Time Written in RNA: The Epitranscriptomic Code of Ageing

D. Guallar[1*]

[1] *Center for Research in Molecular Medicine and Chronic Diseases (CiMUS). University of Santiago de Compostela. Santiago de Compostela, Spain.*
* diana.guallar@usc.es

Cellular ageing is characterized by a conserved set of molecular, cellular, and systemic alterations, known as the “hallmarks” of ageing. Among these, epigenetic alterations (i.e., DNA methylation and histone modifications) have been widely recognized as central players of the cellular decline resulting from the passage of time. In contrast, the role of RNA methylation, a prevalent epitranscriptomic modification involved in regulation of stability, localization and translation of RNA molecules, in ageing has not been studied in detail. Recent evidence indicates that specific RNA modifications change in an age-dependent manner, and influence pathways connected to ageing hallmarks, suggesting a regulatory role for the epitranscriptome in ageing and age-related pathologies.

Our research explores how one specific RNA modification, 5-methylcytosine (m5C), changes during ageing. Using RNA bisulfite sequencing of primary cells isolated from young and old mice, we have uncovered age-dependent remodelling of m5C across coding and non-coding RNAs. Notably, methylation increases with age at sites within motifs associated with the RNA methyltransferases NSUN2. Experimental modulation of this enzyme can partially restore youthful transcriptomic profiles, underscoring the functional relevance of RNA methylation in cellular homeostasis.

These findings establish m5C as an emerging player in the regulatory networks that drive ageing and adaptation to environmental and metabolic challenges. By revealing how reversible RNA modifications shape the ageing transcriptome, this work opens new perspectives for developing strategies aimed at promoting resilience and healthy ageing.

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