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The Deeper Meaning of the 2024 Nobel Prize in Physiology or Medicine

James A. Shapiro

Department of Biochemistry and Molecular Biology, University of Chicago (emeritus), Chicago, Illinois, USA

Correspondence: James A. Shapiro (jsha@uchicago.edu)

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On October 7, 2024, the Nobel Assembly of the Karolinska Institute awarded this year's Nobel Prize in Physiology or Medicine to Victor Ambrose and Gary Ruvkun "for the discovery of microRNA and its role in post-transcriptional gene regulation" (https://www.nobelprize.org/prizes/medicine/2024/press-release/). The prize-winning research was published in back-to-back 1993 papers in *Cell* demonstrating in the nematode worm *C. elegans* that the *lin-4* microRNA regulates the translation and degradation of *lin-14* mRNA post-transcriptionally in the cytoplasm during the transition from the first to the second stage of larval developments by base-pairing to the target mRNA. When Ruvkun and colleagues later identified and characterized the more evolutionarily conserved *let-7* microRNA to play a similar post-transcriptional regulatory role during the transition from late larval to adult stages in animals from mollusks to vertebrates (but not in plants, yeast, bacteria, jellyfish or sponges), the scientific community began to accept microRNAs as part of the canonical developmental regulatory machinery of multicellular organisms [1].

The Nobel committee noted in their 2024 press release, "A new principle of gene regulation, mediated by a previously unknown type of RNA, microRNA, had been discovered." However, at this point, the announcement story becomes somewhat self-contradictory because a different class of microRNAs had already been recognized by a Nobel Prize 18 years earlier. The 2024 release noted:

> "Cellular machinery for producing functional microRNAs is also employed to produce other small RNA molecules in both plants and animals, for example as a means of protecting plants against virus infections. Andrew Z. Fire and Craig C. Mello, awarded the Nobel Prize in 2006, described RNA interference (RNAi), where specific mRNA-molecules are inactivated by adding double-stranded RNA to cells."

In fact, the Nobel committee's detailed scientific explanation of the 2006 prize mentioned the work of Ambrose and Ruvkun as exemplifying the potential of RNAi-like mechanisms, although it turns out that the story is more complex, since post-transcriptional control microRNAs (unlike siRNAs) have only partial sequence complementarity with their target mRNAs and interact with protein cofactors not involved in RNAi (https://www.nobelprize.org/prizes/medicine/2006/advanced-information/).

The Nobel Prize committee seems to be curiously unaware of the fact that the 2006 and 2024 awards are part of a larger scientific movement that is transforming our understanding of genetics: namely, recognition that noncoding ncRNAs play all kinds of roles in the regulation of genome expression and functioning [2]. In complex organisms, these ncRNAs are encoded chiefly in regions of the genome that do not encode proteins. Such regions were previously labeled "junk DNA" [3] or "selfish DNA" [4] by scholars who believed that the unique function of the genome was to encode proteins. In 2006, the Nobel Prize committee wrote,

> "The fundamental principles for the regulation of gene expression were identified more than 40 years ago by the French Nobel Laureates François Jacob and Jacques Monod. Today, we know that similar principles operate throughout evolution, from bacteria to humans (https://www.nobelprize.org/prizes/medicine/2006/summary/)."

In 2024, they wrote in their "advanced Information" about the Prize,

> "Whereas proteins in the nucleus regulate RNA transcription and splicing, microRNAs control the translation and degradation of mRNA in the cytoplasm. This unexpected layer of post-transcriptional gene regulation has critical importance throughout animal development and in adult cell types and is essential for complex multicellular life https://www.nobelprize.org/uploads/2024/10/advanced-medicineprize2024-2.pdfm."

The Nobel Prize committee appears to be reserving the key job of regulating nuclear genome expression to proteins, based on the *lac* operon model of the 1965 Nobel Prize winners, and relegating the regulatory RNA functions to the cytoplasm. But today, we know that it appears there is little to no selfish junk DNA. The mammalian genome is pervasively transcribed [5–7]. ncRNAs play key roles in the nuclear regulation of transcription and post-transcriptional processing of protein-coding pre-mRNA and mRNA molecules [8]. For example, enhancer elements are transcribed into noncoding eRNAs that help establish the proper chromatin configuration for transcription to occur from target promoters [9, 10]. Although most transcripts currently under study for their diverse functionalities are long noncoding RNAs (lncRNAs) and circular RNAs, it was the microRNAs recognized in the 2006 and 2024 Nobel Prizes that led the way in our understanding that RNA molecules could be more than passive intermediates between DNA and protein.

Since the coding regions for many ncRNAs contain repeat copies of abundant mobile genetic elements, including retroviruses and transposons, and the ncRNAs determine so many important phenotypes, such as nervous system development and function [11], we may have to think in new ways about genome evolution in complex multicellular organisms. Transposable element transcripts themselves have important regulatory consequences [12] and their sequences can constitute functional domains for ncRNAs [13, 14]. The evolution of ncRNAs may thus involve the formation of LEGO-like combinations of different repeat and single-copy sequences. It is not difficult to imagine how the insertion of mobile elements into a sequence encoding a regulatory ncRNA can occur physically by transposition or retro-transposition. But mobile repeat elements are the most volatile components in genome evolution [15], and 95% of ncRNAs in mammals are also taxonomically "volatile" [16, 17]. I suggest that this volatility contrasts with the basic maintenance of conserved physiology, morphology, and behavior as new species arise, adapting to our changing environment. How do rapidly changing regulatory ncRNAs affecting virtually every feature of the organism maintain the taxon's basic phenotype, or is their purpose to promote adaptability necessary to sustain life? That question is only one of many that molecular genomics will confront as we enter the new realm of multifunctional RNAs. We can anticipate many more Nobel Prizes for research on RNA coding in the genome, RNA regulation, and RNA evolution.

Author Contributions

James A. Shapiro: Writing–original draft (lead).

Conflicts of Interest

The author declares no conflicts of interest.

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All data are available in the manuscript.

Peer Review

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