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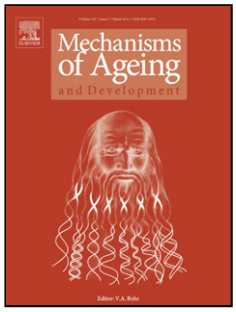

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ACCEPTED MANUSCRIPT

CircRNA accumulation: A new hallmark of aging?

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Highlights

- Circular RNAs (circRNAs) are a newly appreciated class of RNAs that are highly expressed in nervous system tissues
- CircRNAs are globally upregulated during aging in multiple organisms
- CircRNAs might serve as aging and neurodegenerative disease biomarkers
- New methodologies permit the direct interrogation of circRNA function in aging

Abstract

Circular RNAs (circRNAs) are a newly appreciated class of RNAs found across phyla that are generated most commonly from back-splicing of protein-coding exons. Recent profiling of circRNAs genome-wide has shown that hundreds of circRNAs dramatically increase in expression during aging in the brains of multiple organisms. No other class of transcripts has been found to show such a strong correlation with aging as circRNAs—could they be playing a role in the aging process? Here, we discuss the different methods used to profile circRNAs and discuss current limitations of these approaches. We argue that age-related increases in global circRNA levels likely result from their high stability. The functions of circRNAs are only beginning to emerge, and it is an open question whether circRNA accumulation impacts the aging brain. We discuss experimental approaches that could illuminate whether age-accumulation of circRNAs are detrimental or protective to the aging brain.

Abbreviations: circRNA: circular RNA; FACS: Fluorescence-activated cell sorting; FDR: False discovery rate; NGS: Next-generation sequencing; RPAD: RNase R treatment followed by polyadenylation and poly(A)+ RNA depletion; RBP: RNA-binding protein; RCM: Reverse complementary matches

Keywords: circRNA, RNA-Seq, aging, alternative splicing, nervous system

1. Introduction

Aging is characterized by the progressive deterioration of cells, tissues, and organs, ultimately leading to disease or death. Next-generation sequencing (NGS) technologies have enabled the

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