**Victor Ambros (1953-)** [1]

**Victor Ambros** [3] is a professor of molecular medicine at the University of Massachusetts Medical School, and he discovered the first miRNA (miRNA) in 1993. Ambros researched the genetic control of developmental timing in the nematode worm *Caenorhabditis elegans* [4], and he helped describe gene function and regulation [5] during the worm's development and embryogenesis [6]. His discovery of miRNA marked the beginning of research into a form of genetic regulation [5] found throughout diverse life forms from plants to humans [7]. Ambros is a central figure in the miRNA and *C. elegans* research communities, and co-directs the RNA Therapeutics Institute.

Ambros was born in Hanover, New Hampshire on 1 December 1953 to Melissa Brown Ambros and Longin Ambros, and was one of eight children. As a child, Ambros’s family relocated to a farm in Vermont, where he read books about science, astronomy, and inventors. Ambros’s father supported his interest in science, which Ambros said inspired him to become a part of the scientific tradition.

Ambros attended the Massachusetts Institute of Technology [8] (MIT) in Cambridge, Massachusetts for his undergraduate studies, which he completed in 1975. From 1975 to 1979, Ambros continued his education at MIT as a graduate research assistant to Nobel Laureate David Baltimore at the MIT Center for Cancer Research. With Baltimore’s guidance, Ambros studied the molecular properties of the poliovirus. During his graduate studies, Ambros published six papers regarding the molecular biology of the poliovirus. In 1979 Ambros graduated from MIT with a PhD in Biology.

In 1979 Ambros drew the attention of Robert Horvitz, who had recently returned to MIT from working in the lab of Sydney Brenner [9] at Cambridge University [10] in Cambridge, UK. Brenner established *C. elegans* as a model for genetic analysis, and Horvitz worked in his lab for five years towards this end. Horvitz brought many mutants worm strains with him from Cambridge to his new lab. One of these strains contained a mutation in the heterochronic gene named *lin-4*, which controlled the timing of development between larval stages of *C. elegans*. In the Horvitz lab Ambros collaborated closely with fellow lab-member Gary Ruvkun [11]. Together they worked on the heterochronic genes [12] in *C. elegans*. By screening for genes [13] that control developmental timing, Ambros identified three other genes [13], *lin-14*, *lin-28*, and *lin-29*, which sped up or slowed down the transitions between larval stages. Ambros’s and Horvitz’s 1984 publication, "Heterochronic mutants of the nematode *Caenorhabditis elegans*," first described the genes [13] that control developmental timing in a multicellular species.

In 1985 Ambros became a faculty member at Harvard University [14] in Cambridge, Massachusetts. Ambros’s lab was near the lab of fellow *C. elegans* researcher Dan Stinchcomb [15], and the two labs quickly merged. Ambros continued his work on the heterochronic genes [12] by focusing on the epistatic relationships impacting the expression levels of the genes [13]. Ambros discovered that *lin-4* negatively regulates the protein expression levels of *lin-14* and *lin-28*, *lin-14* and *lin-28* inhibit expression of *lin-29*, and *lin-29* activates the differentiation [16] of the larva to adult stages in hypodermal cells. Furthermore, multiple tissues expressed *lin-4* and *lin-14*. The gene regulatory cascade coupled with tissue specific expression led Ambros to the conclusion that the heterochronic genes [12] existed in a hierarchy. Some genes [13], such as *lin-4*, existed at the top of the hierarchy and acted as general signals that could variably control expression of multiple genes [13] in different tissues. During his time at Harvard, Ambros mentored graduate student Craig Mello who would go on to discover RNA interference [17] and earn the 2006 Nobel Prize in Physiology or Medicine [18].

In 1992 Ambros was hired at Dartmouth College and returned to his hometown of Hanover, New Hampshire as an associate professor. Having characterized the epistatic interactions between the heterochronic genes [12] while at Harvard, Ambros, along with collaborators Gary Ruvkun [11], Robert Horvitz, Alan Coulson, Bob Waterston, and John Sulston [19], sought to determine the molecular sequence of the genes [13]. The group started with the two genes [13] at the top of the heterochronic gene hierarchy, *lin-4* and *lin-14*. While Ruvkun’s lab sequenced *lin-14*, Ambros focused on sequencing *lin-4*. Ambros and his lab members, wife Rosalind Lee and Rhonda Feinbaum, discovered two copies of *lin-4* messenger RNA (mRNA), one 60 nucleotides long and the other approximately 20 nucleotides. It was known that this gene negatively regulated both *lin-14* and *lin-28*, but *lin-4* had fewer nucleotides than any other regulatory gene that had been sequenced to date.

When Ambros and Ruvkun compared sequences of *lin-4* and *lin-14* they recognized that the 20 nucleotide mRNA of *lin-4* had a complementary sequence to several regions in the three prime untranslated region (3'UTR) of the *lin-14* mRNA transcript. The 3' UTR is a region at the end of mRNA that is not translated into protein, which in the early 1990s was believed only to contribute to
the stability of mRNA molecules. It was not known that 3'UTRs contain complementary target binding sites for short RNAs, or that 3'UTRs had any role in translational regulation [5] of genes [13]. In 1993 Ruvkun and Ambros published their results in two articles in the same issue of Cell each describing their work. Ambros’s publication, "The C. elegans Heterochronic Gene lin-4 Encodes Small RNAs with Antisense Complementarity to lin-14," marked the discovery of the first miRNA, although the term miRNA would not be coined for eight more years. Ruvkun’s article, "Posttranscriptional regulation [5] of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation [20] in C. elegans," described the regulatory mechanism by which lin-4 negatively regulated lin-14 mRNA after the lin-14 gene had been transcribed. The findings announced by these papers represented a collaborative effort between labs, each discovery being integral to the relevance of the other.

Despite these two publications, the significance of the regulatory relationship between lin-4 and lin-14 was not immediately recognized. Homologous genes [13] to lin-4 could not be found in other species, thus genetic regulation [5] via short RNA binding to 3'UTRs was viewed as a peculiarity of C. elegans. So, throughout the remainder of the 1990s, Ambros’s lab continued to work on the heterochronic genes [12] and the targets of lin-4 relatively inconspicuously. In 1997 Ambros and graduate student Eric Moss showed that lin-4 also regulates lin-28 in a similar fashion to lin-14. In 2000 Ambros discovered the lin-14 gene codes for a transcription factor, a protein that acts in the nucleus [21] to control gene expression levels. He also found that the lin-14 protein had three alternate forms (isoforms), indicating that the lin-14 gene could produce multiple proteins by the mechanism of alternative splicing.

In 2000 and 2001, two findings revealed that many different taxa have miRNAs and that miRNAs have similar functions across taxa. First, in 2000 the Ruvkun lab identified and cloned a second heterochronic gene, lin-7, which was comparable in size to lin-4. lin-7 was conserved in many organisms exhibiting bilateral symmetry, including the fruit fly (Drosophila melanogaster), purple sea urchin (Strongylocentrotus purpuratus), zebrafish (Danio rerio), and humans (Homo sapiens). This finding indicated that these small RNAs were part of a widespread mechanism of post-transcriptional regulation [5]. Second, in 2001, Ambros and Lee discovered an additional fifteen small RNAs which regulate target genes [13] in C. elegans by binding to mRNA transcripts, and proposed the nomenclature microRNA for these molecules. Ambros suggested that there may be hundreds of miRNAs in C. elegans, and that the search for miRNAs should expand to a wide range of taxonomical groups. The expansion of knowledge from one miRNA in worms [27] to many miRNAs in multiple species marked the beginning of the rapid discovery of thousands of miRNAs in organisms ranging from plants to humans [7].

After 2001 Ambros continued to research the structures and functions of miRNAs, in addition to being recognized for his contributions. In 2005 Ambros, Ruvkun, Mello, and Andrew Fire [28], won the Lewis S. Rosenstiel Award [29] for Distinguished Work in Medical Research. In 2008 Ambros, Ruvkun and David Baulcombe, who discovered RNAi in plants, won the Benjamin Franklin Medal in Life Science Award as well as the Albert Lasker Award for Basic Medical Research Award. That same year Ambros took a position at the University of Massachusetts Medical School, and moved to Worcester, Massachusetts. In 2009 Ambros and Sidney Altman wrote forewords to MicroRNAs: From Basic Science to Disease Biology, the first comprehensive textbook on miRNAs.

Victor Ambros’s contributions include the discovery of the first miRNA, and helping to build the miRNA and C. elegans research communities. Beginning in 1989 and ongoing through 2012, Ambros organized the bi-monthly Boston Area Worm Meeting. Additionally he has led several local and international symposia for C. elegans researchers. He led the Keystone Symposium on miRNAs in 2004, and the Keystone Symposium on Biological roles of RNA Silencing in 2011. As of 2012 Ambros, along with Nobel Laureate and co-discoverer of RNAi Andrew Fire [28], serves as co-director for the RNA Therapeutics Institute, which utilizes bioinformatics and integrative biology to develop RNA based therapeutics.

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