Endogenous Retrovirus-derived RNAs play an essential role during morphogenesis in zebrafish

Ana Ariza-Cosano*[1,2], Pilar G. Marchante*[1,2], Álvaro Méndez-Maguilla*[1], Eva Álvarez Barrero*[1], Francisco J. Sanchez-Luque*[3], Guillermo Peris*[1,4], José Luis García-Pérez*[1], Miguel A. Moreno- Mateos*[5], and Sara R. Heras*[1,2]

[1]GENYO, Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government – PTS Granada, Av. de la Ilustración, 114, 18016, Granada, Spain
[2]Dept. Biochemistry and Molecular Biology II, Faculty of Pharmacy, University of Granada – Campus Universitario de Cartuja, 18071, Granada, Spain
[3]Institute of Parasitology and Biomedicine "López-Neyra (IPBLN), CSIC – P.T. Ciencias de la Salud, Av. del Conocimiento s/n, Armilla, 18100 Granada, Spain
[4]Dept. of Computer Languages and Systems, Universitat Jaume I – Castellón de la Plana, 12071,, Spain
[5]Andalusian Center for developmental Biology (CABD). Pablo de Olavide University, CSIC, Junta de Andalucía – Ctra. Utrera Km.1, 41013 Seville, Spain

Abstract

ERVs have shaped the genomes of vertebrates, however, the extent of their influence on evolution, functionality, and disease remains to be elucidated. Although most ERVs have lost the ability to mobilize, their transcription is tightly regulated from pluripotency to morphogenesis, suggesting a crucial role for these elements. During early embryogenesis, various signaling pathways control gene regulatory networks and play a pivotal role in body plan formation. Using zebrafish as a model, we wondered how these signaling pathways impact ERVs expression during morphogenesis. We analyzed expression data from embryos with perturbed retinoic acid, Wnt, FGF and Nodal signaling pathways during early embryogenesis. We observed that the expression of several ERVs was affected, particularly the ERV1-3 subfamily was upregulated by retinoic acid overexpression and downregulated by Nodal signaling inhibition. These results together with the specific expression pattern suggest that ERV1-3 transcripts might play a role during axis specification. Using CRISPR-RfxCas13d approaches, we demonstrate that several guides targeting different regions of the internal part and the LTRs of ERV1-3 elements reduced its transcription levels and replicated a robust and specific phenotype related to Nodal signaling inhibition. To gain mechanistic insights into which specific ERV-derived RNAs are responsible for this phenotype, we conducted genomic and functional characterizations of this subfamily in addition to a differential expression analysis at locus-specific level. We found that only three full-length ERV1-3 copies exhibited significant downregulation and all of these copies show an enrichment of adaxial and paraxial mesoderm transcription factors binding motifs in their LTRs. Additionally, these copies were characterized by the presence of protease, reverse transcriptase, RNAse-H, and integrase ORFs with varying degrees of completeness. Finally, using one of these copies, we partially rescued the phenotype. Altogether, this study provides insights into the co-option of ERV mRNAs during development and their ability to generate new developmental functions.

*Speaker

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