Joan Steitz: RNA is a many-splendored thing

Steitz has spent her career uncovering RNA's different cellular avocations.

When it was first discovered, RNA was thought to have just one job in the cell: that of a messenger carrying the genetic instructions for protein synthesis to the ribosomes. But, since then, different RNA species have been shown to be key to the construction (1) and function of the ribosomal machinery and to control both the spliced state and levels of messenger RNAs (2–4).

Right from the start, Joan Steitz has been in the middle of this RNA revolution. An early experience as an undergraduate hooked her on research. Enthralled by RNA's elegant form and function, Steitz went on to do her graduate work with James Watson at Harvard and followed up with postdoctoral work in Cambridge, England (5). She then set up shop at Yale, continuing her groundbreaking research to discover new niches for RNA in the cell (1–4, 6). We called her to talk about the passion she has for RNA and how it's driven her career.

LOVE AT FIRST SIGHT

You've been quoted as saying you "fell in love with RNA" early on in your career…

I fell in love with RNA in one of my first jobs as an undergraduate. I loved the idea of mRNA, which was discovered at that time. I also found the functions of other RNAs, like ribosomal RNA and transfer RNA, fascinating. And, since then, it just keeps getting better and better; we keep finding out more and more of RNA's functions.

RNA was a real mystery when you started working on it…

When I was a graduate student at Harvard, I was working on an RNA bacteriophage. We were trying to figure out what protein products the messenger RNA encoded. Of course we didn't have sequences—actually the genetic code had just been finalized—so you couldn't just look at the sequence and figure out what the proteins were.

As a postdoc, I worked on a project trying to figure out how ribosomes recognize where to start translation on a messenger RNA. At that early stage it wasn't known whether the coding region would start right at the 5′ end and go all the way to the other end, but there were hints that it was more complicated than that. So my project was to identify the initiation codon and surrounding sequences that determine where the ribosome binds to bacteriophage mRNA to start making proteins.

How did you transition from working on translation initiation to working on other processes, like splicing?

I started my own lab at Yale in 1970, and I continued to work on ribosomes and start site recognition. It was a very weird time in molecular biology because a lot of people thought that all the fundamentals of gene expression had already been discovered and that, when people moved from bacteria and bacteriophage to looking at higher eukaryotic cells, things would just be a lot more complicated but not fundamentally any different. But by the early 1970s it was apparent that weird things were going on in higher cells. For example, there were things like RNA turnover, where 90% of the RNA synthesized in a cell immediately disappears, leaving only 10% as messenger RNA in the cytoplasm. Why were cells making all this RNA and then degrading it immediately? Later, people discovered introns and exons and pre-mRNA splicing, which pretty much solved the problem of RNA turnover. But then the question was, "What's the machinery?" Being an RNA person, I was intrigued by this question. We started working on it, and we discovered small nuclear ribonucleoproteins (snRNPs), which are made up of small noncoding RNAs bound to proteins and which are involved in splicing.

> "RNA just gets better and better."

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Joan Steitz

Later, you worked on a related class of small RNAs, the small nucleolar RNAs (snoRNAs)…

Well, they're related in that both snRNAs and snoRNAs are small RNAs, defined as something less than 150 nucleotides or so. Neither type of RNA encodes proteins; instead they are found in a tightly bound complex with a particular class of proteins. Many of these small RNAs have essentially the same core proteins on them, and they mostly work by forming base pairs between the nucleotides in the small RNA and a substrate RNA. But, in the case of the snoRNAs, they introduce modifications into ribosomal RNA, whereas we know the snRNAs are part of the spliceosome.

UNEXPECTED MEETING

Where else do small RNAs crop up?

I'm excited about viruses at the moment. The fascinating thing about viruses is that they don't invent anything; they're clearly parasites of cells, and everything they do comes from the cells that they infect. But the amazing thing about viruses and small noncoding RNAs made by viruses is that they might look like something that the host has, but then the virus does something completely different with it.

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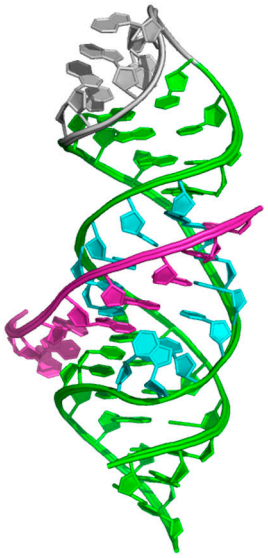

IMAGE COURTESY OF JOAN STEITZ

The ENE region (magenta) of a viral RNA binds a complementary site (cyan) within the same RNA to prevent its degradation.

We've been working with these viral noncoding RNAs for a long time, and they've been intractable. It was difficult to discover what their purpose is, but now the technology is available to do experiments we couldn't do a few years ago. Things like microarrays, sequencing technologies, and proteomics allow us to tackle their functions.

Can you give an example of how viruses repurpose small RNAs?

We've found a region on a noncoding RNA from Kaposi's sarcoma herpesvirus (KSHV) called the ENE that causes the RNA on which it resides to accumulate to very high levels so that that RNA can then do something else for the virus. We're still not sure what the RNA does or why the virus wants so much of it, but we've also found some regions in host noncoding RNAs that look very similar to the ENE. We haven't yet proved that they do the same thing for the host cell as they do for the virus, but they look very similar, and we're very excited about it.

What else are you working on now?

We're working a lot on these viral noncoding RNAs that look like host RNAs but turn out to do something different. We've been working on these problems off and on for so long that I would really love to see them get solved, or at least obtain some sort of an answer. It's so exciting to feel we might be getting close.

We're also excited about microRNAs, which are an RNA species that regulates other RNAs posttranscriptionally. We've found that they themselves are also regulated, on the basis of whether you make them or not, whether they're stable or not, what they regulate, and how they fit into all sorts of other cellular pathways. The microRNA field is a whole new field that has really started to explode in the last decade or so. As we were discussing earlier, RNA just gets better and better and more and more important.

> "Viral noncoding RNAs... look like host RNAs but turn out to do something different."

WORTH THE RISK

Had you envisioned your work unfolding in this way when you started out?

No. At first, I didn't even think about having a faculty position or running a lab, because at that time there were no women around me who had a position like that. If you don't see it, it just doesn't enter your mind as being within the realm of possibility, or at least it didn't for me. So when I went to Cambridge for my postdoc and it came time to choose a project to work on, I chose one that I knew was very risky, because I knew I wouldn't have to go out and look for a faculty job the way my male colleagues would at the end of their postdocs. The project worked, and meanwhile things had changed in the US: the women's movement had happened, and there was increasing pressure on universities to have some women on their faculties. Nevertheless, I was still absolutely shocked when people started offering me real faculty jobs at the end of my postdoc. The situation has continued to get better for women in science, but there's still a lot of room for improvement.

What would you like to see changed?

For women to succeed in science, I think access to flexible childcare is key, because that makes it possible for them to have a family and do their job. In order to really succeed, though, you've also got to have a supportive spouse. My husband has always shared the burdens of family life with me, so I've been very lucky. We were both able to have successful careers and to bring up our son.

Many of the problems that we're left with nowadays are the result of unconscious bias. People—men and women alike—don't realize that they're actually treating women slightly differently from the way they're treating men. These very little things, a little remark here or there, not enough encouragement, cause women to drop out. That's what I think we have to work very hard on, to let people know that it's possible and it's rewarding. If this is what they really want to do, they can figure out a way to do it.

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Even as a postdoc, Steitz hadn't expected she would have a career lecturing students and running a world-class lab.