Nobel Prize in Physiology or Medicine awarded to discoverers of microRNA

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On October 7, the Nobel Assembly at Karolinska Institute awarded the Nobel Prize in Physiology or Medicine jointly to Drs. Victor Ambros and Gary Ruvkun for their discovery of microRNA (the fifth such prize for research specifically on RNA) and its critical role in regulating the expression of genes.

Every cell in the human body carries the same DNA blueprint, but different cell types, such as muscles or nerves, have distinct functions that occur at various stages of an organism's development and life. This requires regulation of the expression of the genes to provide the appropriate instructions for life.

In this regard, the identification in 1993 of microRNAs (miRNA), a new class of very small RNA molecules that play a decisive role in gene regulation, was an immense leap forward in our understanding of biological functions and diseases.

As the Nobel Assembly stated in its press statement:

> Their groundbreaking discovery revealed a completely new principle of gene regulation that turned out to be essential for multicellular organisms, including humans. It is now known that the human genome codes for over one thousand microRNAs. Their surprising discovery revealed an entirely new dimension to gene regulation. MicroRNAs are proving to be fundamentally important for how organisms develop and function.

The discovery was a tremendous advance on the significant work that preceded it, dating back to 1957, when Francis Crick theorized a linear process through which the information contained in DNA is passed through nucleic acids and the formation of proteins. Crick, in a lecture given then, said:

> I shall … argue that the main function of the genetic material is to control (not necessarily directly) the synthesis of protein. There is little direct evidence to support this, but to my mind the psychological drive behind this hypothesis is at the moment independent of such evidence.

Many such discoveries emerge in the course of mundane and tedious work at academic institutions, where the combined efforts of dozens of scientists produce numerous papers written in the complex lexicon of biochemists, which is indecipherable to the uninitiated. Their significance is oftentimes only realized years later, when the scientific conceptions unearthed begin to generate a body of work that both enriches the discipline and paves the way for a deepening understanding of life processes and how they can be influenced for the betterment of society.

Such was the case with the granting of the award in 2023 to Katalin Karikó and Drew Weissman for their decade-long collaboration on mRNA molecules that made it possible to rapidly develop the anti-COVID vaccines in 2020.

With respect to the background of their work, Dr. Victor Ambros, professor of natural science at the UMass Chan Medical School in Worcester, Massachusetts, and Dr. Gary Ruvkun, professor of genetics at Harvard Medical school and researcher at Massachusetts General Hospital, were both postdoctoral fellows at Robert Horvitz's laboratory in the 1980s. They worked with a small roundworm, the *Caenorhabditis elegans* (*C. elegans*), a useful model for investigating how tissues develop and mature in multicellular organisms.

Horvitz received the Nobel Prize in 2002 with Sydney Brenner and John Sulston for their work on the tiny roundworm, which provided important insight into how the nervous system and organs develop, including the process of "programmed cell death," which helps keep growth under proper control.

Ambros and Ruvkun furthered this work on genetic regulation after their postdoctoral research was concluded. They left Horvitz's lab to start their own labs and continue their investigation into various genes involved in controlling the activation of different genetic programs that allow cells to develop at the right time.

Specifically, they looked at two mutant strains of the worm that harbored defects in the lin-4 and lin-14 genes and displayed timing defects in activating genetic programs during their development. Although Ambros had previously shown that the lin-4 gene inhibited the expression of the lin-14 gene, how this blockage occurred remained an intriguing mystery.

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Ambros set out to carefully map and clone the lin-4 gene. To his surprise, the gene produced a very short RNA molecule that lacked the ability to produce a protein. At the same time, Ruvkun showed that the regulation didn't occur at the level of the mRNA transcribed from the lin-14 gene. [The mRNA, or Messenger RNA, are single stranded RNA made from the DNA template that are involved in protein synthesis]. Rather, the regulation occurred later in the process by shutting down the protein production. Also, the genetic code in lin-14 mRNA demonstrated a segment that was required for inhibition by lin-4.

When the two researchers met to discuss and share their results, they hit upon an important discovery that hitherto had not been elucidated—a new principle of gene regulation. Further experiments revealed that the lin-4 miRNA bound itself to complementary sequences of lin-14's mRNA and blocked its protein production. The two investigators co-published their reports—link1 and link 2—in the journal *Cell* in 1993.

Recalling those experiments, Ambros told reporters on the day of the Nobel Prize announcement, "It was surprising that there could be enough information contained in only 22 [nucleic] bases in the genome for this microRNA to regulate another gene so precisely."

He added that as a result of his discoveries, "I had to reorganize my view of the world."

However, the scientific community took little notice of this breakthrough, attributing these findings to *C. elegans*' specific genetic regulatory mechanisms. It would take another seven years for the far-reaching implications of the 1993 paper to emerge.

On November 2, 2000, Ruvkun and colleagues published in *Nature* their discovery of another miRNA known as let-7, which controlled the transition from late larval to adult roundworm. However, unlike lin-4, let-7 was highly conserved and common throughout the animal kingdom. By the following year, researchers had already identified hundreds of these RNAs and coined the term microRNA to describe them.

Since these discoveries, scientists have ascertained that miRNAs not only inhibit protein synthesis, they also signal the cell to degrade the mRNAs produced. And while a single miRNA can regulate the expression of multiple different genes, conversely, a single gene can be regulated by multiple miRNAs, underscoring the complex coordination of networks of genes to ensure the intended development of the organism and its homeostasis.

In fact, miRNAs are abundant in many mammalian cells and target most of the genes contained in animals, including humans. Because miRNAs have been evolutionarily conserved, researchers have deduced that they play an essential role in biological functions. Abnormal regulation of miRNAs has been implicated in contributing to cancers. They function to regulate insulin secretion, have been implicated in cardiovascular disease, and even function to regulate our sleep-wake patterns known as the circadian rhythm.

There is something deeply gratifying in these discoveries, which reveal critical details about the inner workings of life, supplant religious speculation, and further fuel the thirst for scientific knowledge. Precisely through unearthing these mechanisms do new possibilities for addressing disease and illness emerge.

The work to which such scientists devote tireless and tedious decades is built on collaboration with colleagues, mentors, and the entire edifice of their discipline. In addressing what seem like the most elementary questions, they provide insights that spur the entire community on to new discoveries. And what motivates this work and collaboration is not fame and fortune, but simple curiosity and the recognition of the tremendous value it can have for humanity.

At the same time, capitalism's demand that potential scientific breakthroughs yield profit for the ruling class erodes the social gains from these discoveries to the world's detriment. Science is not immune from the impact of the class struggle.

It is important that scientists recognize the social relevance of their work and join ranks with workers internationally against the descent into barbarism and reaction that characterizes the present period. Otherwise, as seen in the official response to the COVID pandemic, where well-known principles of public health and medical science were ignored and the pandemic was allowed to claim millions of lives in order to protect corporate profits, newfound biological knowledge will fall prey to the drive to imperialist war and ever-greater wealth for the ruling elite.

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