INSTITUT DE FRANCE
Académie des sciences

Comptes Rendus
Biologies

Germano Cecere

Epigenetic and gene regulatory functions of small RNAs

Published online: 19 December 2023

https://doi.org/10.5802/crbiol.131

Part of Special Issue: A tribute to François Gros, a founding father of molecular biology

Guest editors: Margaret Buckingham (Professeur émérite et directeur honoraire du département Biologie du développement et cellules souches à l'Institut Pasteur - Membre de l'Académie des sciences) and Moshe Yaniv (Professeur honoraire à l'Institut Pasteur - Directeur de recherche émérite au CNRS - Membre de l'Académie des sciences)

Les Comptes Rendus. Biologies *sont membres du Centre Mersenne pour l'édition scientifique ouverte*
www.centre-mersenne.org
e-ISSN : 1768-3238

Comptes Rendus
Biologies
Published online: 19 December 2023
https://doi.org/10.5802/crbiol.131

A tribute to François Gros, a founding father of molecular biology

Epigenetic and gene regulatory functions of small RNAs

Germano Cecere [a]

[a] Department of Developmental and Stem Cell Biology, Institut Pasteur, Université Paris Cité, CNRS UMR3738, Mechanisms of Epigenetic Inheritance, Paris, France
E-mail: germano.cecere@pasteur.fr

Abstract. In this review article, I summarize the intervention I made during the "Hommage à François Gros" held at the Institut Pasteur in Paris on the 25th of April, 2023. I discuss how the discovery of the existence of an RNA intermediate between genetic information and protein translation has changed our perspective on the role of RNA in gene regulation in these past years. I also discuss new emerging paradigms, highlighting the role of RNA in heritable information similar to the well-known DNA function.

Keywords. Epigenetics, Small RNAs, Gene regulation, RNA.

Note. This article follows a symposium held on 25 April 2023 at the Institut Pasteur in tribute to François Gros.

Published online: 19 December 2023

In a seminal review article published in 1961, François Jacob and Jacques Monod introduced a groundbreaking concept: the existence of an intermediary molecule that bridges the gap between protein synthesis and genetic information [1]. Termed the "structural messenger", this hypothetical molecule spurred intense speculation within the scientific community. Within the same year of the review's publication, François Gros, working in collaboration with James Watson's laboratory at Harvard University, embarked on a quest to decipher the elusive mediator connecting genes to ribosomes [2]. Concurrently, Sidney Brenner and François Jacob, in Matthew Meselson's laboratory at Caltech, embarked on a parallel journey [3]. Through rigorous experimentation, both teams converged on a groundbreaking revelation: an RNA molecule, characterized by its instability, emerged as the long-sought intermediary. This pivotal molecule, named messenger RNA (mRNA), served as the conduit through which genetic information was conveyed from DNA to ribosomes for protein synthesis.

This discovery of mRNA heralded a new era in molecular biology and unveiled RNA's multifaceted roles in gene regulation. No longer a passive messenger, RNA emerged as a central player in orchestrating mRNA synthesis and protein production. In 1993, a pivotal discovery occurred in Victor Ambros's laboratory. A gene whose mRNA product produced a novel RNA species measuring about 22 nucleotides, known as microRNA (miRNA), was unveiled [4]. This miRNA possessed the remarkable ability to modulate the protein expression of other genes by base-pairing to the end of target mRNA molecules [4, 5]. Initially discovered in the nematode *Caenorhabditis elegans*, miRNAs were later identified in diverse animal models, including humans [6]. They emerged as global regulators of gene expression

and play vital roles during development and disease progression [7].

Interestingly, the realm of small regulatory RNAs extended beyond the animal kingdom. Viruses that infect animal cells harness the potential of these regulatory mechanisms. Viral miRNAs manipulate the host's miRNA machinery, facilitating viral replication by modulating host gene expression [8]. The COVID-19 pandemic provided a unique context for investigating viral miRNAs in SARS-CoV-2 infection. Our research team revealed the existence of a SARS-CoV-2-derived miRNA that dampened human immune responses by downregulating mRNAs involved in interferon-mediated responses, shedding light on the intricate interplay between viral infection and host defense [9].

Besides their post-transcriptional regulatory function, small RNAs can also control the RNA synthesis of targeted genomic regions in the nucleus. A class of small regulatory RNAs, known as PIWI-interacting RNAs (piRNAs), has emerged as a conserved RNA-based immune system safeguarding the genome's integrity against nucleic acid parasites [10]. Primarily expressed in the animal germline, piRNAs play a central role in controlling invasive genomic elements such as viruses and transposons. Distinctively, piRNAs repress these elements in the nucleus at the chromatin level, underscoring their role as genome guardians. Recent findings from our team unveiled an intriguing dimension of piRNAs—beyond defense. We discovered global transcriptional repression by piRNAs of endogenous transcriptional programs [11]. This repressive function of piRNAs is essential for proper gamete differentiation and function. Thus, piRNAs can also repress endogenous genes during animal development, highlighting their dual role in genome defense and developmental processes.

In retrospect, the journey from the postulated "structural messenger" to the intricate web of small regulatory RNAs exemplifies the evolutionary trajectory of our understanding. From mRNA's pivotal role in gene expression control to the discovery of miRNAs and piRNAs, RNA's versatility and regulatory prowess have come to the fore.

Recent years have witnessed the emergence of a new paradigm—an insight that shatters the boundaries that once constrained RNA's scope. While RNA's renown rests in its role as a messenger that bridges genes to ribosomes, it now claims its place as a cornerstone in the realm of heritable information—akin to the role of DNA. The revelation that small RNAs traverse generations through gametes, imparting hereditary traits, has etched a new trajectory in biology and genetics [12]. Pioneering work in *C. elegans* illuminated how small RNAs can perpetuate gene silencing across generations [13, 14]. Research from our team has also contributed to this notion, revealing the heritable function of small RNAs in embryonic development and animal fertility [15, 16]. These heritable RNAs not only influence trait inheritance but can also shape animal evolution in response to environmental changes. These tantalizing glimpses into RNA's uncharted role as a bearer of heredity underscore the astonishing adaptability inherent within this once-underestimated molecule.

The revelation of heritable RNA has unraveled yet a novel function that RNA holds, promising to reshape our understanding of biology and chart a course for discoveries yet to come.

Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organizations.

References

[1] F. Jacob, J. Monod, "Genetic regulatory mechanisms in the synthesis of proteins", *J. Mol. Biol.* **3** (1961), p. 318-356.

[2] F. Gros, H. Hiatt, W. Gilbert, C. G. Kurland, R. W. Risebrough, J. D. Watson, "Unstable ribonucleic acid revealed by pulse labelling of *Escherichia Coli*", *Nature* **190** (1961), p. 581-585.

[3] S. Brenner, F. Jacob, M. Meselson, "An unstable intermediate carrying information from genes to ribosomes for protein synthesis", *Nature* **190** (1961), p. 576-581.

[4] R. C. Lee, R. L. Feinbaum, V. Ambros, "The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14", *Cell* **75** (1993), p. 843-854.

[5] B. Wightman, I. Ha, G. Ruvkun, "Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans", *Cell* **75** (1993), p. 855-862.

[6] A. E. Pasquinelli, B. J. Reinhart, F. Slack, M. Q. Martindale, M. I. Kuroda, B. Maller, D. C. Hayward, E. E. Ball, B. Degnan, P. Müller, J. Spring, A. Srinivasan, M. Fishman, J. Finnerty, J. Corbo, M. Levine, P. Leahy, E. Davidson, G. Ruvkun, "Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA", *Nature* **408** (2000), p. 86-89.

[7] D. P. Bartel, "Metazoan MicroRNAs", *Cell* **173** (2018), p. 20-51.

[8] S. Pfeffer, M. Zavolan, F. A. Grässer, M. Chien, J. J. Russo, J. Ju, B. John, A. J. Enright, D. Marks, C. Sander, T. Tuschl, "Identification of virus-encoded MicroRNAs", *Science* **304** (2004), p. 734-736.

[9] M. Singh, M. Chazal, P. Quarato, L. Bourdon, C. Malabat, T. Vallet, M. Vignuzzi, S. van der Werf, S. Behillil, F. Donati, N. Sauvonnet, G. Nigro, M. Bourgine, N. Jouvenet, G. Cecere, "A virus-derived microRNA targets immune response genes during SARS-CoV-2 infection", *Embo Rep.* **23** (2022), article no. e54341.

[10] D. M. Ozata, I. Gainetdinov, A. Zoch, D. O'Carroll, P. D. Zamore, "PIWI-interacting RNAs: small RNAs with big functions", *Nat. Rev. Genet.* **20** (2019), p. 89-108.

[11] E. Cornes, L. Bourdon, M. Singh, F. Mueller, P. Quarato, E. Wernersson, M. Bienko, B. Li, G. Cecere, "piRNAs initiate transcriptional silencing of spermatogenic genes during *C. elegans* germline development", *Dev. Cell.* **57** (2022), p. 180-196, e1–e7.

[12] G. Cecere, "Small RNAs in epigenetic inheritance: from mechanisms to trait transmission", *Febs Lett.* **595** (2021), p. 2953-2977.

[13] A. Fire, S. Xu, M. K. Montgomery, S. A. Kostas, S. E. Driver, C. C. Mello, "Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans", *Nature* **391** (1998), p. 806-811.

[14] A. Grishok, H. Tabara, C. C. Mello, "Genetic requirements for inheritance of RNAi in *C. elegans*", *Science* **287** (2000), p. 2494-2497.

[15] P. Quarato, M. Singh, E. Cornes, B. Li, L. Bourdon, F. Mueller, C. Didier, G. Cecere, "Germline inherited small RNAs facilitate the clearance of untranslated maternal mRNAs in *C. elegans* embryos", *Nat. Commun.* **12** (2021), article no. 1441.

[16] G. Barucci, E. Cornes, M. Singh, B. Li, M. Ugolini, A. Samolygo, C. Didier, F. Dingli, D. Loew, P. Quarato, G. Cecere, "Small-RNA-mediated transgenerational silencing of histone genes impairs fertility in piRNA mutants", *Nat. Cell Biol.* **22** (2020), p. 235-245.