AUTHOR COMMENTARIES - 2008

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Dr. David P. Bartel

A Featured Scientist from *Essential Science Indicators*SM

Earlier this year, ScienceWatch.com *published an analysis of high-impact research in Molecular Biology & Genetics over the past five years. The analysis ranked David Bartel #2 among authors publishing high-impact papers in this field, based on 19 papers cited a total of 4,542 times.*

In Essential Science Indicators *from* Thomson Reuters*, Dr. Bartel's record includes 76 original articles and review papers published between January 1, 1998 and February 29, 2008, with a total of 10,386 cites. These papers can be found in the fields of Molecular Biology & Genetics, Biology & Biochemistry, and Plant & Animal Science.*

Dr. Bartel is a Howard Hughes Medical Institute investigator whose lab is based at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. He is also a Professor in the Department of Biology at MIT.

In the interview below, he talks with correspondent Gary Taubes about his highly cited research.

SW: What motivated your research originally on these small, non-coding RNAs, and particularly the 2000 *Cell* paper (Zamore PD, *et al*., RNAi: double-stranded RNA directs the ATP-dependent cleavage of mRNA at 21 to 23 nucleotide intervals," 101[1]: 25-33, 31 March 200), which is your most-highly cited paper that's not a review?

Tom Tuschl and Phil Zamore [see also] were postdocs in my lab working in collaboration with Phil Sharp [see also] on the biochemistry of RNAi. In 1999, they developed a cell-free system for studying RNAi, and they started using that system to see exactly what was happening. They put double-stranded RNA into the system and saw that it was getting processed down to the 21- to 23-mers.

Later, working independently in his own lab, Tom was able to chemically synthesize those 21- to 23-mers and confirm that they could direct the cleavage of the messenger RNA. He then showed that he could deliver them to mammalian cells to specifically silence mammalian genes. That was a very important technical advance, which has dramatically altered the way that biologists working in mammalian systems do their experiments. His results also implied that mammalian cells had the biochemical machinery to use these small RNAs to direct the repression of messenger RNAs. Reasoning that this machinery was not there just to help gene-knockdown experiments, my lab started exploring whether endogenous small RNAs might be regulating endogenous genes.

SW: Are you surprised that paper has been so influential, or is this what you expected?

Well, it seemed very interesting to us at the time, so I can't say I'm surprised. And there was a lot of interest in RNAi at the time, as there still is.

"I think that virtually every gene, at some point in the growth and development of the animal, is going to be found to be influenced by microRNAs."

SW: What prompted you to write the 2004 review in *Cell* ("MicroRNAs: genomics, biogenesis, mechanism, and function," 116[2]: 281-97, 23 January 2004), which has garnered over 1,300 citations in just four years?

That was for a special issue commemorating some of the classic *Cell* papers. These included the 1993 papers from the labs of Victor Ambros and Gary Ruvkun. So *Cell* was looking for a review of the microRNA research to go with reprints of those papers, and I thought that those papers deserved commemoration.

There was also a lot of new information about microRNAs and ideas about microRNAs that I thought would interest people. Clearly a lot of people were going to start looking at microRNAs, and a lot of people were asking me questions about them.

SW: Did you see the review as a guide to researchers who were now getting into microRNA research?

I was mainly trying to answer the types of questions my colleagues were asking about microRNAs. A lot of people were curious about them. And of course people in my lab had been thinking a lot about microRNAs, so I tried to lay out what the understanding was at that time.

SW: What was the understanding circa 2004?

We were just getting hints of the widespread targeting by mammalian microRNAs. At that point we knew what was happening with plant microRNAs, in terms of each plant microRNA apparently targeting just a few genes. But it looked like the recognition by the mammalian microRNAs was going to be much less precise—they could be regulating many more genes.

SW: How has that story played out in the last four years?

Since then, there have been all kinds of data showing that in animals each microRNA—at least, each highly conserved microRNA—is targeting hundreds of messenger RNAs. In 2005, for instance, we showed that for each microRNA or microRNA family—there are about 80 or 90 of these families in mammals—there are hundreds of messenger RNAs that are preserving their pairing to the microRNA over the course of evolution. They're preserving at a frequency that is much higher than you'd expect by chance. That was the first clear indication that it was true that each microRNA was regulating many messenger RNAs.

SW: How big are these microRNA families?

Some families in mammals just have one member. For instance, miR-223 is the only member of its family, whereas the let-7 microRNA family has at least 12 members—12 different hairpins making microRNAs that appear to have largely overlapping targets.

SW: Can you go into a little more detail about how microRNA regulation differs in plants and animals?

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In flowering plants, you have about 20 families of very highly conserved microRNAs; some are conserved throughout all land plants, and they each regulate a few genes. Usually those genes are highly related to each other and encode transcription factors important for plant development. The microRNAs direct the cleavage of the messages.

In animals, you have more families of conserved microRNAs, and each of them has hundreds of messages that they downregulate. There are a couple cases in which animal miRNAs direct the same type of mRNA cleavage as plant miRNAs do, but for most targets they mediate a different type of mRNA destabilization, or translational repression, or both. These messages code for proteins involved in many different things. In fact, when you add it all up, over a third of the human genes are conserved regulatory targets of microRNAs. And many—most of them, in fact—are targeted by more than one microRNA.

SW: Is that number likely to change?

It will go up.

SW: How high can it go?

To nearly one hundred percent. When I talked about the messages under pressure to preserve their pairing to microRNA, I was talking about highly conserved targets. There are additional microRNA targets that are non-conserved. Their expression is dampened by microRNAs, but this repression is either playing important roles only in particular species or it has no role that is really under evolutionary selection.

So in addition to conserved targets, you have many, many non-conserved targets, because microRNAs in mammals can recognize very short sequences in the messenger RNAs. And these short sites are very common. As a result, you have many, many messages that are downregulated by the microRNAs.

In addition, you have messages called "antitargets" because they are under selective pressure to avoid targeting by some or all microRNAs. Putting it all together, it is hard to escape the conclusion that microRNAs have a very widespread impact on mRNA expression and evolution in animals.

SW: Why do you think this small non-coding RNA story took so long before it was recognized and elucidated?

I think that if people had been looking for microRNAs, if they had known what to look for, they would have been able to see them much earlier. Everything was there 20 years ago to find microRNAs and to start learning what they were doing. Of course it helps a lot to be working now when we have all these genomes sequenced. But it would have been possible, if people had looked for them. Perhaps nobody thought that there could be interesting RNAs of this size range. Transfer RNAs—tRNA—were already considered quite small. They're about 76 nucleotides. And so nobody was looking for anything smaller.

"...when you add it all up, over a third of the human genes are conserved regulatory targets of microRNAs.."

I can't say first-hand what the block was, because I wasn't in the gene-regulation field. But if you look at how the first microRNA was found, by Victor Ambros and his colleagues in 1993, they just followed the genetics. They persevered. When you're mapping a genetic mutation and you don't find a protein, some people are just going to say, "Oh, this is too complex. I'll just go and map a different mutation." To find something this novel, you have to really stick to it, and that's what Victor's lab did. When they didn't see a protein, they thought there still had to be something there and they continued to look for it.

Another barrier is that these microRNAs, in many cases, don't cause huge changes in the output of the proteins, and so it's harder to find the consequences of losing the microRNA when it's knocked out.

SW: How do you see microRNA research evolving in the next few years?

I think that virtually every gene, at some point in the growth and development of the animal, is going to be found to be influenced by microRNAs. So people working with particular genes, more and more, will be considering microRNAs when they're asking how a gene is regulated. And, of course, the dysregulation of many genes is important in human diseases. So microRNAs will be tied more and more to pretty much every disease process in some way—perhaps sometimes in a small way, sometimes in a more substantial way.

SW: What are you working on now in your microRNA research?

We've been doing a lot of work trying to predict the targets of microRNAs; fitting the microRNAs into gene regulatory networks. We're continuing to do that, and now we're looking at what happens to the proteins when you get rid of a microRNA. We want to know which proteins change, and we're using that information to learn more about how targeting happens and about the biological consequences of the microRNA regulation.

A year ago we showed that there's an oncogene, HMGA2, that loses its microRNA regulation, and this appears to play a role as one of the key steps leading to many human tumors. Others have shown that cells can have too much of some microRNAs and that this can lead to tumors, or they can have too little of other microRNAs and that can do it. What we showed is that if you change one of the targets of a microRNA, so that the target can no longer respond to the microRNA, you can also get tumorigenesis. Following up on this finding, we want to learn what happens when other particular targets are no longer regulated by microRNAs.

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Dr. David P. Bartel's most-cited paper with 1,370 cites to date:

Most-cited paper: Bartel DP, "MicroRNAs: genomics, biogenesis, mechanism, and function," *Cell* 116 (2): 281-97, 23 January 2004. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

Dr. David P. Bartel is also featured in " Sequencing Biology's Hottest, 2002-06."

ScienceWatch.com (only) general search results with the term "MicroRNAs" as the keyword.

Keywords: microRNA, RNAi, microRNA families, plant microRNAs, mammalian microRNAs, microRNA regulation, non-coding RNAs, messenger RNA.

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