Dose L1 Retrotransposition Cause Neuronal Loss in Neurodegenerative Disorders?

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Abstract

Neurodegenerative disorders are among debilitating diseases that could affect many aspects of patient's life. Several mechanisms were shown to be involved in neuronal degeneration. However, the direct role of genomic instability is little considered in such disorders. L1 retrotransposons could cause genomic instability in different ways. Studies have shown increasing in L1 retrotransposition due to some reagents like heavy metals, stressors and the ones that may cause neuronal degeneration; Therefore cause cell to die. On the other hand, L1s retrotransposition was shown in neuronal precursor cells (NPCs) providing the first evidence for movement of these elements in nervous system. Here, we propose that stimulation of L1 retrotransposition by environmental and genetic factors in neurons of central nervous system may lead them to apoptosis and result in neurodegenerative disorders. This hypothesis will be verified using L1-RP vector transfecting to definite neuronal cell line. By adding toxic agents including oxidative stress reagents and heavy metals to cell culture, we may track L1 retrotransposition and effects of this movement on cell physiology. Finding the involvement of mechanism in neurodegeneration may result in inventing new drugs for these disorders.

Keywords

L1 retrotransposition, Neurodegenerative disorders, Genomic instability, Apoptosis

Introduction

Neurodegenerative disorders are categorized among main debilitating diseases affecting individuals in different ages depends on its type. The mechanisms involved in generating neurodegenerative disorders are hardly understood. However, neuronal death is defined as a major pathological finding in such disorders (1). Several factors including oxidative stress (2), accumulation of heavy metals, and toxic proteins (1), increasing cytoplasmic calcium ions, glutamate (3), and inflammatory factors (1)...
can cause neuronal death. Among these factors little is known about direct role of genomic instability in neuron degeneration.

Genomic instability or DNA damage due to external and internal factors could threat genomic integrity and cause cell death (4, 5). DNA damage may appear in many different forms; however, one of the main DNA lesions involved in neurodegenerative disorders is DNA double strand breaks (DSBs) (6). In neurons, DNA DSBs could be toxic to the cell due to lack of impressive repair mechanisms of these lesions (7). Studies have shown that repairing mechanisms in neurons are impaired in neurodegenerative disorders (6, 8). Therefore accumulation of DNA lesions such as DSBs and impaired repairing mechanisms in neurons lead them to die and cause neurodegenerative disorders.

One of the intercellular factors resulting in DSBs is LINE-1 retrotransposition (9). On the other hand, L1 retrotransposons have been shown to involve in genomic instability (10, 11).

Human Long Interspersed Nucleotide Element-1 (LINE-1/L1) is non-LTR retrotransposons allocating 17% of human genome. Complete L1 element consists of 5’UTR (including local promoter), ORF1 (encoding RNA binding and chaperone proteins), ORF2 (encoding endonuclease and reverse transcriptase) and 3’UTR (12).

These elements are also called as jumping genes; move naturally in DNA of germ cells (13) as well as somatic (14) and embryonic stem cells (15).

Some transcription factors (16, 17) and environmental agents including stressors and steroid like agents induce L1 retrotransposition through its local promoter in 5’UTR (18, 19). Other studies showed the effects of heavy metals such as nickel in stimulating L1 retrotransposition (20, 21). Stressors and heavy metals are main suspicious agents shown to be involved in Neuronal degeneration.

L1 elements are related to cause some diseases including Duchenne Muscular Dystrophy (22), Hemophilia (23), and Neurofibromatosis (24) through insertional mutagenesis mechanism.

Besides the insertional mutagenesis, L1 retrotranspoision could DSBs (9) and causes ectopic and non-homologous end joining recombination (12). Expression of L1 endonuclease at low level has been shown to create DSBs and cause apoptosis through ATM signaling pathways in germ cells as well as somatic cells (25). Regarding the mode of movement, types of expressed proteins and their nature for increasing recombination in DNA, LINE-1 elements are believed to cause genomic instability (10, 11) and cell death.

Recent studies have revealed occurrence of L1 retrotransposition in neural precursor cells (NPCs) and their possible roles in NPCs differentiation (26), as well as, Neuronal diversification and data storage in the brain (27). Besides, LINE-1 elements have been found to retrotranspose in non-dividing cells (28). Coufal et al. suggested increasing in movement of endogenous L1 elements in human neuronal cells of hippocampus and different rate of L1 retrotransposition in other brain's regions including cerebellum and cerebral cortex (29).

Hypothesis

Collectively our hypothesis is based on 3 evidences: 1- L1 retrotransposition occurred in central nervous system, 2- circumstances stimulating LINE-1 retrotransposition in cells that is resembles to the ones that cause neuronal degeneration and, 3- roles of L1 retrotransposition in generating genomic instability and cell death.

Therefore, we hypothesize that L1 retrotransposition may be increased by factors involved in neurodegeneration (Fig 1). Factors considered in our investigation include some environmental factors such as oxidative stress agents, (heavy) metals and genetic background of individuals. Induction of L1 movement in neurons with impaired repair mechanisms may cause genomic instability and neuron apoptosis (Fig 2.).

Evaluation of the hypothesis

We test our hypothesis using L1-EGFP vector and its mutated form as negative control (25). The cell lines include LN18 (from temporal lobe), IMR32 (Neuroblastoma from brain) and non neuronal but related brain cells such as astrocytoma and glioblastoma. We use also HEK293 cell line as positive control of our study. Firstly, we try to transfer the vector to definite cell lines. After 2-8 days of transfection, L1 vector can integrate itself to the genome. This integration can be confirmed by shining GFP from vector. These permanently transfected cells enable us to track LINE-1 integrated retroelements in the genome. By adding (heavy) metals and oxidative stress reagents with different concentration and time of action to our cell cultures, we can both track L1 movements rate and the effect of this movement on cells. Measurements of neurodegenerative effects of L1 movement induced by toxic agents will be done through quantifying of cell apoptosis with molecular and cellular procedures.

Discussion

Our knowledge on the mechanisms involved in neurodegenerative disorders is mainly confined to deadly effects of environmental and internal stressing factors that are resulting in neuronal apoptosis (1-3). These factors ultimately cause genomic instability and neuronal loss (2, 4). However, one of the other causes of genomic instability in all mammalian genome is movement of L1 retrotransposon elements (10, 11). L1 elements reside in the genome million years ago and can move in copy and paste fashion (12) due to their selfish movement, effects
of some agents including heavy metals, and steroid-like factors (18-21). This mode of movement can cause DSBs therefore more L1 retrotransposition may cause more DSBs resulting in genomic instability and apoptosis (9). Regarding our current data which is traced L1 retrotransposition in central nervous system (26, 29), we hypothesized those environmental factors causing neurodegeneration may be involved in increasing L1 retrotransposition in neurons and result in neuronal loss.

The result of this investigation could pave the way to uncover one of the mechanisms that may involve in neuronal loss in different neurodegenerative disorders and their management.

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Overview Box

First Question: What do we already know about the subject?
Answer: Movement of L1 retrotansposons causes genomic instability. Some external and internal factors and stressing agents result in increased in L1 retrotransposition and apoptosis in non-neuronal cell lines. These factors shown to have effects in neurodegenerative disorders. L1 elements can move in neurons and neuroblasts.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?
Answer: Many mechanisms have been proposed to cause neuronal loss in neurodegenerative disorders, but the exact mechanisms is hardly understood. The data of our hypothesis could uncover one of the ultimate mechanisms involved in neuronal apoptosis and pave the way to provide new drugs to prevent and decreasing the progression of neurodegenerative disorders.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?
Answer: We propose performing further experiments on L1 transgenic mice or other animal models and fibroblasts of neurodegenerative disorders patients.

Figure 1. Hypothetical relation between environmental and internal factors in stimulating LINE-1 retrotransposition, genomic instability and neuronal cell death.
Figure 2. Simple algorithm of our hypothesis. Heavy metals and oxidative stress are common causes of both L1 retrotransposition and neurodegenerative disorders. We may see one of these effects of toxic agents on L1 retrotransposition on cell fate. Each fate can have interpretation in our study.

References