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As Time Goes by: KRABs Evolve to KAP Endogenous Retroelements

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Retroelements, constituting about 50% of the human genome, both contribute to its evolution and threaten its integrity and are thus silenced during development. Jacobs et al. (2014) identify sequence-specific KRAB-ZNF proteins that repress subsets of L1 and SVA retrotransposons in humans, highlighting the evolutionary interplay between retroelements and their hosts.

The corepressor KAP1/TRIM28 plays a central role in the control of many endogenous retroelements (EREs) in human and mouse embryonic stem cells, acting as a scaffold for heterochromatin- and DNA methylation-inducing factors (Rowe et al., 2010; Turelli et al., 2014). How the KAP1 complex is tethered to tens of thousands of diverse genetic units is unclear, but KAP1 is known to be recruited to DNA by KRAB zinc finger (KRAB-ZNF) proteins, which harbor a long array of zinc fingers potentially capable of recognizing polynucleotide chains in a highly sequence-specific manner (Friedman et al., 1996). Moreover, the rapid expansion of the KRAB-ZNF gene family, which counts some 350 members in humans, mirrored an increase in the abundance of EREs in tetrapod genomes. However, until now, only ZFP809 and Gm6871, two murine KRAB-ZNFs, have been assigned to particular EREs, the former to a retrovirus (Wolf and Goff, 2009), the latter to a LINE1 (Castro-Diaz et al., 2014). LINE1, or L1, is the only autonomous transposon still active in humans. It displays an interesting pattern of evolution: at any given time, a single L1 lineage can amplify to thousands of copies before being replaced by a new one, likely under selective pressure from host defense mechanisms (Boissinot and Furano, 2001). Jacobs et al. (2014), in a recent report in *Nature*, identify specific and rapidly evolving KRAB-ZNFs responsible for silencing particular subsets of L1 and SVA retrotransposons in humans.

Jacobs and colleagues (2014) set out a search for KRAB-ZNFs repressing human EREs by utilizing a *trans*-chromosomal mouse embryonic stem cell (mESC) line that contained one copy of human chromosome 11. In this cellular environment, they found that a number of EREs present on this human genomic fragment, notably the primate-specific SVAs and L1PA subset of LINE1 elements, which are normally repressed by KAP1 in human embryonic stem cells (hESCs), were transcribed. Because KAP1 is abundant in mESCs, this suggested that KAP1-recruiting proteins targeting these transposons were absent from the chimeric cell line. The authors hypothesized that these missing factors were KRAB-ZNFs that had emerged during evolution after the EREs found to be deregulated in the *trans*-chromosomal cells had invaded the primate genome. They focused on 14 such proteins highly transcribed in hESCs, and, by individually overexpressing each one of them and evaluating the resulting repression of SVA or L1PA elements in the *trans*-chromosomal mESC or via a reporter gene system, they identified ZNF91 and ZNF93 as respective repressors of 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. They identified mutations and structural alterations in the KRAB 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 six consecutive zinc fingers, which improved recognition of SVA elements. The authors further found that deletion of several zinc fingers in ZNF93, along with a few point mutations, allowed the protein to recognize members of the L1PA family. Intriguingly, some L1PA descendants contain a 129 bp deletion encompassing the ZNF93 target sequence, likely the result of selection to escape this repression.

The dynamics of KRAB-ZNFs and EREs reflect the rapid evolution of ERE-repressor mechanisms on the one hand and ERE mutants escaping their inhibition on the other. Illustrating this principle, another recent study from Castro-Diaz et al. (2014) examined the early embryonic silencing of L1 and revealed that the KRAB/KAP1 system is responsible for repressing a temporally discrete subset of these retrotransposons in both human and mouse ESCs. 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 L1 lineages, including the vast majority of human-specific L1 (L1Hs), have escaped KAP1-mediated repression and instead are repressed via mechanisms requiring DNA methylation. Recent evidence has demonstrated that the PIWI-piRNA pathway regulates L1Hs in hESCs (Marchetto et al., 2013), and together these data support a model whereby newly emerged L1 lineages are first suppressed by small RNA-based mechanisms, triggered by the EREs themselves and leading to DNA methylation, before KAP1-recruiting protein repressors evolve to repress them more stably. Then, with time, mutations accumulate in the oldest L1s, which inactivates their genome-disrupting potential and ultimately alleviates the need for their control.

Is the KRAB/KAP1 system simply a slowly evolving second line of defense against endogenous retroelements? This is not likely, as EREs that have lost their retrotransposition potential are still

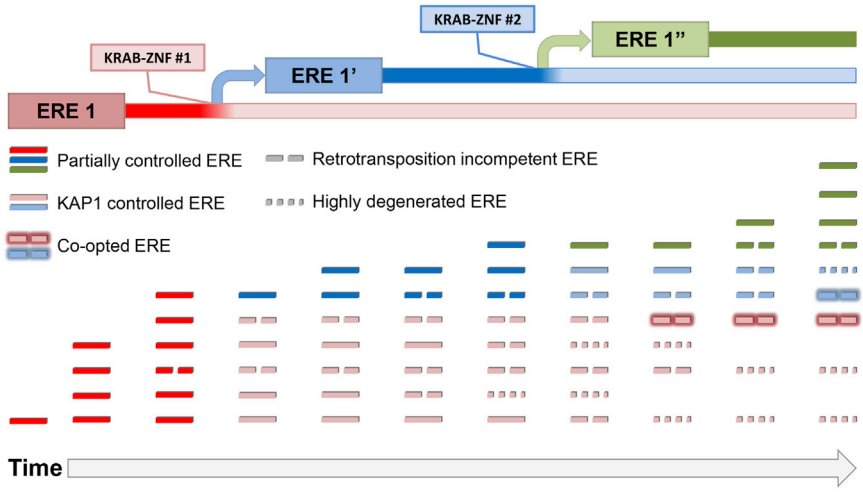

Figure 1. Dynamic Interplay between EREs and the KRAB-KAP System

EREs are initially subject to partial control by mechanisms such as RNA interference, which leave room for some retrotransposition. Over time, a KRAB-ZNF evolves that binds the ERE, leading to its full repression. Rare pre-existing KRAB-ZNF-resistant ERE mutants can then spread through the genome, whereas the previously dominating strain is inhibited. On an evolutionary timescale, old EREs progressively accumulate mutations, which abrogates their retrotransposition potential. Rare integrants undergo positive selection because they fulfill functions beneficial to the host, for instance by providing either promoters or enhancers that rewire transcriptional networks or proteins that take over some physiological role (e.g., the placental syncytin), leading to their cooption and fixation in the genome.

repressed by KAP1-dependent mechanisms. Chromatin marks deposited by KAP1 and cofactors can spread over tens of kilobases and influence the expression of nearby genes. Because many KRAB-ZNFs display cell-type-specific expression, the recognition of EREs by the KRAB/KAP1 system provides a platform for context-specific regulation in time and space, with cooption of particular EREs to serve host functions during development or in the setting of other physiological processes.

The high number of species-specific KRAB-ZNFs expressed in the human brain (Nowick et al., 2009), an organ in which ERE activity can be detected (Muotri et al., 2005), suggests a prominent role for the KRAB/KAP1-ERE interplay in speciation. This hints at an evolutionary compromise in which the need to limit the retrotransposition of EREs, in order to prevent genomic catastrophes, is balanced with the potential benefit of low-level de novo integration, which creates genetic diversity and hence provides ground for evolution (recent estimates suggest that the genome of one in every fifty newborn babies carries a new ERE integrant). Therefore, these studies collectively describe, in addition to an escalating arms race, the gradual domestication of EREs by their hosts for adaptive purposes (Figure 1). With so much insight gained from the analysis of two relatively young human KRAB-ZNFs, uncovering the genomic targets and functions of the remaining 350 or so members of the family, old and new, will surely highlight the full complexity of the KRAB’n’KAP system and its dynamic evolution since it first emerged in our ancestral genome, some 350 million years ago.

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