Scientists

In Search of an Explanation

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Susan Gottesman's research on protein regulation and stability as well as her exploration of the regulatory role of small RNAs caught our attention. Curious to know more, *BioTechniques* contacted her to find out about the ambition, character, and motivation that led to her success.

What are your current research goals?

We work with *E. coli*, focusing on the role of proteolysis in bacterial regulatory pathways and the mechanisms by which such regulatory circuits function. Some members of my group study the regulation of a transcription factor called RpoS. When a cell is growing well, RpoS is degraded rapidly. But when cells become stressed, RpoS is actually stabilized, allowing it to turn on genes that help deal with the stress. The regulatory circuit that communicates the stress level of the cell to the protease that acts on RpoS turned out to be more complicated than expected, so this will be an ongoing project. The remaining members of my lab focus on regulatory RNAs. Once we are able to identify the small RNAs regulating a gene of interest, we try to resolve how that small RNA finds and regulates its target at the appropriate time.

What first interested you in these fields of study?

During my postdoctoral studies at the National Institutes of Health, I looked at a protein called lambda Xis, which

is involved in excision of the lambda prophage from the chromosome. It was known to be functionally unstable, but it wasn't clear what that really meant. At the time, I was trying to use lambda Xis for biochemistry and thought that if the protein could be made more stable, it might be easier to purify. While looking for ways to stabilize the protein, I came across a report showing that mutations to the *E. coli* Lon protease led to phenotypes that suggested the protease might have regulatory effects in the cell. So, I refocused my work and, as it turns out, proteolysis plays a large role in cellular regulation. It took me another 10 or 15 years to show that Lon protease was degrading lambda Xis since another protease could degrade it as well. We were unable to detect this until we tested cells mutant in multiple proteases. But in the meantime, we developed a number of stories about unstable proteins where the instability was required for proper function at the right time and in the right place.

And how did you move from proteolysis into studying small RNAs?

We were studying an unstable protein degraded by an ATP-dependent protease and thought that since the cell was expending so much energy to degrade the protein, it was probably regulating it at other levels as well. So, we set about studying the regulation of its synthesis. We had a plasmid carrying a fragment of the *E. coli* genome that stimulated one phenotype we were looking for. My original thought was that something on the plasmid was titrating a regulatory DNA-binding protein, but when we tried to dissect the plasmid, the causative element wasn't where we thought it should be. It took us a number of years before we started to believe what the data were telling us: the phenotype was not produced by an open reading frame, but by a transcript of a regulatory RNA. Studying that RNA led us to others and

eventually to an interest in looking at RNAs more globally. This was simply an observation in search of an explanation, and it took a while for us to realize how significant it was.

What is the most important open question in your discipline?

We understand a lot about regulatory circuits in *E. coli*, but moving from a very defined system in a lab into real life is still an unknown. What are these bacteria doing in their hosts? What are they doing in their environment? For life outside of the lab, why are these regulatory circuits important and why have they been conserved? Some people are starting to look at that, but it's very hard and we have a long way to go. For example, what is the best system I could use to see the role of *E. coli* small RNAs in the gut? While I might try an infection experiment in mice, in most cases those experiments look at just one or maybe two types of bacteria. But infections normally operate in the presence of other intestinal bacteria and with the host reacting. We can't do experiments under those circumstances since there are just too many variables. How the circuitry we study in the lab will translate into those environments will take even longer to figure out; in those complicated situations, it's hard to get clean answers.

Interviewed by Kristie Nybo, Ph.D. Image courtesy of Jason Varney.

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