Ambros and Ruvkun together sense the antisense

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ABSTRACT

Victor Ambros and Gary Ruvkun were jointly awarded the Nobel Prize in Physiology or Medicine 2024 for discovering microRNAs (miRNAs) and their fundamental role in post-transcriptional gene regulation. The discovery, stemming from studies on heterochronic genes in *Caenorhabditis elegans*, revealed a class of small, non-coding RNA molecules that fine-tune gene expression by cleaving target messenger RNAs (mRNAs) or inhibiting their translation. To understand the importance of their contribution to Physiology or Medicine, the article touched upon the biogenesis and mechanism of action of miRNAs, highlighting their crucial involvement in diverse biological processes, including development, differentiation, and cellular homeostasis. Furthermore, it discusses the implications of miRNA dysregulation in various human diseases, such as cancer, and explores their potential as diagnostic biomarkers and therapeutic targets. The synergistic collaboration between Ambros and Ruvkun, initiated during their postdoctoral fellowships, exemplifies the power of collaborative scientific inquiry and has profoundly impacted our understanding of molecular biology and gene regulation, opening new avenues for future research and medical applications.

Keywords: Nobel prize, 2024, Victor Ambros, Gary Ruvkun, miRNA.

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INTRODUCTION

The Nobel Prize in Physiology or Medicine is awarded annually by the Karolinska Institute in Stockholm, Sweden, to individuals or groups who have made significant contributions to the field of medical science. The highest recognition in Physiology or Medicine inspires and motivates researchers worldwide to pursue innovative and impactful work that benefits humanity. Many laureates have shared the prize with colleagues who contributed to their discoveries, reflecting the importance of teamwork in advancing medical science. Recent awards have acknowledged breakthroughs in genetic research, neuroscience, and immunotherapy; thus, the committee recognizes the evolution and widening of Physiology into the allied sciences through emerging fields and technologies. IJPAS publishes a 'Nobel Accolade' each year to update readers about the latest prize and to show respect to the honorees and the committee. Victor Ambros and Gary Ruvkun share the Nobel Prize in Physiology or Medicine 2024 for their groundbreaking discovery of miRNA and its role in post-transcriptional gene regulation.

By now, miRNA is a known abbreviation for individuals who keep themselves abreast of the happenings in health research. Development biologist Victor Ambros and molecular biologist Gary Ruvkun share the Nobel Prize in Physiology or Medicine 2024 for their groundbreaking discovery of miRNA and its role in post-transcriptional gene regulation. It was 1993 when two articles on the heterochronic genes *lin-4* and *lin-14* of *Caenorhabditis elegans* were published in the 75th volume of 'Cell' back-to-back, nobody would have thought that senior authors of these two articles would jointly bag the Nobel Prize 30 years later. Even though the Ambros-Ruvkun group was not formed by then, they shared their intellect, skills, and data even before publication (as acknowledgments of these publications read), indicating the ontogenesis (if we may say so) of great collaboration that started in the H. Robert Horvitz's laboratory as post-doctoral fellows. The award stands as a testament to the power of collaborative scientific inquiry. Their shared recognition stems from discovering microRNA, small RNA molecules crucial in post-transcriptional gene regulation. This achievement is not merely the result of individual brilliance but also a product of a synergistic collaboration that spanned decades. The foundation of their work was laid in the study of the nematode *C elegans*. With meticulous research, Victor Ambros identified mutations that disrupted the timing of developmental events, known as heterochronic mutations. This led to the identification of the *lin-4* gene. Gary Ruvkun, working in parallel, focused on cloning the *lin-14* gene. Their combined efforts revealed that *lin-4* encoded a small RNA molecule, which was the miRNA, that regulated the expression of the *lin-14* gene.

miRNAs are small, non-coding RNA molecules, typically about 22 nucleotides in length, that play a crucial role in post-transcriptional gene regulation. Since their discovery in the early 1990s, they have emerged as key players in a

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vast array of biological processes, from development and differentiation to disease pathogenesis. Their ability to fine-tune gene expression makes them essential for maintaining cellular homeostasis and responding to environmental cues.

The biogenesis of miRNAs is a complex, multi-step process. It begins in the nucleus by transcribing long primary miRNA transcripts (pri-miRNAs) by RNA polymerase II. These pri-miRNAs contain hairpin structures that are recognized and cleaved by the enzyme Drosha [a Class 2 ribonuclease III enzyme that in humans is encoded by the *DROSHA* (formerly *RNASEN*) gene], generating precursor miRNAs (pre-miRNAs). The pre-miRNAs are then exported from the nucleus to the cytoplasm by Exportin-5. In the cytoplasm, Dicer [a Class 4 ribonuclease III enzyme encoded in humans by the *DICER1* gene] removes the loop region of pre-miRNAs and produces mature double-stranded miRNA molecules. One strand of the mature miRNA, known as the guide strand, is then loaded onto the RNA-induced silencing complex (RISC), while the other strand, the passenger strand, is typically degraded.

The core component of RISC is the argonaute (AGO) protein. The miRNA guide strand directs RISC to target messenger RNA (mRNA) molecules with complementary sequences. The degree of complementarity between the miRNA and its target mRNA determines the outcome of the interaction. If the complementarity is perfect or near-perfect, the RISC cleaves the target mRNA, leading to its degradation. However, the complementarity is imperfect in most cases, particularly in animals. In these instances, the RISC complex inhibits translation of the target mRNA, effectively silencing gene expression. This translational repression is a primary mechanism by which miRNAs regulate protein production.

Victor R. Ambros is an American developmental biologist and molecular geneticist. Born on December 1, 1953, in Hanover, New Hampshire, he pursued his passion for biological science at the Massachusetts Institute of Technology (MIT), where he earned his Bachelor of Science degree in 1975 and his Ph.D. in 1979. His doctoral research, under the supervision of Nobel laureate David Baltimore, focused on the molecular biology of viruses. After completing his postdoctoral studies at MIT, Ambros joined the faculty of Dartmouth College in 1992, where he made his seminal discoveries on microRNA. In 2008, he transitioned to the University of Massachusetts Medical School, where he currently serves as the Silverman Professor of Natural Sciences. He is a member of the US National Academy of Sciences and the American Academy of Arts and Sciences.

Renowned American molecular biologist and geneticist Gary Bruce Ruvkun was born in Berkeley, California, on March 26, 1952. His journey in science began with a Bachelor of Arts in Biophysics from the University of California, Berkeley, in 1973. He later earned his Ph.D. in Biophysics from Harvard University in 1982, where he studied under Frederick M. Ausubel, focusing on bacterial nitrogen fixation genes. Ruvkun joined postdoctoral research at the Massachusetts Institute of Technology (MIT) under the mentorship of H. Robert Horvitz and Walter Gilbert. Ruvkun's research interests extend beyond miRNA to include the genetic analysis of animal antiviral and antibacterial pathways, aging, and even the possibility of life on other planets. His work on insulin-like signaling pathways has provided insights into the regulation of aging and metabolism. Throughout his career, Ruvkun has been affiliated with prestigious institutions such as Harvard Medical School, Massachusetts General Hospital, and the University of California, Berkeley. He has published extensively in scientific journals and has been recognized as a member of the American Philosophical Society and the National Academy of Sciences.

Victor Ambros and Gary Ruvkun shared many awards – the Rosenstiel Award (2004), the Warren Triennial Prize (2008), the Gairdner Foundation International Award (2008), the Benjamin Franklin Medal in Life Science (2008), the Lasker Foundation Award for Basic Medical Research (2008), the Louisa Gross Horwitz Prize (2009), the Massry Prize (2009), the Dr. Paul Janssen Award for Biomedical Research (2012), the Gruber Prize in Genetics (2014), the Wolf Prize in Medicine (2014), the Breakthrough Prize in Life Sciences (2015), the March of Dimes Prize in Developmental Biology (2016), and the Nobel Prize in Physiology or Medicine (2024) apart from a good numbers of other prizes throughout their careers. The recognition of Ambros and Ruvkun with the Nobel Prize underscores the importance of basic research and the power of collaborative scientific endeavors. Ambros's deep understanding of developmental genetics complemented Ruvkun's expertise in molecular cloning and genomics and provided the biological context for identifying and characterizing miRNA molecules. Their dedication to unraveling the mysteries of gene regulation drove them to pursue a line of research that challenged conventional wisdom. The collaboration unveiled a new layer of gene regulation, demonstrating that small RNA molecules could play a significant role in controlling gene expression. Thus, Ambros and Ruvkun demonstrated a perfect example of scientific synergy. Their teamwork has far-reaching implications for our understanding of development, disease, and potential therapeutic interventions, opened up new avenues of research, and has had a transformative impact on the field of biology.

The scope of miRNA regulation is extensive. It is estimated that miRNAs can regulate the expression of a significant portion of the human genome. This broad regulatory capacity contributes to their involvement in a wide range of biological processes. During development, miRNAs play critical roles in cell fate determination, tissue morphogenesis, and organogenesis. They are also essential for maintaining cellular homeostasis by regulating processes such as cell proliferation, differentiation, and apoptosis.

Dysregulation of miRNA expression has been implicated in numerous human diseases, including cancer, cardiovascular disease, neurological disorders, and metabolic diseases. In cancer, for example, miRNAs can act as oncogenes or tumor suppressors. Oncogenic miRNAs, or oncomiRs, are

upregulated in cancer and promote tumor growth and metastasis by downregulating tumor suppressor genes. Conversely, tumor suppressor miRNAs are downregulated in cancer, allowing oncogenes to be overexpressed. The ability of miRNAs to modulate multiple signaling pathways makes them potent drivers of cancer progression.

The potential of miRNAs as diagnostic and therapeutic tools is actively being explored. Their stable nature and detectability in various bodily fluids, such as blood and urine, make them promising biomarkers for disease diagnosis and prognosis. Furthermore, the ability to manipulate miRNA expression using synthetic miRNA mimics or antagonists offers potential therapeutic strategies for treating various diseases. miRNA mimics can be used to restore the function of tumor suppressor miRNAs in cancer, while miRNA antagonists, or antimiRs, can be used to inhibit the activity of oncogenic miRNAs.

Despite the significant progress made in miRNA research, many challenges remain. Understanding the complex regulatory networks in which miRNAs operate and identifying their target genes is an ongoing endeavor. Developing effective and safe miRNA-based therapies also requires further research. However, the continued exploration of miRNA biology promises to yield valuable insights into gene regulation and pave the way for novel diagnostic and therapeutic applications. As our understanding of these tiny regulators deepens, their potential to revolutionize medicine and biology continues to grow.

The Nobel Prize for Physiology or Medicine 2024 is a testimony distinguishing the dedication of Victor R. Ambros and Gary B. Ruvkun toward the novel notion of gene regulation that has led to a paradigm shift in our understanding of molecular biology.