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Perspective

The *Alu* neurodegeneration hypothesis: A primate-specific mechanism for neuronal transcription noise, mitochondrial dysfunction, and manifestation of neurodegenerative disease

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Abstract It is hypothesized that retrotransposons have played a fundamental role in primate evolution and that enhanced neurologic retrotransposon activity in humans may underlie the origin of higher cognitive function. As a potential consequence of this enhanced activity, it is likely that neurons are susceptible to deleterious retrotransposon pathways that can disrupt mitochondrial function. An example is observed in the *TOMM40* gene, encoding a β-barrel protein critical for mitochondrial preprotein transport. Primate-specific *Alu* retrotransposons have repeatedly inserted into *TOMM40* introns, and at least one variant associated with late-onset Alzheimer's disease originated from an *Alu* insertion event. We provide evidence of enriched *Alu* content in mitochondrial genes and postulate that *Alus* can disrupt mitochondrial populations in neurons, thereby setting the stage for progressive neurologic dysfunction. This *Alu* neurodegeneration hypothesis is compatible with decades of research and offers a plausible mechanism for the disruption of neuronal mitochondrial homeostasis, ultimately cascading into neurodegenerative disease.

Keywords: Alternative splicing; Alzheimer's disease; Epigenetics; H3K9; Inflammation; LINE; Neuroepigenetics; Nonsense-mediated decay; Parkinson's disease; Retrotransposon; SINE; Somatic mutation; Somatic mosaicism; Spliceosome; A-to-I editing

1. Introduction

The molecular mechanisms underlying sporadic neurodegenerative disorders such as late-onset Alzheimer's disease (LOAD) and Parkinson's disease (PD) remain unclear. Although traditional genome-wide association studies (GWASs) have identified numerous candidate genes associated with both LOAD and PD, the explanatory power of these genes is low (approximately 3%–4% per locus in LOAD cases), and effective therapies that disrupt the progression of idiopathic neurodegenerative diseases have yet to be developed [1–4]. Considering this disparity, a growing number of researchers are hypothesizing a link between non-Mendelian mechanisms and sporadic neurodegenerative disease. Functional hypotheses for such mechanisms include epigenetic effects, novel structural variants influencing alternative gene splicing and gene expression, maternal inheritance of mitochondrial DNA mutations, and microbial infection [5–10]. A common thread across decades of sporadic neurodegenerative disease research is the hypothesis that mitochondrial dysfunction contributes to neuron stress and neuron degeneration, ultimately leading to the diseased state [11–19].

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Pathologies associated with age-related neurodegenerative diseases (e.g., senile Aβ plaques, tau aggregates, cerebral atrophy, and age-related cognitive impairment) are not restricted to humans, having been identified in a number of nonhuman primates (e.g., chimpanzee, gorilla, orangutan, rhesus macaque, tamarin, and gray mouse lemur) that collectively span at least 65 million years of primate evolution [20–24]. Of these species, the one that is most distantly related to human, the gray mouse lemur (*Microcebus murinus*), routinely develops age-related pathologies (within captive individuals in established colonies) that are similar to both Alzheimer's disease (AD) and PD [25]. The evolutionary perspective that can be gleaned from the spectrum of ~65 million years of primate evolution is critically important for understanding the origin of neurodegenerative disease in humans.

Despite the fact that primates share similar age-related disease pathologies, the manifestation of devastating human-specific symptoms associated with sporadic neurodegenerative diseases across the global distribution of our species is suggestive of a common neurologic mechanism that evolved in humans [23,24,26,27]. Following this logic, identification of the genetic factors that contribute to sporadic neurodegenerative disease in humans requires an understanding of the origin of primates and the genetic mechanisms underlying the evolution of enhanced neurologic function that separates humans from our closest primate relatives. Therefore, central to this perspective are the following observations: (1) although primates share common age-related neurodegenerative pathologies, humans display a spectrum of neurologic disorders that are uniquely human; (2) a growing body of evidence supports the hypothesis that non-Mendelian mechanisms contribute to the manifestation of neurodegenerative disease; and (3) mitochondrial dysfunction is consistently hypothesized to be associated with sporadic neurodegenerative diseases such as LOAD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS).

Here we propose a hypothesis, informed by primate evolution, for an age-related genetic mechanism that can contribute to tissue-specific mitochondrial dysfunction eventually resulting in neuronal death. It is important to note that our hypothesis centers on molecular mechanisms underlying cellular stress at the very initial stages of neurologic disease, therefore preceding macroscopic pathologies (e.g., pervasive plaque formation) that are frequently diagnostic of the disease state. We begin with the observation that structural variants of primate-specific retrotransposons (*Alu* elements) within the translocase of outer mitochondrial membrane 40 (*TOMM40*) gene are statistically associated with LOAD and that these transposable elements can influence gene function through non-Mendelian pathways. Retrotransposons are mobile elements that can replicate by reverse transcription of an RNA intermediate and then insert themselves into new locations across the genome [28]. Broadly defined, retrotransposons include long terminal repeats, long interspersed elements (LINEs), and short interspersed elements (SINEs). Of these, *Alu* elements are a highly successful primate-specific SINE and *Alus* are the most abundant mobile elements in the human genome having more than a million copies that comprise ~11% of genomic DNA.

Although traditionally viewed as "junk DNA," a number of discoveries have shown that retrotransposons have played a fundamental role in primate evolution, including the evolution of our own species, having contributed to the formation of novel genes and gene transcription networks as well as having a role in human disease [29–35]. Moreover, retrotransposons (including *Alu*) remain active in the human central nervous system throughout life, and it is hypothesized that this activity underlies the origin of higher brain function [32,33,36,37]. We postulate that enhanced somatic retrotransposon activity in human neurologic networks is accompanied by tissue-specific mitochondrial vulnerability that increases with time and/or fluctuating epigenetic landscapes, and can thus be a contributing mechanism to sporadic neurodegeneration. This in turn leads to the specific hypothesis that retrotransposons, operating through primate or human-specific pathways, are a plausible source for environment or age-induced mitochondrial dysfunction that can ultimately contribute to neuron atrophy and death.

2. Mitochondrial integrity and neurodegenerative disease

The human brain has exceptionally high energetic demands, and metabolically active neurons depend on healthy mitochondrial populations for their survival and function. Disrupting mitochondrial homeostasis in neurons can have devastating neurologic consequences, and therefore mitochondrial dysfunction has long been hypothesized to be associated with neurologic diseases (reviewed in [38] and [39]). First proposed in 2004 by Swerdlow and Khan, the "mitochondrial cascade hypothesis" provides the framework by which mitochondrial dysfunction can contribute to the development of sporadic neurodegenerative disease [13]. Although not without controversy, the hypothesis that dysfunctional mitochondria play a role in LOAD, PD, and other neurodegenerative conditions is a consistent theme across decades of research. The mitochondrial genome encodes only 13 proteins, yet mitochondria depend on an estimated 1500 nuclear-encoded proteins for their functionality. Thus, genetic mechanisms that contribute to genomic instability of the nuclear genome, including deleterious retrotransposon-mediated pathways, can directly impact mitochondrial function and contribute to neurologic disease. A clear example involves the relationship between genetic variation of the *TOMM40* gene and neurodegenerative diseases including LOAD, PD, HD, and ALS [40].

2.1. *Insights from* TOMM40

The translocase of the outer membrane (TOM) complex is responsible for importing more than 90% of all preproteins