EDITORIAL

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MicroRNAs: discovery, breakthrough, and innovation

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The Nobel Assembly at Karolinska Institute awarded the 2024 Nobel Prize in Physiology or Medicine jointly to Victor Ambros and Gary Ruvkun "for the discovery of miRNA and its roles in post-transcriptional gene regulation."

The discovery of the first microRNA (miRNA), lin-4, in 1993 by Ambros and Ruvkun's groups in *Caenorhabditis elegans* opened up a new field of molecular biology. MiRNAs are now recognized as powerful regulators of various cellular activities and have been linked to many diseases, and miRNA-mediated clinical trial has shown some promising results for treatment of cancer and viral infection.

Victor Ambros was born in 1953 in Hanover, New Hampshire, USA. He received his PhD at Massachusetts Institute of Technology (MIT) in 1979 and remained there as a postdoctoral fellow in H. Robert Horvitz's (The 2022 Nobel Prize Laureate in Physiology or Medicine, for the discovery concerning genetic regulation of organ development and programmed cell death) laboratory. *Lin-4* was first characterized by Horvitz's lab as a gene that regulates temporal development of *C elegans* in the 1980s.[1,2] At the same time, Ambros joined Horvitz's lab in MIT, where he met Gary Ruvkun. Gary Ruvkun was born in Berkeley, California, USA, in 1952. He received his PhD at Harvard University in 1982 and became a postdoctoral fellow in Horvitz's lab. During their postdoctoral periods, Ambros and Ruvkun were interested in genes that control the timing of activation of different genetic programs, ensuring that various cell types develop at the right time in *C elegans*. Two mutant strains of worms, *lin-4* and *lin-14*, were known to display defects in the timing of activation of genetic programs during development.[3,4] In 1984, Ambros joined the faculty of Harvard and moved to Dartmouth in 1992. In 1985, Ruvkun started his lab at Harvard Medical School. Both Ambros and Ruvkun continued to study *lin-4* and *lin-14* after leaving Horvitz's lab. In 1993, Ambros's team found that *lin-4* is not a protein, but a non-coding RNA processing from an RNA precursor with short hairpin structures. The mature lin-4 sequence was only 22 bases, which makes them very surprised.[5] Although Ambros's team discovered lin-4, its regulatory mechanism was explored by Gary Ruvkun. Ruvkun's research found that lin-4 regulated lin-14 expression through incomplete RNA base pairing.[6] It was at this point that a new principle of gene regulation mediated by miRNA, a previously unknown type of RNA, had been discovered.

Although their findings are sufficient to prove the basic characteristics of miRNA regulation on gene expression, it did not immediately attract the attention of many scientists at that time, and some considered the role of miRNA to be specific to *C elegans* (and likely irrelevant to humans and other more complex animals).

Surprisingly, in 2000, Ruvkun's team identified the second miRNA, encoded by *let-7*.[7] *Let-7* regulated the expression of *lin-41* gene by targeting its mRNA, which was just the same as the regulatory mechanism of *lin-4*. Unlike *lin-4*, *let-7* gene was highly conserved and present throughout the animal kingdom from sea urchins to humans. This breakthrough discovery means that miRNA is not limited to *C elegans*, and opened the door for the follow-up miRNA studies. Today, we finally realize that miRNA has universal significance in gene regulation. In 2006, the Nobel Prize in Physiology or Medicine was awarded to Andrew Fire and Craig Mello in recognition of their contributions in RNA interference (RNAi, which refers to the phenomenon that some small double-stranded RNAs can silence gene expression). Many people also think that Victor Ambros and Gary Ruvkun, as the founder of miRNA, should also leave their names on Nobel list.

Victor Ambros is currently working at MIT. In 2008, he won the Lasker Prize for Basic Medicine with Gary Ruvkun and David Baulcombe. In 2015, together with David Allis, Gary Ruvkun, Alim Louis Benabid, Jennifer Doudna, and Emmanuelle Charpentier, he won the Life Science Breakthrough Award. Victor Ambros was elected as a member of the National Academy of Sciences in 2007 and a member of the American Academy of Arts and Sciences in 2011. Gary Ruvkun now works at Harvard Medical School and is an academician of the American Academy of Sciences.

As a type of regulatory RNAs, miRNA undoubtedly plays a crucial role in blood system. Over the past few decades, the roles of miRNAs in normal and malignant hematopoiesis have been actively investigated, which help explain many unique phenotypes in blood system. For example, the connection between sickle cell disease (caused by erythrocytes carrying a variant hemoglobin allele) and malaria (caused by infection of the malaria parasite *Plas*modium) was reported a long time ago. However, the nature of this intrinsic resistance remains incompletely understood. In 2012, LaMonte et al demonstrated a surprising mechanism that a miRNA enriched in sickle red blood cells is translocated into the parasite,

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incorporated covalently into *Plasmodium falciparum* mRNAs and inhibits parasite growth.[8–10] This finding revealed a startling and unique mechanism of cross-species trans-splicing in *P falciparum*-infected erythrocytes where the effector molecule of parasitic inhibition is the miRNA itself. Again, the mutations in *USB1* gene cause poikiloderma with neutropenia (PN), a rare genetic disorder with defects in blood development. In 2023, a study in Science reported that USB1 removes adenosines from miRNAs that are essential for blood cell formation, which, if not removed, results in miRNA degradation and the clinical features of PN.[11,12]

Ever since miRNAs were first recognized as an extensive gene family more than 20 years ago, a broad community of researchers was drawn to investigate the universe of small regulatory RNAs, such as siRNA, miRNA, and piRNA. Although the core features of miRNA biogenesis and function were revealed early on, recent years continue to uncover the fundamental mechanism and molecular dynamics of core miRNA machinery,[13] as our series of work revealed such specific regulation of miRNA processing machinery could determine miRNA biogenesis, as well as lineage commitment of blood cells.[14–17] In the future, more novel insights will be enabled by recent technological advances, including massively parallel assays, cryogenic electron microscopy, single-molecule imaging, and CRISPR–Cas9 screening.

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