Dynamics and regulation of non-LTR retrotransposons in mammals

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INTRODUCTION:

Retrotransposons are endogenous genomic sequences that have had a central role in shaping our genome and the genomes from other mammals over millions of years. In fact, approximately 45% of the human genome is comprised of interspersed repeats resulting from replicative copy and paste events of retrotransposons. Although most of these sequences represent fossils of previously active retroelements, each eukaryote has a specific complement of recently active transposable elements, posing a threat to genomic stability throughout all cellular populations due to retrotransposition events. In response, mammals have developed intrinsic immunity mechanisms that provide resistance against the deleterious effects of retrotransposition. This final project is a review of the most important known mechanisms that human and mouse have to protect their genomes against the deleterious effects caused by, virtually, the unique mobile elements that are currently active and that are these of the non-LTR retrotransposons subgroup: LINE1 and their non autonomous partners SVA and Alu.

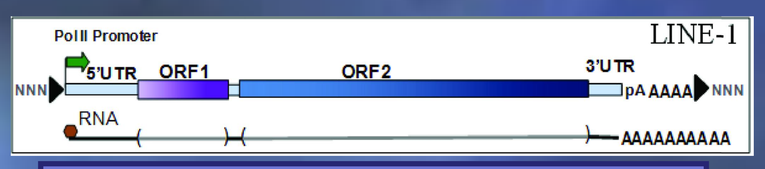

Fig 1. Schematic representation of the structural organization of human L1 (LINE-1).

Fig 2. Schematic representation of the structural organization of human Alu (SINE).

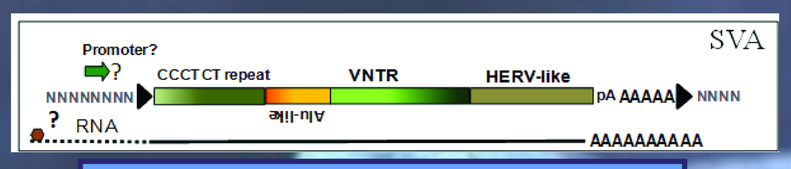

Fig 3. Schematic representation of the structural organization of human SVA.

REGULATORY MECHANISMS:

DNA methyltransferases

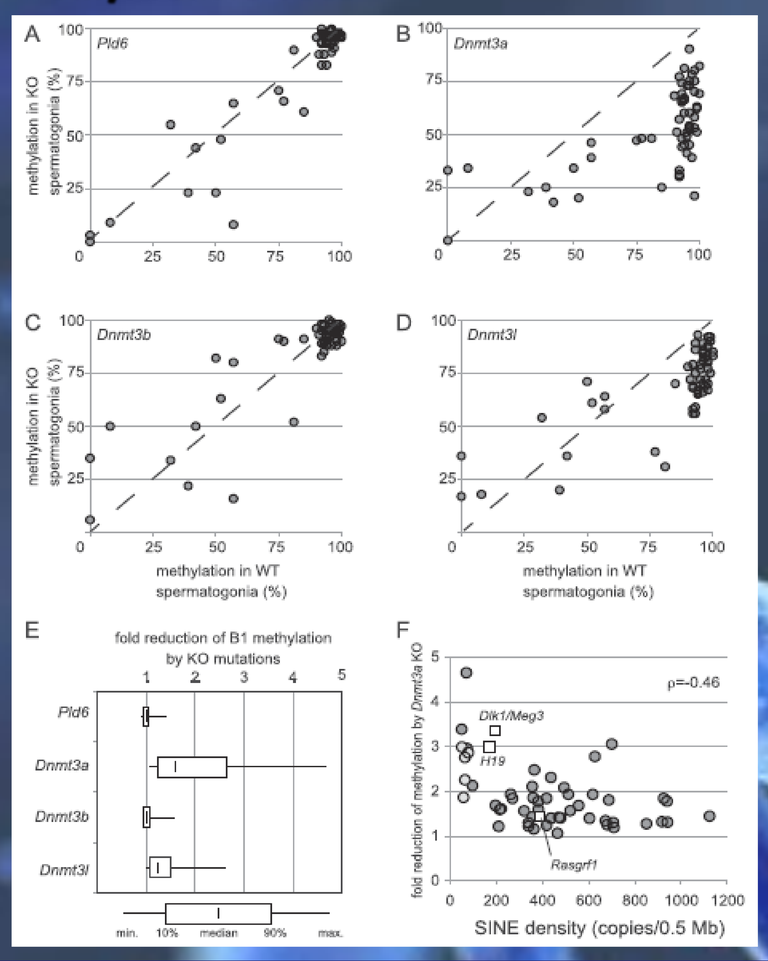

Fig 4. A) B) C) D) Effects of mutations of piRNAs (*Pld6*) and DNA methyltransferases on *de novo* B1 methylation. E) Fold reductions in individual B1 methylation due to mutations. F) Fold reductions in methylation due to *Dnmt3a* KO mutation at individual B1 loci (dark grey circles), B1 loci selected from SINE-poor domains (light grey circles) and the methylation levels at three methylated regions for genomic imprinting in wt and *Dnmt3a* spermatogonia (open squares).

piRNA-PIWI system

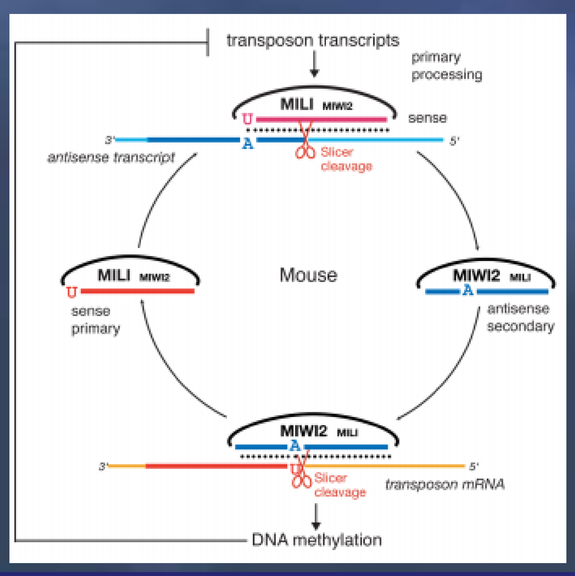

Fig 5. Formation of piRNAs in mouse by a Ping-pong amplification. piRNA clusters are not the major source of primary piRNAs. mRNAs of active transposable elements likely represent the substrate for primary processing resulting in sense piRNAs that preferentially associate with MILI, whereas MIWI2 is specifically enriched in secondary antisense piRNAs as compared to MILI. Antisense piRNAs guide DNA methylation of transposable elements.

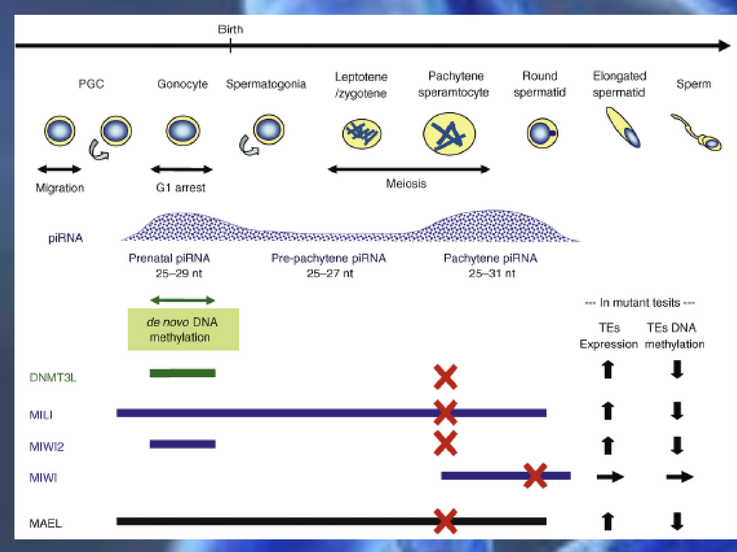

Fig 6. Transposon silencing in mouse spermatogenesis. Upper part: shows the stages of spermatogenesis and when the three piRNAs groups are expressed. Lower part: Horizontal thick lines show the expression periods of genes indicated (DNMT3L, MILI, MIWI2, MIWI and MAEL) during spermatogenesis. Red crosses show the time points when loss of individual genes shows phenotypic abnormality. How transposon and DNA methylation are affected when individual genes are abrogated in their mutant mice is summarized on the right-hand size.

APOBEC family

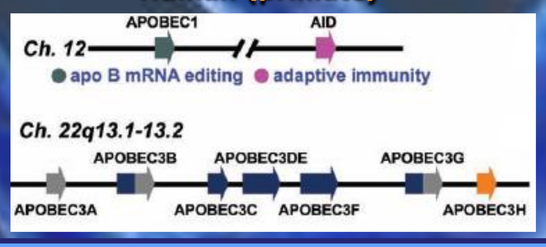

Fig 8. A schematic representation of the human genome containing members of the *AID/APOBEC* family.

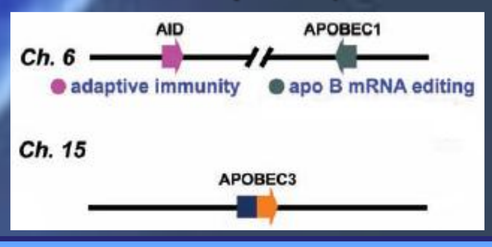

Fig 9. A schematic representation of the murine genome containing members of the *AID/APOBEC* family.

MOV10 RNA Helicase

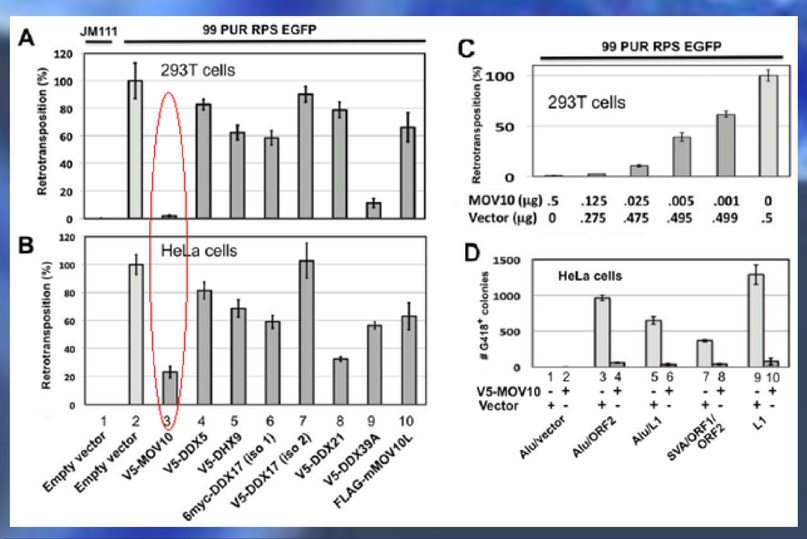

Fig 7. Evidence from cell culture retrotransposition assays that MOV10 inhibits insertion of non-LTR retrotransposons.

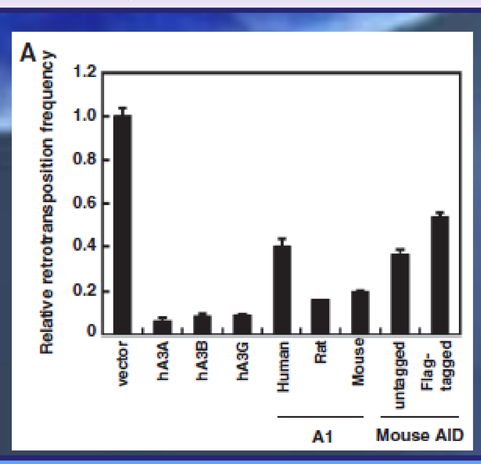

Fig 10. Inhibition of L1 retrotransposition by APOBEC proteins in 293T cells. Relative retrotransposition frequency in the absence of APOBEC proteins (vector) was set as 1.0.

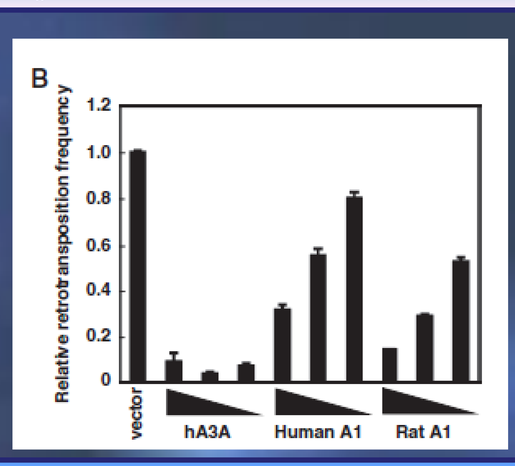

Fig 11. Transposition frequency of L1 in 293T cells along with the expression plasmids for APOBEC family proteins. Amounts of APOBEC-expression plasmids were varied (0.5, 0.25 and 0.125 μg).

CONCLUSION:

These regulatory mechanisms are essential to protect human and mouse genomes of the deleterious effects caused by retrotransposons.

Most of them act in the germline, which is where transposons are more active due to the many germline-specific genes being expressed.

Despite retrotransposition's negative effect, cellular machineries have evolved to support a balance between retrotransposition insertions that cause deleterious gene disruption and those that confer beneficial genetic diversity, and a regulatory mechanism.

However, it is still a long way to learn and understand how these and other regulatory mechanisms inhibit retrotransposition in mammals.

More functional genomic screens and better in vitro retrotransposition assays are needed, to determine precisely where and how host factors interact with the retrotransposons molecular machinery, to block their life cycle.

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