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As time goes by: Evolutive interplay between endogenous retrolements and the KRAB'n'KAP system

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Abstract

Close to 50% of the human genome is derived from endogenous retroelements, which are both formidable evolutionary forces and threats to its integrity. Accordingly, these genetic invaders are subjected to transcriptional repression from the very first days of embryogenesis. Reporting in Nature, Jacobs et al. help us understand the sequence-specificity of this process, by identifying two members of the KRAB-containing zinc finger protein family responsible for silencing particular subsets of L1 and SVA in humans (Jacobs et al., 2014). A ray of light is shed on evolutionary forces that shape the interplay between mobile elements and their hosts.

The corepressor KAP1/TRIM28, acting as a scaffold for heterochromatin- and DNA methylation-inducing factors, plays a central role in the control of many endogenous retroelements (EREs) in human and mouse embryonic stem cells (Rowe et al., 2010; Turelli et al., 2014). However, how this repressor complex is specifically tethered to tens of thousands of these genetic units while sparing the rest of the genome is yet to be formally determined. Prime suspects are members of the KRAB zinc finger (KRAB-ZNF) protein family: their KRAB domain can recruit KAP1, and their long array of zinc fingers is predicted to recognize highly specific DNA targets (Friedman et al., 1996). Moreover, the rapid expansion of the KRAB-ZNF gene family mirrored an increase in the abundance of EREs in tetrapod genomes, a parallel evolution also reflected in the large fraction of both KRAB-ZNFs and EREs that are species-specific (Thomas and Schneider, 2011). However, until now, only ZFP809 and Gm6871, two murine KRAB-ZNFs, had been assigned to particular EREs, the former to a retrovirus (Wolf and Goff, 2009), the latter to an L1 (Castro-Diaz et al., 2014). L1, or LINE, is the only autonomous transposon still active in humans. It displays an interesting pattern of evolution, with at any given time a single L1 lineage amplifying to thousands of copies before its replacement by a new one, likely under selective pressure from host defense mechanisms (Boissinot and Furano, 2001).

Jacobs and colleagues set out a search for KRAB-ZNFs repressing human EREs (Jacobs et al., 2014). They took as starting point a trans-chromosomal mouse embryonic stem cell (mESC) line containing one copy of human chromosome 11. In this cellular environment, they found that a number of EREs present on this human genomic fragment, notably primate-specific SVAs and L1PA elements normally repressed by KAP1 in human embryonic stem cells (hESCs), were now being transcribed. This suggested that transacting repressors specific for these elements were missing from the chimeric mESC. However, the

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plot remained thick, as the human genome encodes for some 350 KRAB-ZNFs. The authors wed out the list of potential candidates by focusing on KRAB-ZNFs that had emerged during evolution after the EREs deregulated in the trans-chromosomal cells and, amongst these primate-specific contenders, zoomed onto 14 that are present at high levels in hESCs. By individually overexpressing each one of them and evaluating the resulting shut down of SVA or L1PA elements in the trans-chromosomal context or via a reporter gene system, they identified ZNF91 and ZNF93 as the sequence-specific DNA-binding proteins respectively responsible for repressing these two ERE subfamilies.

The authors then reconstructed the evolutionary history of these two human KRAB-ZNFs, tracing back their probable ancestors in the primate lineage. From there, they identified mutations and structural alterations in the zinc finger arrays that likely led to the specific recognition of their current ERE targets. In the case of ZNF91, the changes involved the duplication of 6 consecutive zinc fingers that improved recognition of SVA elements. This is particularly noteworthy, as the region targeted by the KRAB/KAP1 complex in this ERE is the variable number tandem repeats (VNTR) region, which is itself highly repetitive in nature. As for ZNF93, a deletion of several zinc fingers along with a few point mutations allowed the protein to recognize members of the L1PA family. Intriguingly, L1PA descendants contain a 129 bp deletion covering the ZNF93 target sequence, highly suggestive of a path to escape the restriction imposed by this repressor. Was the loss of zinc fingers in the ancestor of ZNF93 itself the response to a corresponding deletion in the 5’ UTR of a previously repressed L1, which the ERE subsequently countered with an even larger deletion?

One thing is certain: the dynamics of KRAB-ZNFs and EREs reflect the interplay of two powerful and opposing forces. This is supported by another study recently published in Genes and Development (Castro-Diaz et al., 2014). By examining the early embryonic silencing of L1, it revealed that the KRAB/KAP1 system is responsible for repressing a temporally discrete subset of L1 in both human and mouse ESC. The KRAB/KAP1-controlled human L1 elements are predicted to have entered the ancestral genome between 26.8 and 7.6 million years ago. Younger lineages, including the vast majority of human-specific L1 (L1Hs), are untouched by this process and instead become activated when DNA methylation is prevented. Together with recent evidence demonstrating that the PIWI-piRNA pathway regulates L1Hs in hESC (Marchetto et al., 2013), these data support a model whereby newly emerged L1 lineages are first suppressed by partly self-imposed, DNA methylation-inducing small RNA-based mechanisms, before KAP1-recruiting protein repressors are selected and take over. Then, with time, mutations accumulate in the oldest L1s, which inactivates their genome-disrupting potential and ultimately alleviates the need for their control.

Is then the KRAB/KAP1 system simply a slowly evolving second line of defense against endogenous retroelements? We do not think so, because EREs keep being repressed long after losing their retrotransposition potential through mutations. However, as the chromatin marks deposited by KAP1 and cofactors can spread over tens of kilobases, ERE-nucleated repression can keep influencing the expression of nearby genes. A point illustrated by Jacobs and colleagues for ZNF91-targeted SVAs, in line with observations made previously for this

and other classes of retroelements (Kunarso et al., 2010; Rowe et al., 2013; Turelli et al., 2014). Coupled with the cell-type specific expression of many KRAB-ZNFs, this strongly suggests that the recognition of EREs by the KRAB/KAP1 system provides a platform for context-specific regulation in time and space, be it during development or in the setting of other physiological processes.

Evidence such as the high number of species-specific KRAB-ZNFs expressed in the human brain (Nowick et al., 2009), an organ where ERE activity can be detected (Muotri et al., 2005), suggests a prominent role for the KRAB/KAP1-ERE interplay in speciation. This hints at the following evolutionary compromise. On the one hand, there is the need to limit the retrotransposition of EREs in order to prevent genomic catastrophes. On the other hand, there is the potential benefit of a low level of de novo integration, which creates genetic diversity hence provides ground for evolution (recent estimates suggest that the genome of one in every fifty newborn babies carries a new ERE integrant). One could thus sketch a scenario whereby the genome is taming EREs progressively, initially allowing the rare seeding of new loci by retrotransposons that, over time, can either be eliminated by mutations or recombination, or become coopted as platforms to modulate gene regulatory networks. Therefore, it is not just an escalating arms race that we are witnessing, but rather the subtle domestication of EREs by their hosts for adaptive purposes.

With so much insight gained from the analysis of two relatively young human KRAB-ZNFs, one might only get excited at the prospect of uncovering the immense amount of untapped knowledge in the remaining 348 members of the family, old and new. Only then will one be able to appreciate the full complexity of the KRAB'n'KAP system and of its dynamic evolution since it first emerged in our ancestral genome, some 350 million years ago.

You must remember this…

The fundamental things apply

As time goes by.

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