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The role of Alu-derived RNAs in Alzheimer's and other neurodegenerative conditions

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ABSTRACT

Non-coding RNAs have emerged as essential contributors to neuroinflammation. The Alu element is the most abundant potential source of non-coding RNA in the human genome represented by over 1.1 million copies totaling ~10% of the genome's mass. Accumulation of "Alu RNA" was observed in the brains of individuals with dementia and Creutzfeldt-Jakob disease – a degenerative brain disorder. "Alu RNAs" activate inflammatory pathways and apoptosis in the non-neural cells. In particular, the "Alu RNA" cytotoxicity is suggested as a mechanism in retinal pigment epithelium (RPE), a compartment damaged in the process of age-related macular degeneration. In RPE cells, the deficiency of Dicer is reported to lead to an accumulation of P3Alu transcripts, subsequent activation of the ERK1/2 signaling pathway, and the formation of NLRP3 inflammasome. In turn, these events result in RPE cell death by apoptosis. Importantly, RPE cells are of neuroectodermal origin, these cells display more similarity to neurons than to other epithelial cells. Thus, it is plausible that the mechanisms of "Alu RNA" cytotoxicity in brain neurons are similar to that in RPE. We hypothesize that accumulation of polymerase III-transcribed noncoding RNA of Alu (P3Alu) may contribute to both neuroinflammation and neurodegeneration associated with Alzheimer's disease (AD) and other degenerative brain disorders. This hypothesis points toward a novel molecular pathway not previously considered for the treatment of AD.

Introduction

Neuroinflammation is the main cause of the slow and progressive dysfunction, and the loss of connectivity in the central nervous system. It is the primary pathological feature of neurodegenerative conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD), neurotropic viral infections, stroke, paraneoplastic disorders, traumatic brain injury, and multiple sclerosis (MS) [1]. Despite different triggering events, central neurodegeneration is accompanied by chronic immune activation, particularly in microglia [1].

In the United States alone, the prevalence of AD is 5.4 million (1.7%, 44 million worldwide) [2,3], PD – 1.0million (0.31%, 6.3 million worldwide) [4], and MS −0.4 million (0.12%, 2.5 million worldwide) [5]. In 2016, the US economy is estimated to have spent $236B on AD and other dementias [2]. Patients with AD and other dementias comprise 50.4% of nursing home residents, 44.7% of hospice patients, and 39.6% of residential care community residents [6]. AD is ranked as the sixth leading cause of death in the United States [7]. Although amyloid beta peptide (Aβ) is shown to play a role in AD, therapies eliminating Aβ from the brain have unfortunately failed to stop cognitive decline [8].

Recently, the association of several immune responsive genes with AD [9–16] has revived interest in a possible etiological role for inflammation in AD. Neuroinflammation is thought to play a major role in the decline of neuronal function. It has been shown that the synaptic loss in AD is mediated by activated microglia via complement system

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[17], which is normally involved in synaptic pruning [18], but in the state of inflammations, it also eliminates functionally important synapses [19]. The loss of synapses remains the best correlative marker of dementia in AD [20]. In a mouse model of AD, microglia also participates in removing Aβ [17], which is associated with its activation.

The activated microglia secrete cytokines and other inflammatory molecules with neurotoxic properties, which, in turn, further propagate the process of neurodegeneration [21–23]. For example, the levels of interleukin-1β (IL-1β), a critical component of brain neuroinflammation, are increased in the AD brain [24]. This increase is thought to contribute to AD pathology by stimulating the expression of amyloid precursor protein (APP) encoding gene and the hyperphosphorylation of Tau, thus, causing hippocampus-dependent memory impairment [25]. The amounts of another proinflammatory cytokine, interleukin-6 (IL-6), in an AD brain are paralleled by a decrease in the extent of amyloidosis but have no lifelong effect on AD pathogenesis in mice [26,27]. In AD patients, anti-inflammatory therapies with either non-steroid or steroid anti-inflammatory drugs have not consistently provided the expected beneficial effect [28,29]. It is likely that effects of inflammation *per se* could be secondary to that of other pathogenetic processes that directly aid the neurodegeneration and the loss of synapses in AD.

Non-coding RNAs have emerged as essential contributors to neuroinflammation in recent years. Notably, Pol III-transcribed Alu RNAs (P3Alu) have been largely overlooked as possible activators of neuroinflammation.

Most likely, this happened because 1) assaying P3Alu is technically challenging, and 2) its neuroinflammatory role has been overshadowed by the fame of Alu repeat as a selfish jumping gene. Recently, it has been suggested that Alu elements may cause neuroinflammation via the retroposition and the disruption of mitochondrial function [30]. In this manuscript, we will focus on Alu-derived RNAs – P3Alu – and the reports indicating their potential regulatory functions which may contribute to neuroinflammation.

The Alu element is the most abundant Short INterspersed Element (SINE) in the human genome. It is represented by over 1.1 million copies totaling ~10% of the genome's length [31,32]. The sequence of a large fraction of these copies has degenerated with evolution, suggesting that a loss of function has occurred, while another fraction of Alu repeats, commonly associated with upstream regions of mRNA encoding genes, was found to be conserved suggesting a regulatory function [33,34]. Moreover, a genome-wide epigenetic analysis showed that Alu repeats contain epigenetic markers of active enhancers (i.e., H3K4 is monomethylated, while H3K4 trimethylation and H3K27 acetylation are absent) and are able to interact with nearby promoters, implying their role as modulators of gene expression in adjacent genomic areas [34].

Key abbreviations:

P3Alu-Pol III-transcribed Alu RNA
P2Alu-Pol II-transcribed Alu RNA
Alu RNA-transcribed by either or a mix

Differences between Pol II transcripts containing Alu sequences and Pol III-generated Alu transcripts

The Alu element is transcribed by Pol III from its own promoter (P3Alu). However, Alu sequences are frequently found in Pol II transcribed RNAs in particular 3′UTR regions. These two types of Alu transcripts differ structurally and their physiological impact. Only the bona fide Pol-III Alu transcripts contribute to retrotransposition events. Nevertheless, the majority of studies linking Alu expression to various pathophysiological processes do not differentiate between Pol-II or Pol-III derived Alu transcripts. Below we describe these differences, which may become critical for future targeting of Alu-derived transcription in patients with dementia.

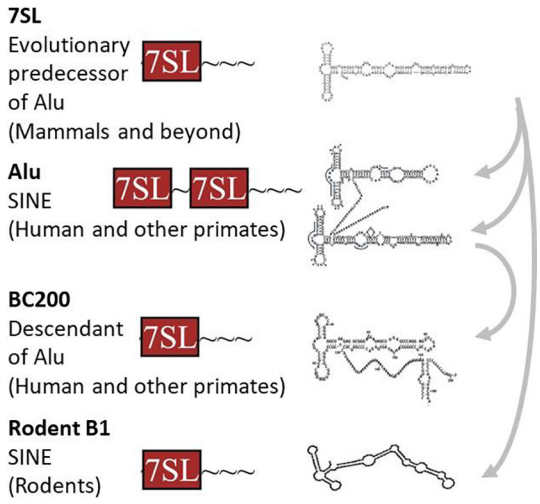

Fig. 1. (ALU). Alu and related RNAs. 7SL is its evolutionary predecessor of several SINEs. Alu is the most abundant Small INterspersed Element (SINE) in humans (~10% of human genome mass). Alu is composed of 2 non-identical 7SL derived sequences. Both BC200 and B1 are also derived from 7SL sequences. BC200 is thought to have similar function in brain as the rodent BC1 SINE.

Alu elements originate from a tandem non-identical dimer of the 5′ portion of the Pol III-transcribed 7SL RNA (Fig. 1 (ALU)). The 7SL RNA forms a Signal Recognition Particle Ribonucleoprotein complex (SRP RNP) thataids in sorting the proteins coming from the ribosomes. P3Alu transcripts are substantially similar to 7SL RNA as they retain the same propeller structure and are able to bind the SRP proteins SRP9 and SRP14, forming an SRP RNP-like complexes [35,36]. These Alu RNPs have been proposed to inhibit polysome formation and both cap-dependent and IRES-mediated translation initiation [37]. P2Alu are mRNAs that retain Alu sequences located in introns or untranslated regions (UTRs). After splicing out, Alu-containing introns remain associated with Alu-binding proteins Dyskerin, Nop10, Nhp2, and Gar1 and Wdr79, thus forming non-SRP-like RNPs, which protect processed P2Alus from degradation and direct them for selective retention in the nucleus [38]. Some of the spliced our Alu-containing introns end up as circular RNAs.

The structures of Pol II and Pol III transcripts differ in several ways (Fig. 2 (DIF)). Pol II transcripts are polyadenylated at their 3′ ends and capped with 7-methylguanosine at their 5′ ends (Fig. 2 (DIF)). This capping happens simultaneously with transcription by Pol II. The cap protects Pol II transcripts from nucleases, and also permits Pol II transcripts to be spliced, transported to the cytoplasm, and translated. Human Pol III transcripts, on the other hand, are neither capped at their 5′ ends, nor polyadenylated at their 3′ ends. Instead, Pol III-transcribed Alu transcripts usually terminate with a uridines (UUUU-OH) at their 3′ ends. Alu RNA fold into a propeller structure similar to 7SL which prompts its association with four SRP proteins (SRP9 and SRP14, two of each), to form a P3Alu RNP and localizes to the cytoplasm.

The impact of P3Alu and P2Alu on cells differs as well. The main role of P3Alu transcripts are to provide the substrate needed for Alu retrotransposition. However, when overexpressed and exported to the cytoplasm, P3Alu transcripts are proposed to interfere with the protein synthesis [37]. The cellular effects of mRNA-like P2Alu transcripts are more diverse; these molecules are reported to be involved in regulation of transcription [39–42] and translation [37,43,44] and participate in activation of inflammation and apoptosis [45–47], two key processes contributing to neural pathology [48,49]. In addition, P2Alus have been implicated in maintaining the nucleolus: inhibition of P2Alus with siRNA leads to the degradation of the nucleolus, while their overexpression increases its size [50].

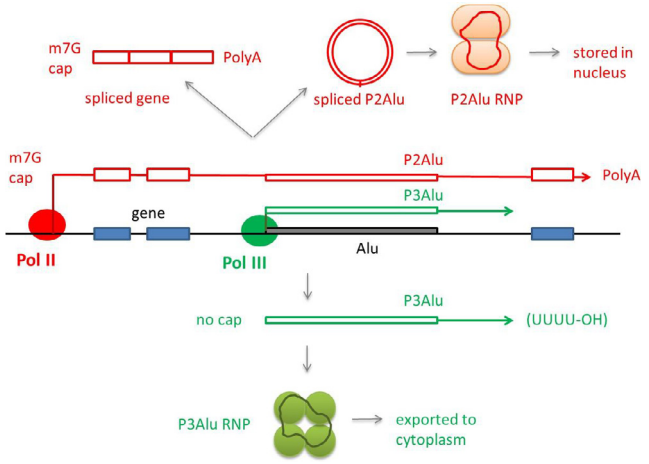

Fig. 2. (DIF) Difference between Pol II and Pol III transcripts of Alu. In red color: P2Alus are Pol II transcribed mRNA that contain Alu sequences, Alu containing introns are spliced out (to from circular RNAs) and are bound by RNP proteins. Some P2Alu-RNP particles are transported to the nucleus for storage. Many mRNAs retain the Alu sequences in their 3′UTRs. In green color: P3Alus are transcribed from their own promoters by Pol III and transcription ends at the genomic flanking sequence when the RNA polymerase encounter the termination signal of at least 4 Ts. Thus, Alu RNAs contain uridines at their 3′ end. SPR proteins bind P3Alu to form an RNP that is transported to the cytoplasm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

"Alu RNA" (P2Alu/P3Alu is undefined) was found to contribute mechanistically to pathology in atherosclerosis [51], macular degeneration [52–54], body muscle development [42] and systemic lupus erythematosus (SLE) – Sjogren's syndrome [46,47]. Elevated expression of unspecified "Alu RNA" was observed in peripheral blood samples collected from sporadic Creutzfeldt-Jakob disease [55] and Alzheimer's disease (AD) [56].

P3Alu in a stress response

Both Alzheimer's disease mouse models and human brain tissue exhibit hallmarks of cellular stress [57,58]. Increase in the levels of SINEs RNAs, of which in human, Alu is the most successful member with over 1 million copies, is a prominent feature of the stress response. In human, rabbit and mouse cells, the levels of SINE-derived transcripts transiently rise after translational inhibition and heat shock treatment [59,60]. Similarly, exposures to hyperthermic shock or a sublethal dose of ethanol lead to increase in the levels of SINE-derived transcripts from specific loci in somatic as well as germinal tissues of mice [61]. In an essence, SINEs can "*behave like regulated cell stress genes*" [61,62], and transiently activated in course of various cellular stresses [61].

Interestingly, SINE products are reported to mediate disassembly of cytoplasmic stress granules (SGs),pro-survival organelles, formed in the cytoplasm upon cellular stress. SGs prevent apoptosis by sequestering signaling molecules and by reprogramming RNA translation [63,64]. SGs contain non-coding RNAs, 40S ribosomal subunits, translation initiation factors, and a variety of RNA-binding and signaling proteins [65–67]. Neuronal SGs are particularly complex, being enriched in chaperones and autophagy factors [68]. Formation of SGs have been observed in AD, HD, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and spinocerebellar ataxia (SCA) [69], however, their dynamics are disrupted [70–72]. Upon stress, polysomes are disassembled, and their 40S subunits are associated to SRP9/14, then routed to form the SGs. Thus, Alu RNAs, whose levels go up following stress, may compete for SRP9/14 binding and promote disengaging of SPR9/14 from 40S subunits [73]. It is plausible to hypothesize that the abnormal transcription of P3Alu upon stress may aid neurodegeneration by sequestering SRP9/14 and, thus, disturbing the dynamics of SGs.

DICER suppresses endogenous production of cytotoxic Alu RNA

RNA interference (RNAi)-guided regulation of the gene expression by P2Alu RNAs begins with the formation of double stranded Alu RNA (dsRNA) hairpins. Normally, dsRNA of Alu and other endogenous RNA is processed without causing interferon response, while dsRNA of RNA viruses typically trigger cytoplasmic antiviral interferon response [74] leading to apoptosis [75]. Degradation of Alu hairpins is done by two type III RNAses: Drosha and Dicer [76]. In the main RNAi pathway which is involved in posttranscriptional gene silencing, Drosha cleaves dsRNA hairpins in the nucleus during transcription [77]. The resulting dsRNA fragments are transported to the cytoplasm [78] and cleaved by Dicer into shorter dsRNAs forming microRNAs or siRNAs, which together with Argonaute proteins downregulate target mRNAs in the cytoplasm by either degrading them or by inhibiting their translation [76,79,80]. Alternatively, dsRNA may be processed directly in the nucleus by Dicer [81] in a complex with Pol II [76]. Predictably, inactivation of Dicer leads to accumulation of dsRNA and stimulation of the antiviral interferon response pathway, leading to apoptosis [76,52].

Normally, Dicer keeps P2Alu RNAs concentrations at low levels of 100–1000 s of copies per cell. Thus, this enzyme is critical for the suppression of cytotoxic Alu RNA [54,52]. The levels of P2Alu RNA inversely correlate with expression levels of Dicer. Accumulation of P2Alu RNA induces interferon response [76,81], induces the Extracellular signal-Regulated Kinase (ERK1/2) pathway leading to apoptosis [82,83], activates nuclear factor NFκB [84], up-regulates expression and secretion of interleukin-1β [84], activates NLRP3 inflammasome [45,52], and elevates the production of reactive oxygen species (ROS) [84].

The mechanisms of Alu RNA cytotoxicity are well studied in retinal pigment epithelium (RPE) [54]. In these cells, the deficiency of Dicer leads to an accumulation of Alu transcripts and subsequent activation of the ERK1/2 signaling pathway and formation of the NLRP3 inflammasome. In turn, these events result in RPE cell death by apoptosis, causing so-called geographic atrophy (GA) [45,53,54,83]. Importantly, RPE cells are of neuroectodermal origin [85], therefore, they display more similarity to neurons than to other epithelial cells. It is likely that the mechanisms of Alu RNA cytotoxicity in brain neurons are similar to that in RPE. The summary of proposed DICER-associated P3Alu accumulation in cell pathology is shown in Fig. 3 (DICER).

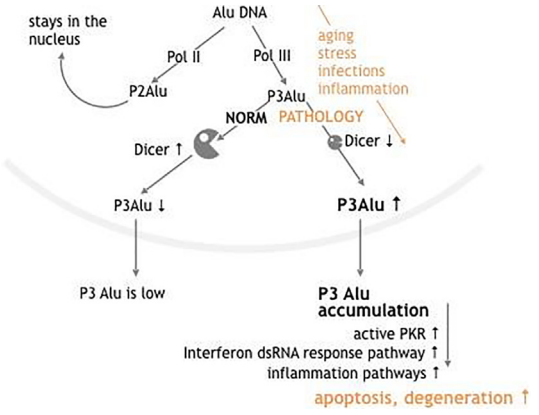

Fig. 3. (DICER) P3Alu transcripts are kept at low levels by DICER activity in the nucleus, however, when DICER activity is disrupted due to stress, the P3Alu transcripts accumulate in the cytoplasm, where they activate interferon dsRNA response and inflammation pathways, leading to cell death via apoptosis. The effect of deregulation of Dicer on P3Alu may be direct or indirect.

Stimulation with retinoic acid induces Pol III-dependent transcription of Alu repeats

Alu repeats contain functional transcription factor binding sites for brain development (PAX4, PAX6, OTX2, NRL, POU3F2, POU3F3), interferon response (IRF1, IRF2, TCF1, TCF2), stress response (SP1, ER, RAR) [86–88], and chromatin remodeling (polycomb factors) [51]. A subset of Alu repeats contains a 6 bp direct binding site for the retinoic acid nuclear receptors (RAR) [87], known as DR2 motif essential for neural specification and homeostasis [89,90]. When activated by retinoic acid binding, RAR induces Pol III-dependent transcription of Alu repeats [91]. Possibly, thus generated P3Alu transcripts are processed in the cytoplasm by DICER RNAseinto Repeat Associated Small Interfering RNA (rasiRNA), which binds to AGO3. These rasiRNA-AGO3 complexes target certain mRNAs for degradation through the recruitment of decapping complex and the digestion by XRN1 exonuclease. Among such P3Alu-targeted transcripts are Nanog and Tdgf1 mRNAs involved in cell differentiation [91]. Interestingly, treatments with retinoic acid (RA) and the synthetic agonists of the RARα signaling pathway prevent the development of AD symptoms, primarily through inhibition of the production of amyloid beta (Aβ) and its fibrils [92,93].

Neurodegeneration via P3Alu-induced inflammasomes

Accumulation of Alu-derived transcripts in Retinal Pigment Epithelium (RPE) and the resultant degeneration of cells through the activation of the NLRP3 inflammasome has been already mentioned above [45,54]. Inflammasomes have been significantly implicated in neurodegenerative disorders [94–96], it is possible that NLRP3 activation and subsequent neurodegeneration are mediated by Alu-derived transcripts, in a manner similar to that demonstrated for RPE.

Notably, recent studies demonstrated that Alu RNAs play an important role in the iron-dependent degeneration of RPE, which also proceed with an aid of NLRP3 inflammasome. Iron induces accumulation of Alu RNAs by sequestering the cofactor poly(C)-binding protein 2 (PCBP2) and the resultant suppression of DICER1 [52]. Iron overload is also a common feature in the pathogenesis of AD, PD, and ALS [97]. In particular, iron overload is observed in senile plaques and neurofibrillary tangles in AD [98,99] and in the substantia nigra in PD [100,101].

The hypothesis

Accumulation of Alu RNA was observed in the brain in dementia [55], AD [55], and a degenerative brain disorder – Creutzfeldt-Jakob disease [56]. In particular, AD cortex shows an upregulation of truncated versions of Alu, known as BC200 [102] and NDM29 [103]. Interestingly, BC200 RNA is transported into neuronal dendrites both in the human brain and in transgenic mice overexpressing respective construct and is capable to form heterodimers with SRP9/14, thus, contributing to the formation of SGs [104,105]. Innon-neural cells, accumulation of Alu-derived transcripts activates inflammatory pathways [45–47], the interferon pathway [106] and apoptosis [54,106]. Therefore, we hypothesize that accumulation of Alutranscripts may play a substantial role in neuroinflammation and neurodegeneration associated with AD.

Support for the hypothesis comes largely from research on the retina. The contribution of Alu transcript accumulation to the retinal degeneration is well substantiated. We argue that since the retina is of the same developmental origin as the neurons, and since the retina and neurons share many common regulatory features, Alu RNAs may play a similar degenerative role in the neurons. Additional supportive evidence comes from data on Alu transcription in brain samples collected from patients with AD-related neurodegenerative disorders as well as the studies performed in non-neural cell types.

The hypothesis outlining involvement of Alu dependent transcription in the processes of neuroinflammation and neurodegeneration points toward a novel molecular pathway not previously considered for the treatment of AD, but highly amenable for modulation. At present, Alu transcription-dependent compensatory responses to stress and genuine toxicity of the Alu-containing transcripts are difficult to disentangle. It is, however, clear that the studies inquiring into mechanistic roles of these transcripts in AD and in the normally functioning neurons are warranted.

Studies needed

Despite the fact that AD brain samples and a variety of neurodegeneration models have been a subject in numerous RNAseq experiments, the expression profiles of the repetitive sequences including Alu have been largely ignored so far. As the transcripts originating within intronic and intergenic repetitive sequences constitute 40–48% of the total brain transcriptome [107], it is important to choose RNAseq chemistry and data analysis pipelines in a way that includes transcripts of repetitive sequences. The way to achieve this is by taking only a cytoplasmic fraction, not selecting for polyA and reading each cDNA from both ends [108]. Therefore it would be prudent to experimentally measure of cytoplasmic P3Alu and P2Alu accumulation in the models of neurodegeneration and in AD brain samples. Finally, the studies of upstream and downstream signaling events would be required, follow the footsteps of similar works done in the retina and non-neural cells.

Potential impact

If the hypothesis of Alu transcripts accumulation is substantiated, it may lead to the development of novel diagnostic assays and preventative and therapeutic approaches. Since P3Aluaccumulation seem to be related to genome destabilization, it is likely that we might find other blood and CSF biomarkers, which would correlate with P3Alu accumulation. If the involvement of genome destabilization in AD is proven, this could stimulate the development of genome-targeted preventative and therapeutic approaches to tackle this condition.

Conflict of interest

None.

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