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Review

TRIM28 and the control of transposable elements in the brain

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ABSTRACT

TRIM28 is an epigenetic co-repressor protein that mediates transcriptional silencing. TRIM28 participates, together with the large family of Kruppel-associated box domain zinc finger proteins (KRAB-ZFP) transcription factors, in the repression of transposable elements (TE). Recent advances indicate that TRIM28-based repression of TEs occurs in the mammalian brain and may provide beneficial effects through the regulation of transcriptional networks. Here, we provide an overview of TRIM28-related functions, highlighting the role of controlling TEs in neural progenitor cells and discuss how this mechanism may have contributed to the evolution of the complex human brain. Finally, we outline future considerations for the field.

Contents

1. Introduction

Human brain development differs markedly from that of other mammals and its developmental complexity is thought to be important for the emergence of higher cognitive functions. How this complexity and cellular diversity is achieved remains largely unknown although increasing evidence point to a role for regulatory elements in this process. TRIM28, an epigenetic co-repressor protein, has recently emerged as an essential factor in brain development with the capacity to establish primate- and human-specific transcriptional networks through the regulation of transposable elements (TEs). In this review, we discuss how TRIM28 together with Kruppel-associated box domain zinc finger proteins (KRAB-ZFPs) mediate repression of TEs and how this may be involved in fine-tuning gene expression in neural progenitor cells during brain development.

2. TRIM28 – A master regulator of transposable elements

TRIM28 (also known as KAP1 and TIF1β) is an enigmatic epigenetic co-repressor protein and is expressed in most cell-types, including a very high expression during early development and in pluripotent stem cells (PSCs) (Cammas et al., 2000; Rowe et al., 2010). Mouse PSCs that lack TRIM28 spontaneously differentiate (Quenneville et al., 2011; Rowe et al., 2010) and the absence of TRIM28 in mice causes embryonic lethality at around embryonic day 5.5 (Cammas et al., 2000). TRIM28 is also highly expressed both in the developing and adult brain (Brattas et al., 2017; Fasching et al., 2015; Jakobsson et al., 2008). We have found that

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homozygote deletion of TRIM28 during embryonic brain development is lethal, while a heterozygous deletion results in animals with behavioural changes characterized by hyperactivity (Fasching et al., 2015). In addition, deletion of TRIM28 in post-mitotic forebrain neurons in mice results in complex behavioural changes (Jakobsson et al., 2008) and heterozygous germ line deletion of TRIM28 has been described to result in abnormal exploratory behaviour (Whitelaw et al., 2010). Together these findings demonstrate that TRIM28 plays an important role both in the developing and the adult brain. Recently, heterozygous TRIM28 insufficiency has been found to result in a bi-stable obesity in mice and humans suggesting that the contribution of TRIM28-haploinsufficy to phenotypes is complicated and subjected to some degree of chance (Dalgaard et al., 2016). It will be very interesting to investigate if also behavioural phenotypes are subjected to the same type of regulation.

TRIM28 acts as a scaffold protein that recruits repressive chromatin modifying factors such as the histone methyltransferase SETDB1 that establishes H3K9me3 (Schultz et al., 2002), the histone deacetylase NuRD complex (Schultz et al., 2001) as well as heterochromatin protein 1 (HP1) (Ryan et al., 1999). This large protein complex efficiently mediates transcriptional repression upon recruitment to specific genomic sites. TRIM28-induced transcriptional silencing is characterised by H3K9me3 and can spread over long genomic distances (Groner et al., 2010), a mechanism most likely propagated by the HP1 proteins. Additionally, histone variant H3.3 has been shown to co-localize with TRIM28 at repetitive elements in embryonic stem cells and contributes to H3K9me3 mediated repression of TEs (Elsässer et al., 2015). During early development, this repression results in the establishment of stable gene silencing that is maintained even if TRIM28-binding is lost (Wiznerowicz et al., 2007).

TRIM28 is a multifunctional protein. For example, TRIM28 has been implicated in the establishment of imprinted genes through ZFP57 (Quenneville et al., 2011) and it also plays an important role in the control of DNA damage where it is rapidly localized to DNA-break foci (Ziv et al., 2006). In addition, TRIM28 is involved in regulating transcription, including polymerase pausing (Bunch et al., 2014). However, the most well studied function of TRIM28 is its role as a master regulator of transposable elements (TEs).

The first realisation that TRIM28 might be involved in the control of TEs came with the observation that TRIM28 played a key role in the restriction of infectious moloney murine leukemia virus in mouse pluripotent stem cells (Wolf et al., 2008; Wolf and Goff, 2007). Subsequent perturbation experiments of TRIM28, as well as the co-factor SETDB1, in mouse PSCs demonstrated that deletion of TRIM28 or SETDB1 resulted in activation of numerous endogenous retroviruses (ERVs) (Matsui et al., 2010; Rowe et al., 2010). Analyses of TRIM28 binding sites, using ChIP-seq, confirmed that TRIM28 binds directly to thousands of ERVs as well as TEs of other families in both mouse and human PSCs (Castro-Diaz et al., 2014; Jacobs et al., 2014; Rowe et al., 2013; Turelli et al., 2014).

Below, we highlight recent advances that start to provide mechanistic insight into how TRIM28 uses TEs in the control of gene regulatory networks in brain development including the establishment of primate-specific networks. We also point out key questions that the field needs to address in the next few years.

3. Transposable elements in the human genome

As much as 50% of the human genome is derived from TEs (Jern and Coffin, 2008), which can be compared to protein-coding sequences that only make up 2% (Fig. 1). The vast majority of TEs in the human genome are retroelements, which include ERVs, long interspersed nuclear elements (LINE), short interspersed nuclear elements (SINE) and the composite SINE-VNTR-Alu (SVA) elements. They can spread in the genome through a copy and paste mechanism (Fig. 1), called transposition, resulting in at least 4.5 million individual copies of retroelements throughout the human genome, including both fragments and full-length elements. This figure is, however, likely to be an underestimation since more ancient TEs have degenerated with time making their identification and classification impossible (de Koning et al., 2011).

On one hand, TEs pose a threat to genomic integrity as their activation may result in transposition events that upon integration in the genome might result in deleterious mutations. The host has therefore evolved numerous mechanisms to prevent transposition to occur. On the other hand, TEs have the potential to be exapted and provide benefit for the host in a number of ways. Already in the 50' s and 60' s it was recognised that TEs are genetic elements that have the potential to alter the genetic landscape and influence gene expression when they integrate into new sites of their host genome (McClintock, 1950; Britten and Davidson, 1969).

Today, it is becoming increasingly clear that TEs act as important gene regulatory elements. For instance, TEs bring binding sites for transcription factors that may impact on nearby gene expression, including the TE acting as either an alternative promoter, enhancer or another regulatory element (reviewed in Chuong et al., 2017; Friedli and Trono, 2015). Furthermore, there is evidence pointing to a role of certain TEs in maintaining or establishing genome architecture (Cournac et al., 2016). TEs can also serve as a source of regulatory non-coding RNAs, including both miRNAs and lncRNAs (Lu et al., 2014; Spengler et al., 2014). In addition, a number of TE-derived proteins have been co-opted, best illustrated by the ERV-derived Syncytins, which play a key role in the placenta across mammals (Dupressoir et al., 2009, 2011; Mi et al., 2000). Thus, there is abundant evidence that TEs impact on host genomes and that they may have played a key role in human evolution.

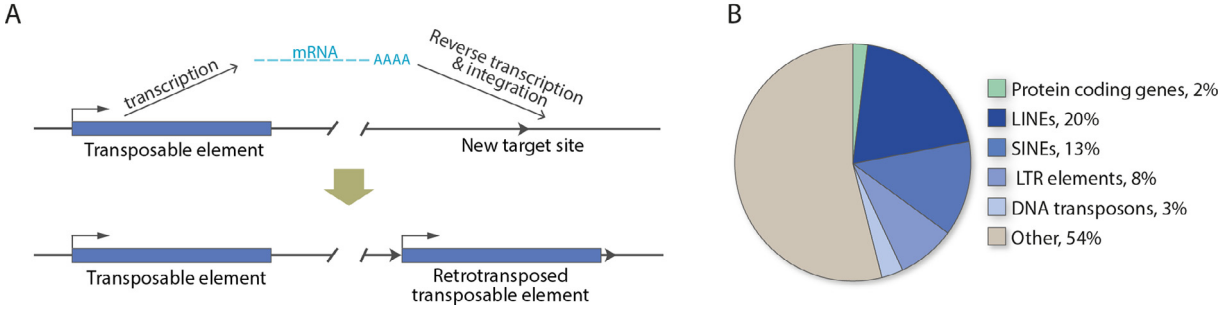

Fig. 1. (A) Schematic drawing of a retrotransposition event. A transcript originating from a transposable element is first reverse-transcribed and then integrated into a different site of the genome of the same cell. By re-entering the genome, TEs will disrupt the sequence of the genome and potentially cause harmful (or beneficial) mutations. (B) Composition of the human genome, including the contribution of transposable elements.

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Since TEs are inserted into random genomic positions during evolution, there are major differences in the genomic composition of TEs between different species. For example, many TEs in the human genome are human-specific and therefore potentially contribute to species-specific gene regulatory networks. Thus, it is tempting to speculate that TEs have contributed to the evolution of primates and humans, including the emergence of the complex primate brain.

Interestingly, several studies also link transcriptional activation of TEs to specific brain disorders including ALS, Rett syndrome and schizophrenia (Karlsson et al., 2001; Li et al., 2015; Muotri et al., 2010). How TEs contribute to human brain disorders remains disputed but one interesting possibility is that these elements may serve an important role as regulatory elements in the brain and their dysregulation may impact on this process.

4. KRAB-ZFPs – TRIM28 interacting transcription factors that recognize TEs

The localisation of TRIM28 to TEs depends on the genomic recruitment by KRAB-ZFPs. The human genome encodes for around 350 KRAB-ZFPs (Imbeault et al., 2017), making it the largest family of transcription factors in the human genome. These genes emerged around 400 million years ago and have undergone a rapid evolution in the primate linage resulting in several human-specific KRAB-ZFPs (Imbeault et al., 2017; Nowick et al., 2010). The zinc finger protein domain dictates the DNA-binding properties, whereas the KRAB domain mediates recruitment of TRIM28. With few exceptions, the KRAB-domain is a potent transcriptional repressor that blocks the activity of PolII and PolIII promoters as well as enhancers (Szulc et al., 2006; Thakore et al., 2015). This has led to the use of KRAB domains in several engineered repressor proteins, including dCas9-KRAB fusions (Gilbert et al., 2013).

Two large-scale DNA-binding experiments have revealed that about two thirds of the KRAB-ZFPs bind directly and specifically to different TE-derived sequences, including ERVs, LINE-1, SINEs and SVA (Imbeault et al., 2017; Najafabadi et al., 2015). The TE-binding KRAB-ZFPs are the evolutionary youngest members of this gene family, while more ancient KRAB-ZFPs appear to have taken on other roles and do no longer recruit TRIM28. It has been challenging to probe the functional role of the TE-binding KRAB-ZFPs and this field is really in its infancy. However, the perhaps best example of a KRAB-ZFP that controls TEs is ZFP809, which has been demonstrated to bind and repress the ERV-like VL30 elements *in vivo* in the mouse (Wolf et al., 2015).

A recent study suggested that there is an on-going "arms-race" between KRAB-ZFPs and TEs in the human genome (Jacobs et al., 2014). According to this model, KRAB-ZFPs would evolve to bind specific TEs and silence their activity. With time, TEs would then mutate the ZFP binding site and regain activity, as the KRAB-ZFP repressive activity is lost. The KRAB-ZFP would further re-evolve to silence the TE. Thus, suggesting that there is a dynamic competition between KRAB-ZFPs and TEs that drive their evolution. The effects of the "arms-race" activity is demonstrated by ZNF93, which binds to primate-specific LINE-1 elements but has lost the ability to bind to human specific L1s (Jacobs et al., 2014). However, the hypothesis of an arms-race model as the sole explanation of KRAB-ZFP gene selection has recently been challenged since many of the KRAB-ZFPs appear to have evolved to target ancient families of TEs that lost the transposition activity long ago (Imbeault et al., 2017). Instead, the KRAB-ZFP mediated regulation of transposable elements may contribute with additional layers of gene regulatory effects, such as controlling the expression of nearby genes (Imbeault et al., 2017; Ecco et al., 2016). With this in mind, the evolution of KRAB-ZFPs may have been driven not only to avoid potential transposition events, but also to provide gene regulation through the binding of TEs.

5. TRIM28/KRAB-ZFPs binds to TEs in neural progenitor cells

At the time of discovery of TRIM28 and KRAB-ZFP mediated silencing of TEs, this mechanism was initially believed to be specific to PSCs having germ cell competence. The repression of TEs was thought to constitute an innate immune response to prevent the activation of TEs during the genome-wide DNA-demethylation occurring in early development. Upon differentiation, TE silencing was then stabilized by DNA methylation and TRIM28-binding would no longer be required for TE silencing. In contrast to this hypothesis, we found that when TRIM28 is deleted in mouse neural progenitor cells (NPCs), a somatic cell type that has undergone DNA re-methylation, we found that ERVs and other TEs were transcriptionally activated (Fasching et al., 2015). In subsequent experiments performed in human NPCs, we similarly found that TRIM28 binds to TEs and establish H3K9me3 at these loci (Brattas et al., 2017). Results from other labs also show that TRIM28 and KRAB-ZFPs bind and establish H3K9me3 at TEs in other somatic tissues in both mouse and human cells (Ecco et al., 2016; Turelli et al., 2014).

An interesting aspect of TRIM28 binding to TEs is that the H3K9me3 mark can spread to the surrounding genome (Groner et al., 2010). This suggests that TRIM28-bound TEs have the capacity to serve as "hubs" that mediate chromatin remodelling resulting in transcriptional silencing of adjacent genes. In line with this, we found that knockdown of TRIM28 in human NPCs resulted in an up-regulated expression of protein-coding genes located in near proximity of TRIM28-bound TEs. Thus, there is a striking correlation between upregulation of TE-expression and activation of nearby genes (Brattas et al., 2017; Fasching et al., 2015), indicating

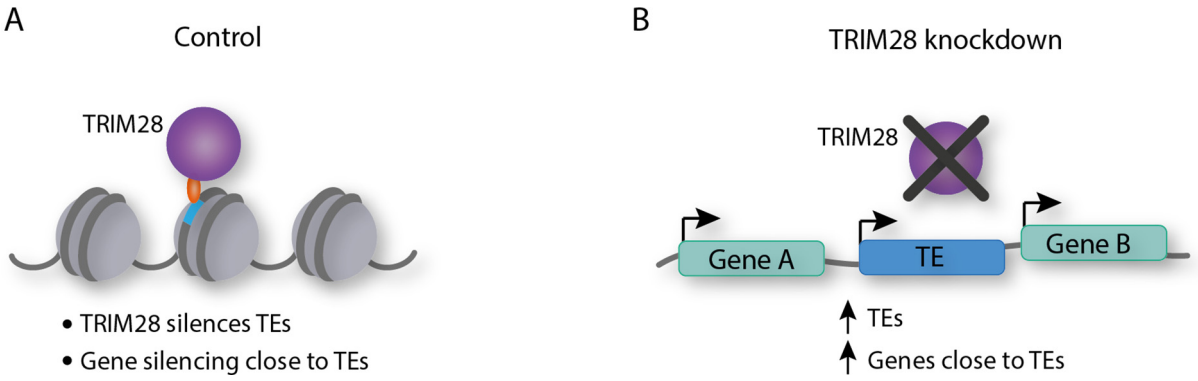

Fig. 2. Schematic model of TRIM28-mediated repression of TEs and nearby genes.

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that TEs can influence the expression of protein coding genes (Fig. 2). Similar effects after TRIM28 knockout/knockdown have been observed also in PSCs and in other differentiated tissues (Ecco et al., 2016; Jacobs et al., 2014; Rowe et al., 2013; Turelli et al., 2014; Wolf et al., 2015). It thus appears that the loss of TRIM28-binding is accompanied with a loss of H3K9me3, which may then be replaced by enhancer or promoter marks (Rowe et al., 2013; Turelli et al., 2014). The findings that TRIM28 binds to thousands of TEs in NPCs and influence nearby gene expression implicates this network in the establishment of species-specific transcriptional regulation, since the setup of both KRAB-ZFPs and TEs are highly divergent across species.

With this in mind, it is also worth noting that KRAB-ZFPs are dynamically expressed in all human tissues and are highly expressed in the brain, suggesting an important role for KRAB-ZFP-TE networks in brain function and development (Imbeault et al., 2017). Interestingly, primate-specific KRAB-ZNFs are enriched among transcription factors with altered expression between the human and chimpanzee prefrontal cortex and appear to be at key positions in a regulatory network of the human prefrontal cortex (Nowick et al., 2009), making it tempting to speculate on the role of KRAB-ZFP-TE networks in the speciation of humans.

6. Concluding remarks

Our knowledge about TRIM28 and KRAB-ZFP so far indicate that they play an important role in the developing as well as the adult brain, and animal studies suggest that this network influence behaviours linked to psychiatric disorders. However, it is necessary to point out that a shortcoming of many of the TRIM28-studies is that they do not discriminate between TE and non-TE related functions of TRIM28, making it difficult to attribute the observed phenotypes to TE-dysregulation. In addition, the underlying reasons for why TRIM28 binds TEs and deposit heterochromatin in NPCs remain unresolved but most likely include several parallel mechanisms. First, TRIM28 binding may serve a restrictive role in preventing transposition events. In both the mouse and human brain it has been reported that LINE-1 elements are capable of transposing (Coufal et al., 2009; Erwin et al., 2016; Evrony et al., 2015; Muotri et al., 2005; Upton et al., 2015), but it remains unknown if TRIM28 is involved in repressing this process as no studies have investigated the effects of loss of TRIM28 on L1 transposition activity in NPCs. Second, TRIM28 may bind to TEs in order to prevent aberrant enhancer activity from these elements hereby balancing out species differences in TE composition (Hummel et al., 2017). Direct comparative studies between closely related species would be necessary to resolve this issue. Third, TRIM28 binding to TEs may infer genome stability by limiting recombination between TEs. Finally, and perhaps the most exciting possibility, is the finding that deletion of TRIM28 impacts on nearby gene expression. This has led to the speculation that TRIM28 mediated control of TEs contributes with beneficial effects to the host transcriptional network. According to this model, TE sequences have been domesticated and now play an important role in fine-tuning transcriptional levels of numerous protein coding genes. Considering the fact that hundreds of KRAB-ZFPs are expressed in the brain that in turn bind to thousands of TEs, it is likely that many protein coding genes are under the influence of a TRIM28-TE network. This is a very attractive hypothesis since TEs are very suitable to drive evolution and the presence of many primate- and human specific TEs may then implicate these elements in the evolution of the complex primate brain.

We favour a model where all these mechanisms are at play at once. However, the experimental data that support these mechanisms is still sparse. For example, despite the growing number of studies demonstrating that TRIM28 bound TEs influence nearby gene expression, there is yet no data demonstrating that this is beneficial to the host. Future studies of TRIM28/KRAB-ZFP controlled regulation in the brain need to resolve the underlying mechanisms, in other words, they should determine if TE-regulation contributes to host fitness and if dysregulation of these networks contribute to human brain disorders. Addressing these questions will likely provide evidence that TEs play a key role in the control of transcriptional networks in both the healthy and diseased brain.

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