Profile and dynamics of LINE-1 RNA and ORF1p expression in the aged and diseased brain

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Abstract

Aging and the dysregulation of transposable elements are two closely linked processes, particularly characterized by the derepression of LINE-1 retrotransposons. On the one hand, aging is marked by LINE-1 derepression, and on the other hand, LINE-1 derepression leads to genomic instabilities, epigenetic alterations and inflammation which are hallmarks of aging and neurodegeneration. LINE-1 activation could therefore be involved in the pathogenesis of age-related neurodegenerative diseases. However, our knowledge of the expression and localization of LINE-1-encoded proteins in the central nervous system is limited. This study investigates, in the mouse and human brain, the expression and interactions of LINE-1 and its encoded protein ORF1p, a chaperone and RNA-binding protein. By establishing a novel approach combining brain mapping with deep-learning algorithms for cell segmentation on large-scale pyramidal images, we characterized ORF1p expression in the murine brain under physiological conditions. ORF1p is expressed in $\approx 20\%$ of murine brain cells and is neuron-specific. In aged mice, ORF1p expression in neurons increased in several brain regions including the midbrain and striatum to up to 30%. The transcriptomic analysis of TE expression in human post-mortem dopaminergic neurons revealed an increase in full-length LINE-1 expression in aged compared to younger neurons. Dysregulation of TE transcripts was also observed in post-mortem tissues from individuals affected by Alzheimer or Parkinson disease compared to controls. In mouse brain and human dopaminergic neurons in culture, ORF1p interacts with proteins related to mRNA splicing, ribosome biogenesis and nuclear proteins involved in nuclear envelope biology and transcription, which were modified during in vitro stress. This work contributes to a better understanding of the extent of ORF1p protein and LINE-1 expression in the brain under pathophysiological and aging conditions, strengthens the hypothesis that LINE-1 activation is linked with brain aging and opens the way to decrypt ORF1p biology.

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