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Review

Nomadic genetic elements contribute to oncogenic translocations: Implications in carcinogenesis

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ABSTRACT

Chromosomal translocations as molecular signatures have been reported in various malignancies but, the mechanism behind which is largely unknown. Swapping of chromosomal fragments occurs by induction of double strand breaks (DSBs), most of which were initially assumed *de novo*. However, decoding of human genome proved that transposable elements (TE) might have profound influence on genome integrity. TEs are highly conserved mobile genetic elements that generate DSBs, subsequently resulting in large chromosomal rearrangements. Previously TE insertions were thought to be harmless, but recently gains attention due to the origin of spectrum of post-insertional genomic alterations and subsequent transcriptional alterations leading to development of deleterious effects mainly carcinogenesis. Though the existing knowledge on the cancer-associated TE dynamics is very primitive, exploration of underlying mechanism promises better therapeutic strategies for cancer. Thus, this review focuses on the prevalence of TE in the genome, associated genomic instability upon transposition activation and impact on tumorigenesis.

1. Introduction

Genetic rearrangements have been widely reported as the primary cause of various malignancies, the mechanism behind still remains largely unknown (Nambiar and Raghavan, 2011). The draft of human genome revealed that more than 98% of the DNA consisted of repeat sequences and designated as “junk” due

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their unknown biological function until recently. However, recent research has been focused on functional analysis of these intergenic repeat regions. Interestingly, some of these repeat sequences have the ability to move around and incorporate into any part of the genome and were termed as transposable elements (TEs) (Biemont and Vieira, 2006). Mobilization of TEs causes reshuffling of sequences, genetic rearrangements, gene structure modification and alterations in the gene expressions (Nguyen et al., 2006; Sin et al., 2006). Thus, TEs also forms the basis of genesis of structural variations leading to inter-individual variability and initiator of some severe diseases (Redon et al., 2006; Iafrate et al., 2004; Kidd et al., 2008; O'Donnell and Burns, 2010). Comparative genomic studies have shown that TEs share an evolutionary significance and around 10,000 TEs specific to human have been inserted within the past 6 million years (Ahmed and Liang, 2012). Structural rearrangements at the microscopic levels resulting in genomic instability are the main reason for most of the diseases including cancers, apart from its evolutionary significance (Lengauer et al., 1998; Belancio et al., 2008, 2010).

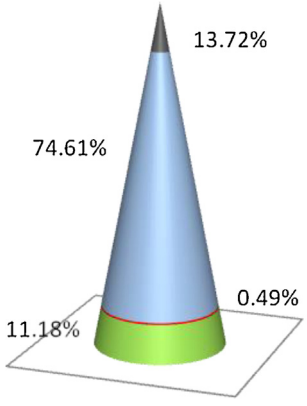
Theory of McClintok on mobile genetic regions as controlling elements (Kazazian et al., 1988) and identification of disruption of factor VIII gene in Hemophilia due to the insertion of long interspersed elements opened up way for the search of such elements that control the stability and functionality of the genes in the human genome (Kazazian et al., 1988). Since then, several studies have been carried out to understand the complexity of the human genome. However, we are yet to completely understand the long-lasting problem of TE associated genomic instability and the consequent development of diseases, especially cancer (Cordaux and Batzer, 2009). TE induced strand breaks, translocation, recombination, insertional mutagenesis still remains a puzzle whose latent regulatory potential upon analysis, would unfold several important mechanisms in maintaining genome stability (Ward et al., 2013; Rebollo et al., 2012). The ENCODE research consortium aims to uncover non-coding functional elements of the human genome (Yavartanoo and Choi, 2013). As we are heading towards next generation sequencing (Keane et al., 2013), it is essential to critically focus on the strategic insertion of these mobile repeat sequences, double strand breaks and the tightly regulated repair system of the genome to channelize better methods targeting TE-associated genomic instability to treat cancers- associated. Thus, this review aims in critically analyzing the frequency of TEs in the genome, mobility activation and consequent insertion into new regions creating double strand breaks (DSBs), possible implications of TE mediated genomic instability and carcinogenesis. In addition, application of these signatory TEs as a marker to detect cancer staging has also been discussed.

2. Nomadic genetic elements

Human transposable elements comprise of both DNA and RNA transposon families and are classified based on their mode of amplification as Class I and Class II. In Class II or DNA transposons, a portion of the DNA itself acts as the template for transposition following "excision-reinsertion" method or the rolling-circle method (Levin and Moran, 2011). The DNA transposons identified in the human genome include Mariner/TC1 super family (mariner, Hsmar-1), hAT superfamily (MER-1-Charlie, SPIN), piggyback, constructed transposons (*Sleeping beauty*) (Saha et al., 2012; Woodard et al., 2012; Goodwin et al., 2010; Maiti et al., 2013) (Fig. 1). There is not much evidence showing DNA transposons' involvement in disease development suggesting that they would have been ceased as evidenced by evolutionary studies (Kines and Belancio, 2012).

Class I or RNA Transposons, also known as retrotransposons are the highly active TE in the human genome. Unlike class II, retrotransposons amplify from DNA using RNA intermediate and have been shown to be associated with the origin of several cancers [reviewed in (Benoît, 2013)]. They are sub-divided into those having Long Terminal Repeats (LTR) and non-LTR elements. The LTRs include the human endogenous retroviruses (HERVs) resembling retroviruses in their organization and functioning (Maksakova et al., 2006). The human genome mainly consists of non-LTRs such as long interspersed elements (LINEs), *i.e.* LINE-1 (L1), LINE-2 and LINE-3, Short Interspersed Elements-SINEs (*Alu*) and SVAs [hybrid of SINE-R-VNTR (Variable Number Tandem Repeats)-*Alu* elements]. Out of the vastly distributed LINEs, L1 is the most common and constitute to 17% of the genome (Belancio et al., 2008; Batzer and Deininger, 2002; Ovchinnikov et al., 2001). L1 is autonomous in activity with 2 open reading frames of which ORF2 is essential for *Alu* retrotransposition (Dewannieux et al., 2003). It has been found that not all L1 are transpositionally competent and only 80–100 retrotransposition competent L1 are present in the human genome causing bulk insertions (Brouha et al., 2003) (Fig. 2).

The non-autonomous, actively retrotransposing non-LTRS are *Alu* and SVA. About 13% of TEs is constituted by the Short Interspersed Elements (SINEs) which have only one active member in it-*Alu* comprising 11%. *Alu* is found to be responsible for several diseases such as breast cancer and MLL where BRCA1 and BRCA2 are sites of *Alu* insertion and tandem duplication of a part of *Mll* gene occurs due to ectopic recombination of flanking *Alu* (Miki et al., 1996a; Teugels et al., 2005). Recently, it has been shown that *Alu*-related transcript of TPJ2 gene in colorectal cancer was differentially expressed in normal cells compared to cancer cells proving as a good marker for detection (Kim et al., 2013) and is also proved to have a regulatory effect on mRNA expression (Liang and Yeh,



DNA Transposons (%)	
MER1	58.79
MER2	23.06
Mariner	4.49
Others	13.66

LINEs (%)	
L1	99.57
Others	0.43

LTR Retrotransposons (%)	
MALR	62.91
ERV1	21.29
ERVL	12.29
Others	3.72

SINEs (%)	
AluS	59.71
AluJ	16.31
AluY	14.91
Others	9.07

Fig. 1. TE Distribution. Pictorial representation of TE distribution (in percentages) in the genes and within their neighborhood. Percentages based on the data available in (Miki et al., 1992)MER—Medium Reiterated frequency sequence, ERVE—Endogenous Retrovirus.

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