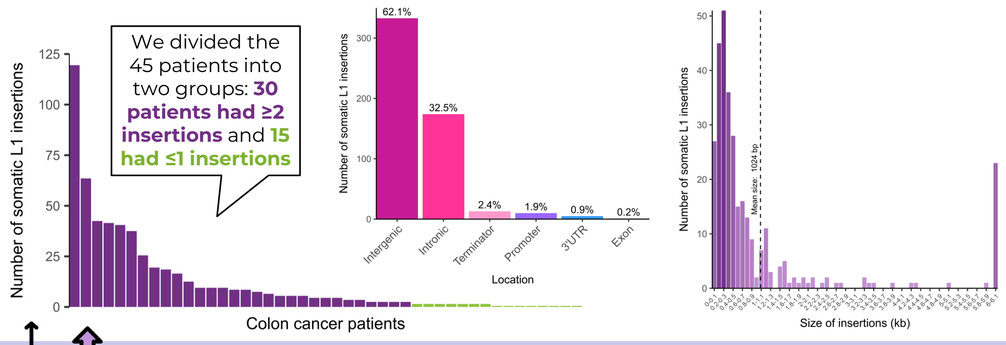


DESeq2 Features with **low expression** were filtered with `edgeR`'s `filterByExpr`. `FDR<0.05` was considered significant

SQuIRE 1. Maps reads to `STAR` index allowing for **multiple alignments**.
2. Quantifies reads aligning to TEs in `RepeatMasker` annotation using an iterative **expectation-maximization algorithm** to assign multi-mapped reads

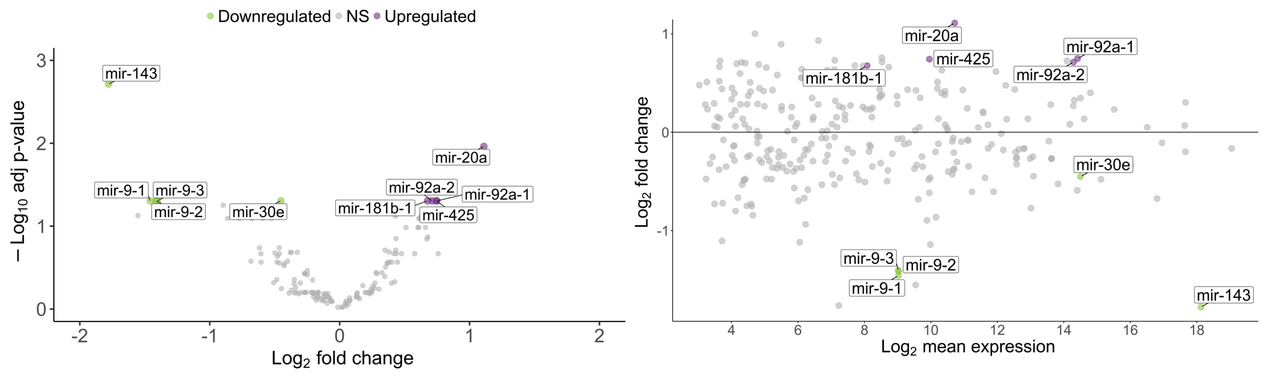
RESULTS

1. Identification of 536 tumor-specific *de novo* L1 insertions

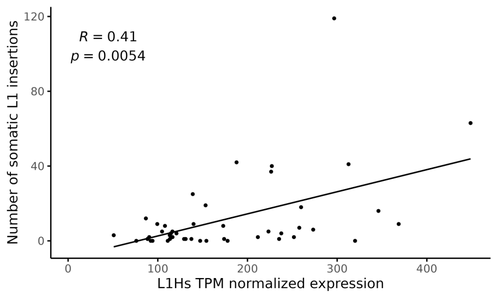


2. Patients with L1 insertions express less tumor suppressor miRNAs and more oncomiRs

- **miR-143, miR-9 and miR-30e** (tumor suppressor miRNAs) were **downregulated** in the insertion group, while **miR-20a, miR-92a, miR-181b and miR-425** (oncomiRs) were **upregulated**
- miR-143 stands out as a **potential L1 inhibitor** due to its biological relevance in colon cancer



3. L1Hs expression correlates with tumor-specific L1 insertions and with some DE miRNAs expression

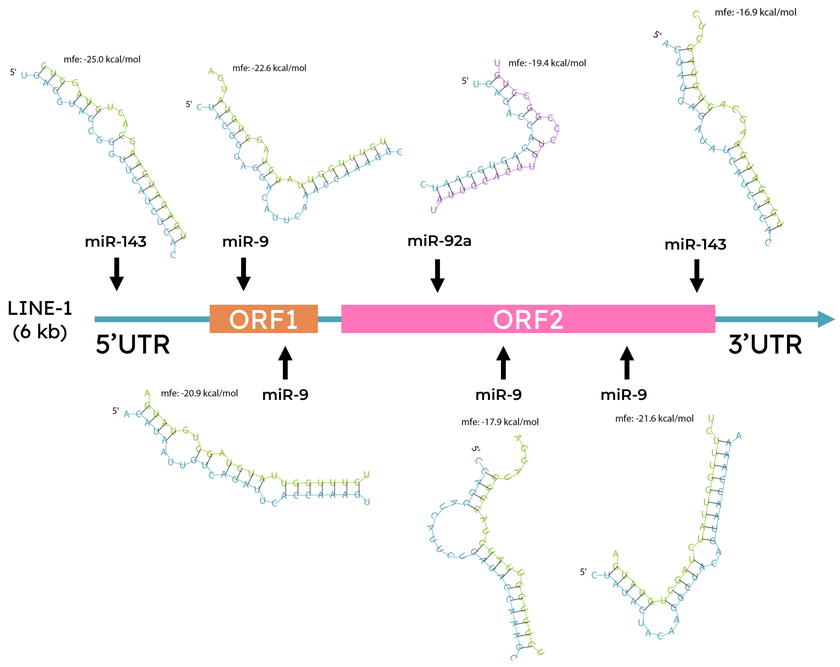


DE miRNA	Spearman correlation	p-value
mir-143	0.24	0.12
mir-9-1/2/3	0.11	0.48
mir-30e*	**-0.54**	**0.00017**
mir-20a*	**0.33**	**0.027**
mir-92a-1/2*	**0.31**	**0.038**
mir-181b-1	0.26	0.079
mir-425	0.043	0.78

- L1Hs RNA levels **positively correlated with the number of L1 insertions**
- L1Hs RNA levels **negatively correlated with miR-30e expression**
- L1Hs RNA levels **positively correlated with miR-20a and miR-92a expression**

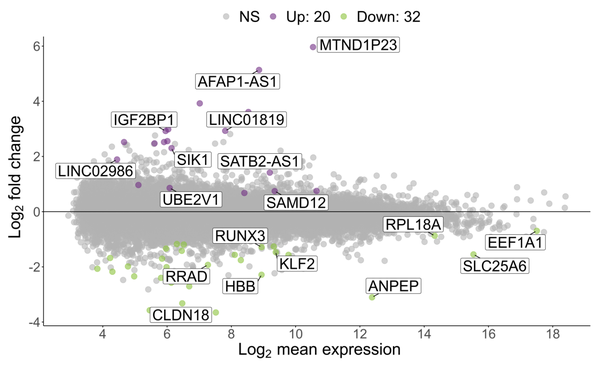
4. miR-143 and miR-9 have potential canonical binding sites in L1 mRNA

- We could predict several **canonical binding sites** throughout the L1Hs mRNA for **miR-143 and miR-9**, which suggests they are direct regulators of L1 retrotransposition



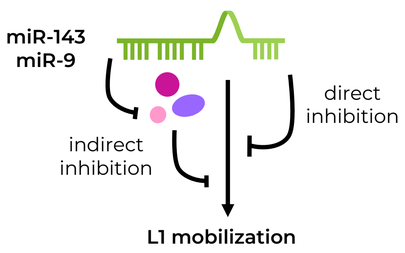
5. Some DE genes are targets of DE miRNAs and could regulate L1 retrotransposition

- **IGF2BP1**, a target of miR-9 that is upregulated in the insertion group, was previously suggested to increase L1 retrotransposition
- Some of the DE targets could be **unknown L1 regulators**



DE miRNA	Upregulated targets	Downregulated targets
miR-143	0	0
miR-9	**IGF2BP1**	0
miR-30e	0	EEF1A1
miR-20a	SAMD12, SIK1	RPL18A, RUNX3
miR-92a	SIK1, UBE2V1	EEF1A1, HBB, KLF2, RPL18A, RRAD
miR-181b	HEPHL1	RPL18A
mir-425	0	0

CONCLUSIONS



1. Downregulation of some tumor suppressor miRNAs and upregulation of some oncomiRs is correlated with tumor-specific *de novo* L1 insertions in patients with colon cancer
2. Tumor suppressor miRNAs miR-143 and miR-9 have potential canonical binding sites to L1Hs mRNA and could directly regulate L1 retrotransposition
3. Differentially expressed target genes of differentially expressed miRNAs may be unknown L1 regulators

REFERENCES

1. Tristán-Ramos P et al. (2020). The tumor suppressor microRNA let-7 inhibits human LINE-1 retrotransposition. *Nature Communications*, 11(1), 5712.
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