Review Article

Alu Mobile Elements: From Junk DNA to Genomic Gems

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Alus, the short interspersed repeated sequences (SINEs), are retrotransposons that litter the human genomes and have long been considered junk DNA. However, recent findings that these mobile elements are transcribed, both as distinct RNA polymerase III transcripts and as a part of RNA polymerase II transcripts, suggest biological functions and refute the notion that Alus are biologically unimportant. Indeed, Alu RNAs have been shown to control mRNA processing at several levels, to have complex regulatory functions such as transcriptional repression and modulating alternative splicing and to cause a host of human genetic diseases. Alu RNAs embedded in Pol II transcripts can promote evolution and proteome diversity, which further indicates that these mobile retroelements are in fact genomic gems rather than genomic junks.

1. Introduction

Alu repeat elements are the most abundant interspersed repeats in the human genome. They are a family of short interspersed nuclear elements (SINEs) that use the reverse transcriptase and nuclease encoded by long interspersed nuclear elements (LINEs) to integrate into the host genome [1–3] and are found in the human genome in a number of ~1,100,000 copies, covering ~10% of its total length [4]. Functioning as transacting regulators of gene expression, pol III transcribed Alu and B1/2 (Alu-like elements in mouse) RNAs can interact with pol II and repress mRNA transcription [5–7]. Inverted Alu repeats are target for A-to-I editing by adenosine deaminases (ADARs) and can cause alternative splicing and drive proteome diversity [8]. Beside its role in human genomic evolution and diversity, Alu insertions and Alu-mediated unequal recombination contribute to a significant proportion of human genetic diseases [9]. Alu RNAs can also induce age-related macular degeneration following direct cytotoxicity to retinal pigment epithelium (RPE) cells [10].

In this brief paper, the author will describe the structure of human (Alu) and murine (B1, B2, B4, and B4) retroelements, a broad overview of the contribution of Alu retrotransposition to human diseases, and finally describe in depth a novel role of double-stranded Alu RNAs affecting the progression of age-related macular degeneration (AMD) and Alu editing by ADARs.

2. Structure of Alu and Murine Mobile Elements

Alu typical sequences are ~300 nucleotides long and are classified into subfamilies according to their relative ages (for review see [11]). They have a dimeric structure and are composed of two similar but distinct monomers: left and right arms of 100 and 200 nucleotides long, respectively, held together by an A-rich linker and terminated by a short poly(A) tail (Figure 1(a)). Each of the Alu subunits originated from 5′ and 3′ terminal segments of 7 SL RNA [12–14]. Alu sequences contain internal Pol III promoter elements (Box A and Box B) and they are CG and CpG rich [11]. Alu subunits fold independently and conserve secondary structure motifs of their progenitor 7 SL RNA (Figure 1(b)). They were initially considered as selfish entities propagating in the host genome as “junk DNA” [15]. Now, it becomes more and more evident that the evolution of Alu subfamilies interacts in a complex way with other aspects of the whole genomic dynamics. Alu elements are specific to primates [11] and only one type of SINE in the human genome. The mouse genome contains four distinct SINE families: B1, B2, ID, and B4. B1 and B2 elements occupy approximately 5% of the mouse genome.
with about 550,000 and 350,000 copies, respectively [16]. Similar to Alu, B1 SINEs are also thought to be derived from 7SL RNA and transcribed by pol III into ~135 nucleotide B1 RNA, which approximates the left arm of Alu [17] (Figure 1(c)). B1 SINEs are monomers with an internal 29 nucleotide duplication [18]. Like the B1 element, B2 is transcribed by the polymerase III promoter sequence. Unlike B1, it shares significant homology at the 5' end with tRNA, and they are believed to be derived from tRNA [19] and encode the ~200 nucleotide B2 RNA (Figure 1(c)) [20]. ID repeat elements are believed to be derived from a neuronally expressed BC1 gene, and they are 69 nucleotides long and are small in number about 42,200 copies; however, they have major presence in the rat genome [21]. The B4 repeat element appears to be a
Several genetic disorders can result from different types of mutations that arise following the insertion of an Alu retroelement. The human genome project hg18 identified 584 human reference-specific Alu insertions [43]. Alu insertion can influence the genome stability, and it accounts for 0.1% of all human genetic disorders [9] such as hereditary desmoid disease [50], cystic fibrosis [51], Dent’s disease [52, 53], X-linked agammaglobulinemia [54–57], hemophilia A and B [58–60], autoimmune lymphoproliferative syndrome [61], Apert syndrome [62], neurofibromatosis type I [63], benign isolated glycogen kinase deficiency [64], hyper IgM with immunodeficiency syndrome [65], Menkes disease [66], Alstom syndrome [67], retinitis pigmentosa [68], acholinoesterasemia [69], autosomal dominant optic atrophy [70], hemolytic anemia [24], autosomal branchio-oto-renal syndrome [71], acute intermittent porphyria [72], mucolipidosis II [73], and several types of cancer [23, 74–77] to cite a few. There are several mechanisms by which Alu can alter genomic structure. In addition to the potential impact of Alu retroelement insertions in causing human diseases, their broad dispersion throughout the genome provides opportunity for unequal homologous recombination and cross-over. Recombination between Alu retroelements on the same chromosome results in either duplication or deletion of the sequences between the Alus. When the recombination occurs on different chromosomes, it leads to chromosomal translocations or rearrangements. Several human diseases have been reported to be associated with Alu recombination events such as Gaucher’s disease [78], hypercholesterolemia [79–82], chronic granulomatous disease [83], α-thalassemia [84, 85], diabetes [86], thrombophilia [87], hypobetalipoproteinemia [88], and spastic paraplegia type 11 [89].

The vast majority of Alu insertions that have led to human disease insert into coding exons, near the promoter/enhancer regions, or into introns relatively near an exon. Alu insertions contribute to disease by either altering the transcription of a gene by affecting its promoter (changing the methylation status or introducing an additional regulatory sequence) or disrupting a coding region, or disrupting the splicing of a gene. These mechanisms have been intensively discussed previously, and the reader is directed to several elegant reviews [11, 90–92]. Although Alu elements are broadly spread throughout the human genome, some genes, chromosomes, and regions seem to be more prone to disease-causing insertions than others.

5. Alu RNA Accumulation Induces Age-Related Macular Degeneration (AMD)

Alu RNA expression and accumulation, rather than retrotransposition, insertion, or recombination per se, has been recently shown to be involved in the advanced “dry” age-related macular degeneration disease [10], the leading cause of blindness in elderly worldwide [10, 93]. This atrophic form, geographic atrophy (GA), involves alterations of pigment distribution, loss of RPE cells and photoreceptors and diminished retinal function due to an overall atrophy of the cells [94]. All studies confirm the strong age dependence of the disease, which likely arises from a complex interaction of metabolic, functional, genetic, and environmental factors [95–97]. Although the molecular mechanisms underpinning this disease are not completely understood, there is intriguing
evidence that exogenous double-stranded RNA (dsRNA) can activate toll-like receptor-3- (TLR3-) mediated inflammatory and chemokine protein secretion and -induced RPE cell death [98–100]. TLR3 knockout mice are protected against RPE degeneration induced by exogenous dsRNAs [100]. The phenomenon observed in mouse model for AMD has led to the hypothesis that the activation of TLR3 by endogenous dsRNAs may cause AMD in humans. Kaneko and coworkers [10] detected abundant dsRNA immunoreactivity in the RPE from diseased but not normal human eyes. Sequence-independent amplification of these immunoprecipitated and isolated dsRNAs showed amplicons belongs to the Alu Sq subfamily (GenBank accession nos. HN176584 and HN176585). It has become clear that bidirectional transcription and dsRNA formation are more prevalent than had been previously thought [101–103]. Alus are capable of folding back to generate hairpin structures. Two close (< 2 kb) Alu elements in opposite orientation might base pair leading to the formation of a long stable dsRNA and becoming a major target for adenosine deaminase acting on RNA (ADARs) A-to-I editing [104]. Although the precise role of RNA editing is still speculative, it might influence the stability of dsRNA and its nuclear retention [105–107]. Alu RNAs seem to be free and nonembedded polymerase III transcripts [10] and were accumulated mainly in the cytoplasm of RPE cells indicating that they might escape ADARs editing and nuclear retention. However, there are no available data, to the best of our knowledge, concerning ADARs and paraspeckle-associated complex activity in the RPE from GA compared to normal eye, and this area will undoubtedly need further investigations. Once in the cytoplasm, Alus should be cleaved by DICER1 since they have been shown to be substrates for DICER1. The RNase DICER1, micro RNA- (miRNA-) processing key enzyme, has been shown to be dramatically downregulated in the RPE from GA compared to normal eye which explains the accumulation of Alu RNAs [10]. Interestingly, DICER1 which is also expressed in the nucleus of RPE cells and its function (whether dicing Alu or not) as well as its nuclear expression levels in GA compared to normal eye are still unknown. In parallel experiment in mice, loss of Dicer1 induced B1/B2 (Alu-like elements) accumulation and RPE cell degeneration. Alternatively, this leads to additional biological questions such as in normal conditions where DICER1 is fully functional, what are the Alu- (or B1/B2-) cleaved products? How long are they? And what is (are) their biological function(s)?

Unexpectedly and in contrast to exogenous dsRNAs, Alus induced RPE cell death independently of miRNA and TLR3 as well as a variety of other TLRs and RNA sensors [108]. In vivo and in vitro functional studies showed that Alus induced RPE cell death via innate immune sensing pathway and activated NLR family, pyrin domain containing 3 (NLRP3) inflammasome [108]. Activation of the NLRP3 inflammasome triggered activation of caspase-1 and induced maturation of interleukin-18 (IL-18) which in turn activated the myeloid differentiation primary response gene 88 (Myd88) pathway (phosphorylation of interleukin-1 receptor-associated kinase-1 and -4 (IRAK1 and IRAK4)) [108] (Figure 2). The effect of Alu RNA on RPE cell degeneration was mediated also via activation of extracellular signal-regulated kinase (ERK1/2 MAPK [109]; however, the up- and downstream cascades are still unknown and further investigations are warranted. It is conceivable that ERK1/2 activation might be downstream of IL-18 and MyD88 [110–112], and several other potential Alu-mediated signaling pathways might be involved.

6. ADAR Gene Family and Alu RNA Editing

The adenosine deaminases acting on RNA (ADARs) are proteins that bind to double-stranded RNA and cause the modification of adenosine to inosine via a hydrolytic deamination reaction [113]. Editing of RNA from A to I in the coding regions of specific genes can lead to functional alterations of the protein product [114, 115], whereas editing of the noncoding regions may affect splicing, stability, or the translational efficiency of these target mRNAs [116, 117]. The precise role of RNA editing is still speculative, and ADAR may act as an antiviral defense mechanism against dsRNA viruses [118], or antagonize dsRNA subjected to the RNAi-mediated gene silencing pathway [119, 120], and/or against dsRNA formed by Alu repeat elements or by sense and antisense transcripts.

Three ADAR family members have been identified [121–125], and they are conserved in their C-terminal deaminase region as well as in their double-stranded RNA-binding domains. Mammalian ADAR1 and ADAR2 are ubiquitously expressed in many tissues; however, ADAR3 is mainly expressed in the brain [126]. ADAR3 has been shown to contain both single- and double-stranded RNA-binding domains. The dsRBDs of ADARs resemble those of dsRNA-activated protein kinase PKR which is an interferon inducible involved in antiviral mechanisms [127, 128] as well as Drosha and Dicer, key enzymes involved in miRNA biogenesis [129]. The ADAR editing efficiency increases with longer dsRNA [130]. RNA secondary structural features consisting of hairpins containing mismatches, bulges, and loops are edited more selectively than completely base-paired duplex RNA. The editing efficiency depends also on the sequence context of nucleotides surrounding the adenosine moiety to be edited [131]. Intriguingly ADAR3 is not active on the other known substrates of ADAR1/2 or on long dsRNA in vitro. ADARs act as a dimer in mammals, and ADAR1 and 2 do not form heterodimers and must form homodimers to be active [132]; however, ADAR3 does not dimerize which explains its lack of activity. There are two isoforms of ADAR1, the longer ADAR1p150 which is expressed in the cytoplasm and the nucleus and the shorter ADAR1p110 which remains in the nucleus [133]. Both isoforms harbor a nuclear localization signal [134]. Both ADAR1 and ADAR2 are present in the nucleolar compartment and are translocated to the nucleoplasm upon the presence of an active editing substrate [135, 136]. They are upregulated by inflammation and in presence of mRNA rich in inosine [137]. The ADARs proteins as well as their dsRNA substrates that mediate the A-to-I editing are important, and both of them determine what will be the overall effect of RNA editing.
Alus are the major targets of ADAR A-to-I editing [104, 138–141] because they create long hairpin structures for which ADARs can deaminate. A computational analysis showed that 88% of the A-to-I editing events were found to be located in the Alus, even though they only comprise 20% of the total length of transcripts [140], and the editing was found to be the most prevalent in the brain compared to other tissues [139]. One may ask a question whether the Alu hairpin structures upon editing become more stable or unstable (reduced in its double strandness)? Previous studies are inconsistent; Levanon’s and Blow’s groups [139, 141] indicated that the effect of editing is aimed at destabilization of Alu dsRNA; however, Athanasiadis et al. [104] suggested that the overall effect is to stabilize the Alu dsRNA and this area need further investigations. The next question is what are the functional and biological consequences of Alu editing by ADARs? As the authors mentioned previously, Alu editing by ADARs may regulate the transcriptional activities of Alu during cellular stress or affect processing, stability (destability), nuclear retention, and export of Alu RNAs. While there is no direct biochemical evidence for RNAi-mediated chromatin silencing in higher eukaryotes, there is hypothesis that in mammalian cells nuclear dsRNA can induce transcriptional gene silencing associated with DNA methylation [142]. Furthermore, recent studies indicate a direct connection of the involvement of ADARs in the RNAi gene silencing pathway [143].

6.1. Other Cellular Mechanisms That May Deal with Alu dsRNAs. More than twenty proteins harboring dsRNA-binding domains (DRBPs) have been identified, and there are several distinct ways in which dsRNAs might be detected and resolved. The nuclear factors associated with dsRNA (NFAR) [144–147], nuclear members of the DRBPs, may interact with Alu dsRNA, although Alu dsRNAs induce RPE cell degeneration independently of PKR [108] and NFARs are physically associated with PKR, and they may function in PKR-mediated signaling events in the cell [147].
dsRNA may also interact with spermatid perinuclear RNA-binding protein (SPNR) which is expressed in several tissues including testis, ovary, and brain. Although SPNR protein expression is limited to testis, neurological defects in mice lacking SPNR function indicate other roles for SPNR outside spermatogenesis [148]. Alu dsRNA might be degraded by dsRNA-specific nucleases [149] or unwound by dsRNA helicases [150, 151]. The RNA helicase A (RHA) has two DRBPs and binds to dsRNA as well as to ssRNA and ssDNA through a carboxyl-terminal RGG box [152, 153]. Other nuclear members of DRBPs such as the negative regulatory element binding protein (NREBP) [154, 155] and kanadaptin [156, 157] may interact with Alu dsRNA, although their role is still speculative. We have shown that Dicer dysregulation induced Alu accumulation and cytotoxicity in RPE cells, but we cannot rule out a potential involvement of other cytoplasmic members of DRBPs such as protein activator of PKR (PACT) [158] and staufen [159], and further studies are needed to determine whether Alu dsRNA binds to these nuclear and cytoplasmic DRBPs and their biological relevance in normal and diseased eye.

7. Concluding Remarks

Repeat elements are landscape-determining components of our genome, and they are "hot spots" elements that can affect our health through at least two known different mechanisms: (1) self-propagation and retrotransposition and (2) accumulation and cytotoxicity. Still, several questions remain unresolved: why and how Alu RNAs accumulate in the RPE of GA patients? It is possible that chronic stress insults (oxidative stress, heat shock, viral infection, etc.) in combination with increasing age and senescence induce Alu RNA accumulation [160–163]. Another important question is: are Alu RNAs accumulated in other age-related neurodegenerative diseases? However, some studies have suggested that the central nervous system is a privileged environment for transposition. In addition, DICER1 and the fine tuning of the miRNA gene network have been shown to be crucial for neuronal integrity. Indeed, genetic ablation of DICER1 induces neurodegeneration via hyperphosphorylation of tau protein and activation of ERK1/2 [164, 165]. Furthermore, the NALP3 inflammasome has been shown to be involved in Alzheimer's disease (AD) [166]. Altered DICER1 and miRNA regulation have been shown to be involved in other neurodegenerative diseases such as Huntington's [167] and Parkinson's diseases [168]; however, the Alu RNA profiling has not been reported yet.

The new sequencing technologies combined with rigorous functional analyses are available to study the mobiline, and they will certainly yield more valuable insights into both functional properties of the genomic gems and disease pathogenesis.

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