Thoughts on ‘Self’ vs ‘Other’ and a Potential New Role for Transposable Elements in Primordial Germ Cells.

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ABSTRACT

The ability of single cells to differentiate into multicellular organisms evolved rapidly - over a mere 600 million years. This was driven in part by Transposable Elements (TE) and it is generally accepted that evolution as a whole has been advanced by their persistence. TE-altered DNA contributes to the self-definition of specialized cell types by fine-tuning cell type-specific heterocheromatin formation, RNA splicing and editing and gene dosage regulation1,2. However, it is a common assumption that TE and their remnants, abundantly transcribed during early germ cell maturation, must be immediately silenced by the release of anti-TE piRNA, lest these foreign, mutagenic hooligans damage the growing cell.

I propose an alternate hypothesis for the role for TE and their remnants: that they mark the presence of ‘TE-evolved’ DNA—that is, DNA of no use to a ‘basic’ replicating cell, but of value to a differentiated one. The bulk expression of TE and their remnants during early germ cell maturation followed by piRNA-mediated silencing results in a kind of genetic “reboot”, necessary to restrict transcription to the original ‘self’ genes of the primordial cell, while maintaining the evolutionarily accrued genomic information with which to make a multicellular organism—just silenced.

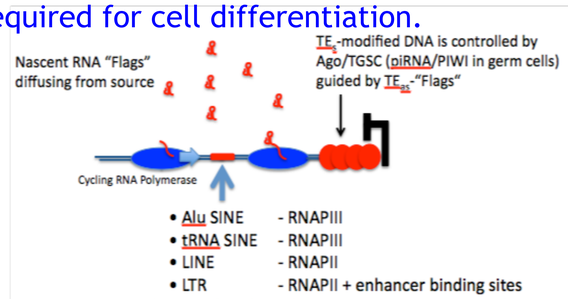
Interestingly, the loss of piRNA-mediated silencing does not lead to loss of embryonic development; it leads to loss of fertility 2 . In the context of this new hypothesis this makes some sense: TE silencing is not necessary for cell differentiation -- a process dependent on the sequential expression of specific transcription factors. Rather, TE silencing is required to maintain the ‘primordial’ identity of developing germ cells and Primordial Germ Cells (PGC).

The concept of ‘self’ vs ‘other’ DNA and RNA is frequently discussed in current literature, yet the definition of ‘other’ is often merged with the idea of ‘foreignness’ or ‘junk’. By these criteria, the only true ‘self’ is that of the primordial cell. But the ‘self’ DNA and RNA of one cell type might be ‘other’ to another cell type, without being foreign or useless to the organism. In fact, the ability to identify true foreignness is one of the wonders of the immune system and Crispr. Perhaps TE and their remnants**, far from being foreign bits** of RNA, are tags that signal the presence of recently evolved RNA. Indeed, TEs and their remnants may contribute to the totipotency of the epiblast and the pluripotency of stem cells: **TE are a mechanism for identifying and controlling both old and new ‘selves’, allowing a ‘genetic reboot to ‘baseline’ to occur during early embyrogenesis and gametogenesis. They are not foreigners within a homogeneous organism, they are the ‘self’ of self differentiation.**

TEs = Transposed Evolved Self

BACKGROUND

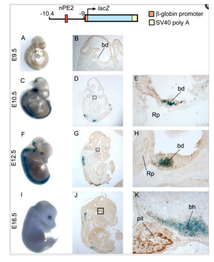
I. Transposable Elements (TE) are jumping Transcription ON/OFF signals that participate in gene regulatory networks. Unlike networks based on transcription factor binding[3] (reviewed in Feschotte, 2008) a transcription network can be established based on small RNA-mediated communication between two genes, each having primed an Agonaute with complementary nascent TE RNA “Flags”. A newly jumped ON/OFF signal might participate in the evolution of a network required for cell differentiation.



Nuclear RNA Network.com[4] is an animated video of the development of a direct gene-to-gene network based on these ideas. (Let me know if you would like a copy.)

I. TE remnant-controlled expression of cis-linked genes occurs during cell differentiation and continues in mature cells: Embyrogensis Somatic Cells

The enhancer nPE2 originated from the exaptation of a SINE retroposon in the lineage leading to mammals and remained under purifying selection for the last 170 million years

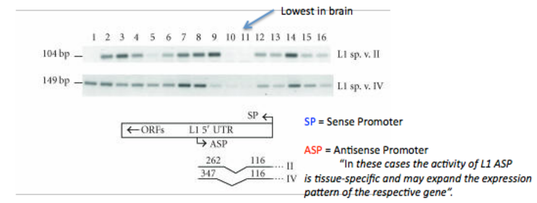


A 170 million year old SINE is an enhancer for **Pro-opiomelanocortin (POMC)** = self or non-self?

Spatiotemporal lacZ Expression Pattern Driven by nPE2 (a **CORE-SINE-Derived Sequence**) during mouse embryogenesis. Colocalization of ß-galactosidase activity within ACTH immunoreactive hypothalamic neurons was observed.[4] (Santangelo, 2007)

L1 Antisense Promoter Drives Tissue-Specific Transcription of Human Genes

Here we show that L1 ASP is capable of functioning as an alternative promoter, giving rise to a chimeric transcript...of the following genes: *KIAA1797, CLCN5, and SLCO1A2. The activity of L1 ASP is tissue-specific also in cases where L1 ASP produces antisense RNAs complementary to COL11A1 and BOLL mRNAs.*(Mätlik, 2006)[5]

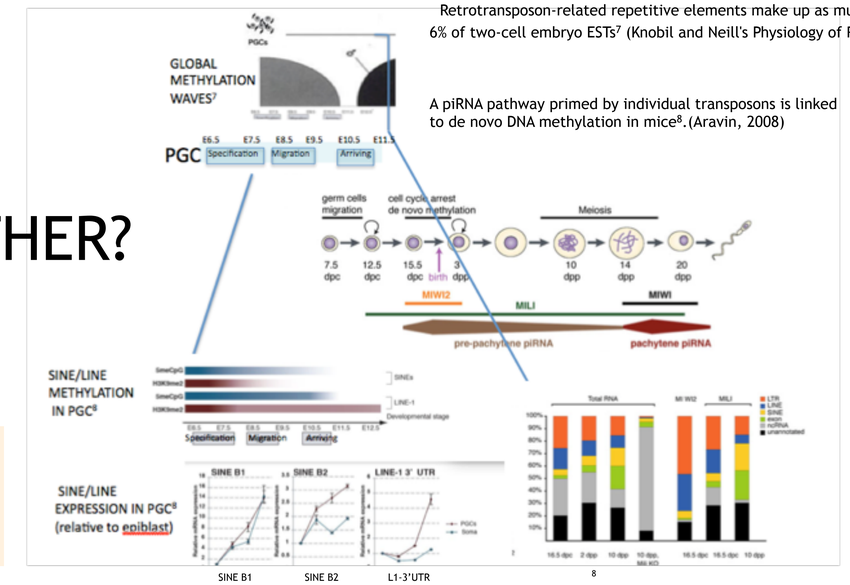


Distribution of L1 splice variants II and IV. The presence of splice variants was estimated by RT-PCR in 16 normal human tissues cDNAs were derived from the following human tissues: 1, thymus; 2, prostate; 3, spleen, 4, small intestine; 5, colon; 6, ovary; 7, testis; 8, peripheral blood leukocytes; 9, placenta; 10, skeletal muscle; 11, brain; 12, kidney; 13, heart; 14, lung; 15, pancreas, and 16, liver.

III. During early embryogenesis and gametogenesis, different TE remnants are expressed at different times, then methylated in coordinated waves by piRNA/MILI (in mouse), rather than by the de novo methyltransferases DNMT3A and DNMT3B.

Retrotransposon-related repetitive elements make up as much as 6% of two-cell embryo ESTs[7] (Knobil and Neill’s Physiology of Reproduction).

A piRNA pathway primed by individual transposons is linked to de novo DNA methylation in mice[8].(Aravin, 2008)



SINE B1 SINE B2 L1-3′UTR

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WHY BOTHER?

Early results of ENCODE:

“Our genome is simply alive with switches, millions of places that determine whether a gene is switched on or off,” said Ewan Birney, of the European Bioinformatics Institute in Cambridge, who co-ordinated data analysis for the $123m project. “There are more switches than you could believe.”

References:

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