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Review

Retrotransposons and piRNA: The missing link in central nervous system

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ABSTRACT

From times when the whole genome were not available to the present explosion of genome knowledge, the biology of non-coding RNA molecules are an unknown ocean of gems. One among them are PIWI-interacting RNAs (piRNAs) that restrict the mobility of various retrotransposons. PIWI proteins and piRNAs once thought to be germline specific was now explored to be expressed in different somatic cells. Emerging proofs of piRNAs from central nervous system has raised serious questions regarding the role of retrotransposons and its silencing mechanism. In this review, we have focused on the existing knowledge of retrotransposons and piRNAs in the central nervous system and have provided future insights. Meta-analysis of retrotransposons in various mammalian genomes and piRNA targets showcased the abundance of LINE transposon and the possibility of piRNA mediated retrotransposon expression. Thus, understanding the retrotransposons-piRNA pathway will provide a new vision for the study of development, physiology and pathology of the central nervous system.

1. Introduction

Higher eukaryotic genomes are large repositories of transposable elements, known as jumping genes or transposons. These repetitive regions are also sources of various endogenous small non-coding transcripts that regulate gene expression, both at the transcriptional and post transcriptional events. Several milestones have been achieved in studying the role of non-protein-coding genes and their corresponding translation products. Whereas, the role of jumping genes and its regulatory networks still remain unexplored due to lack of in-depth knowledge. Among those innumerable questions that surround transposons, the most imperative are: (1) what are these jumping genes and what do they do in our genome? (2) What decide these transcripts to retrotranspose and where does these element land? It is not that all transpositions result in ruinous effects. These transposons drive the evolution of genomes by expediting the translocation of genomic sequences, the shuffling of exons and the repair of double-stranded disruptions (Mülhardt et al., 1994; Takahara et al., 1996; Morgante et al., 2005).

Central nervous system (CNS) is not an exception for retrotransposition due to its random evolution to sustain memory formation (Muotri et al., 2005). Continuous variations in the genetic expression of CNS make every individual unique. While there are several remarkable discoveries in protein-coding RNAs, proving the variability and mosaicism of the human brain, it is still insufficient to understand the mechanisms behind its development and pathophysiology. Studies on transposons has also added its credential to this basic phenomenon. Retrotransposon are altered in a variety of neurodegenerative diseases, suggesting that misregulation of transposable elements can be detrimental (Coufal et al., 2009; Muotri et al., 2009). Activation of transposable element with disease may contribute to neuronal decline (Li et al., 2013). Regulation of these retrotransposons are sustained through various intrinsic factors, including small non-coding RNAs (sncRNAs).

Ground-breaking studies from Lee et al. (2011), Dharap et al. (2011) and Rajasethupathy et al. (2012) has added a new member called PIWI-interacting RNAs (piRNAs) that regulate retrotransposons in the CNS. Investigation of piRNA in the CNS has demonstrated several interesting and novel mechanistic insights into the world of non-coding RNAs. This has also probed our group to investigate the presence of piRNA in the heart during various patho-physiological conditions. Although, there are several independent reviews focusing the mechanism and biogenesis of piRNA and retrotransposons, in this review we provide a comprehensive analysis of the known facts and meta-analysis of retrotransposons and piRNAs in the CNS.

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2. Retrotransposons in mammals

The mammalian genome is richly occupied by mobile elements which accounts nearly 45% of the sequence content. Barbara McClintock was awarded the Nobel Prize for Physiology or Medicine in the year 1983 for her epoch-making discovery of transposable elements (TEs) formed as part of the eukaryotic evolution. Transposons are broadly classified into class-I retrotransposons and class-II DNA transposons. Though, DNA transposons are also known to cause genomic variations (Feschotte and Pritham, 2007), this review intends to discuss about the more active retrotransposons. Retrotransposons utilize a copy–paste mechanism to integrate into random genomic locations, thereby altering the chromatin structure and nearby gene expression (Lerman et al., 1983; Skowronski and Singer 1985; Kazazian et al., 1988).

Retrotransposons are broadly classified into long terminal repeat (LTR) and non-LTR retrotransposons. LTR retrotransposons are similar to retroviral in structure and mechanism (Boeke and Stoye, 1997). Non-LTR retrotransposons are devoid of LTRs and instead take on the likeness of an integrated mRNA. These are prehistoric genetic elements that have persisted in mammalian genomes for millions of years (Eickbush and Malik, 2002), highly alive and active in the human genome. It is generally hypothesized that the modern day retroviruses, LTR retrotransposons and non-LTR retrotransposons share a common ancestor. Retrotransposons were primarily known to be active only in the germline, but recent evidences from various groups have shown the expression of the retrotransposons in somatic cells (Kubo et al., 2006) including the CNS (Muotri et al., 2005; Coufal et al., 2009).

3. LTR retrotransposons

The LTR autonomous retrotransposons are among the most abundant (~9%) constituents of mammalian genomes. The LTR retrotransposons contain genes encoding both structural and enzymatic proteins (Fig. 1a). The LTR *gag* encodes structural proteins that form the virus-like particle (VLP), in which reverse transcription takes place. The LTR *pol* encodes a protease that cleaves the Pol polyprotein, a reverse transcriptase that copies the retrotransposon's RNA into cDNA and an integrase that integrates the cDNA into the genome (Voytas and Boeke, 2002; Sandmeyer et al., 2002). RNA polymerase II from a promoter located within the 5′ LTR is utilized to transcribe the LTR. Classically, two RNA molecules are packaged into one virus like particle and the RNA is subsequently made into a full length DNA copy through a reverse transcription reaction. This process is first primed from a tRNA that pairs to a sequence near 5′ LTR and the resulting partial cDNA is relocated from 5′ LTR to 3′ LTR, where reverse transcription proceeds. A second priming event initiates at a polypurine tract near the 3′ LTR. This cDNA primed from the polypurine tract undergoes an additional strand transfer, resulting in double-stranded cDNA molecule. Later, this cDNA is integrated back into the host genome. One of the main differences between retrotransposons and infectious retrovirus is the presence of an envelope (*env*) gene in retrovirus, which allows them to infect another cell. Retrotransposons have an extra ORF in the same position as the *env* found in retroviral genomes (Leblanc et al., 2000; Pelisson et al., 2002).

4. Non-LTR retrotransposons

Non-LTR retrotransposons are ancient genetic elements that have persisted in eukaryotic genomes and take on the likeness of an integrated mRNA. These elements are best known for their enormous success of multiplication in the human genome (Eickbush and Malik, 2002). Non-LTR transposons can be broadly classified as: autonomous non-LTR (long interspersed nuclear elements (LINEs) and non-autonomous LTR (short interspersed nuclear elements (SINEs)). LINE-1 (L1) elements occupy the major constituent of LINE in mammalian genome. The human genome is estimated to contain 80–100 retrotransposition – competent L1 (RC-L1) and ~10% of these elements are classified as highly active (Brouha et al., 2003). By comparison, the mouse genome is estimated to contain at least 3000 active L1s (DeBerardinis et al., 1998; Goodier et al., 2001). A retrotransposition-competent L1 element of 6.1 kb contains: (1) 5′-UTR region with an internal, CpG-rich promoter, (2) *ORF1* (~1-kb) encoding a protein of

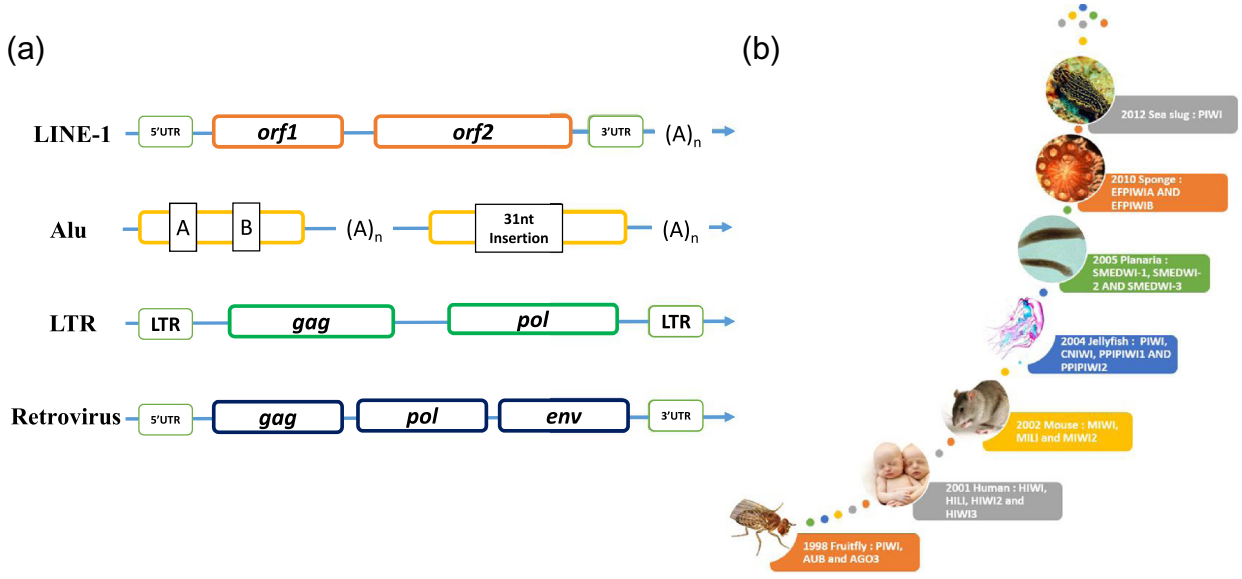

Fig. 1. Schematic representation for the characteristics of transposons and for the discovery of PIWI protein. (a) LINE-1 and LTR are autonomous retrotransposons capable of copy-paste mechanism to retrotranspose and integrate into the genome. Alu elements are non-autonomous retrotransposons utilizing the proteins encoded by LINE transposons. (b) PIWI protein were first reported in Fruitfly (Cox et al., 1998), Human (Sharma et al., 2001), Mouse (Deng and Lin, 2002), Jellyfish (Denker et al., 2008), Planaria (Reddien et al., 2005), Zebrafish (Houwing et al., 2007), Sponge (Funayama et al., 2010), Sea squirt (Rinkevich et al., 2010), *C. elegans* (Lee et al., 2012) and Sea slug (Rajasethupathy et al., 2012).