MASSACHUSETTS GENERAL HOSPITAL

News

Groundbreaking research at Massachusetts General Hospital reveals a new world of RNA regulations at an unprecedented small scale, earning Gary Ruvkun, PhD, and two corecipients the 2008 Lasker Award for Basic Medical Research.

Tiny Molecules, Vast Potential

MicroRNAs revolutionize our understanding of gene regulation

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A scientific revolution represents a seismic shift in the way people understand the world. Consider Watson and Crick's discover of the double-helix structure of DNA, a historic breakthrough that unlocked the secrets of gene control.

Today, Gary Ruvkun, PhD, is at the helm of a new scientific revolution: that of tiny RNAs. And this revolution has deep roots at Massachusetts General Hospital.

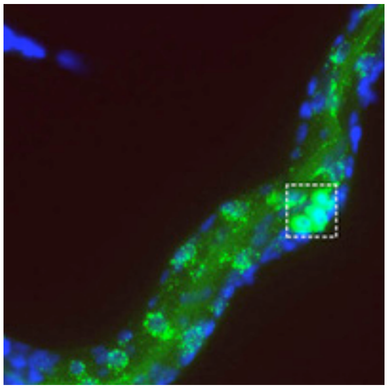
Ruvkun is an investigator at Mass General's Department of Molecular Biology and Center for Computative and Integrative Biology. Along with colleagues Victor Ambros, PhD, University of Massachusetts Medical School, and David Baulcombe, PhD, FRS, University of Cambridge, Ruvkun determined that tiny molecules of RNA, or microRNAs, can control the activity of critical genes in animals and plants.

This revolution is now in full swing, as hundreds of labs are investigating the role of microRNAs in a host of biological processe from fat metabolism to cancer. As Ruvkun notes, these little wonders seem to possess great "explanatory power" across many fields.

"They're now part of the methods and intellectual approaches being used in everything from how learning and memory work to how cells crawl and move," he says. "People are thinking about them in a lot of different ways."

In September, Ruvkun and his two colleagues were named corecipients of the 2008 Lasker Award for Basic Medical Research. This honor is widely considered to be the American version of the Nobel Prize, and many Lasker recipients have gone on to cla the Nobel. Ruvkun and Ambros were also awarded the Warren Triennial Prize by Massachusetts General Hospital in October.

It All Began With Roundworms



An image of a roundworm produced in Dr. Ruvkun's lab

Watson and Crick's 1953 paper describing the structure of DNA explained how the instructions for making living things are passed on from one generation to the next. It also established the paramount importance of genes in unlocking the various mysteries of life.

Nearly 30 years later, in 1982, Ruvkun and Ambros were fellows at the Massachusetts Institute of Technology investigating a process called "gene expression" in a microscopic roundworm species. Gene expression determines the form a cell will take, for example a skin cell, nerve cell or blood cell, as well as traits such as hair and eye color. Malfunctions in gene expression can cause cancer and many other diseases.

The two researchers collaborated to isolate two genes that operate in concert to regulate gene expression during a worm’s transition through key developmental stages to adulthood. Even after Ruvkun moved on to Mass General and Ambros to Harvard University, the pair continued to study these genes and share their findings with each other.

In 1993 they announced the discovery of the first microRNA, a gene product only 22 nucleotides long that previously had gone unnoticed. They also showed how this microRNA acts to control developmental timing in roundworms. There was only one problem: The microRNA they had identified exists only in worms. "And that made us slightly marginalized in the field of developmental biology," says Ruvkun.

Seven years later, Ruvkun's team at Mass General uncovered a second type of microRNA in roundworms. Like the first microRNA, this one controlled developmental timing. But it was also present in nearly identical forms across a wide range of animal species, from fruit flies to fish to humans, providing a new lens for viewing biology.

"The second microRNA got us out of the 'worm ghetto' and got other biologists to pay attention to what we were finding," says Ruvkun. "Within a year, other researchers had figured out there were hundreds of these microRNAs in other organisms."

Looking to MicroRNAs for Answers

Recent studies have revealed that between 500 and 1,000 microRNAs are involved in a multitude of activities, both normal (e.g., embryonic development, muscle function) and disease-related (e.g., cancer and inflammation). Researchers have just begun examining their potential for the diagnosis, prognosis and treatment of many different diseases.

The tiny RNA revolution highlights the significance of basic research, which are laboratory-based studies aimed at gaining knowledge about a particular subject. Basic research like that conducted by Ruvkun often informs clinical research, which studies new ways to treat diseases and disorders.

As Ruvkun offers, basic research doesn't always receive the attention it deserves. "Everyone wants to trumpet immediate implications of scientific discoveries—how is this going to affect me?" he says. "But just because the impact of basic research isn't immediate doesn't mean it's not important. It's a long-term investment."

Ruvkun cites two compelling examples of how the scientific community has begun looking to microRNAs for answers. One laboratory has identified a microRNA that could play a critical role in heart disease. Another has found that understanding microRNA differences between two tumors can help in classifying tumors and determining whether they are treatable.

“This revolution is one percent over,” says Ruvkun. “The future of microRNAs is brimming with exciting possibilities, and there's a lot more that's going to happen."

Part of the Center for Computational and Integrative Biology, the Ruvkun Lab is currently investigating the role of microRNAs and their effects on metabolism and longevity, including the genes involved in the regulation and storage of fat.

Watch a video about the 2008 Lasker Award winners