People & Ideas

Pascale Cossart: The ins and outs of *Listeria*

Cossart studies how *Listeria monocytogenes* manipulates the biology of its host cells.

Listeria monocytogenes is a bacterium that lives freely in the environment but can also thrive inside an animal host cell. To do this, *Listeria* first hoodwinks a host cell into internalizing the bacterium (1, 2). Next, it stages a breakout from the internalization vesicle into the cytoplasm, where it then takes over various cellular processes (3–5) in order to replicate. Later, it escapes the host cell to start the cycle over again. Pascale Cossart is a leading authority on how *Listeria* bacteria play these dirty tricks on their host cells (1–5).

As a professor at the Pasteur Institute in Paris, France, Cossart has helped write the proverbial book on the biology of *Listeria*, penning chapter after chapter on this organism and its relationship with its host cells. But she transitioned through several subjects before beginning her studies on *Listeria*. It isn't always easo to adopt a new research niche, but Cossart says she feels lucky to have had the energy and curiosity to keep turning new pages in her work. We spoke with her about her story to date and what her next chapter will be about.

A GOOD BOOK

What made you decide to pursue a chemistry degree at university?

When I was growing up I wasn't especially interested in science. I didn't come from a scientific family, and at first I didn't really know what I wanted to do. I was young for my class, and in school I was placed in a class that had a strong emphasis on classic studies: Latin, Greek, and literature. But when I was about 13 years old, I had to buy a chemistry book for class. I brought it home from the bookstore and read it from front to back. It was just a small book, but I loved it. I knew then what I wanted to do.

The chemistry department at my university focused on pure chemistry, so I didn't encounter biology until I started my master's degree, when I went to an introductory lecture on biochemistry. By that point I had been in a chemistry lab for about a month and realized I did not want to do research in chemistry. So, at the end of this first biochemistry lecture I had a long talk with the professor and ended up joining his lab. There, I was working on protein chemistry and had started to work on my PhD. But then the person who was supervising me left to take a position elsewhere in France, and I decided to take this opportunity to start something more interesting in a different environment.

Was that scary?

No, it was exciting! I was very young, and I wasn't worried about getting a research position or about my career. I wanted to go the United States.

I applied for several fellowships and took one in Jacinto Steinhardt's lab in the chemistry department at Georgetown because I thought it would be interesting to be in Washington, DC. But just before I left France, I met the person I wanted to marry. So I worked a lot, completed my master's of science, and returned to France after a year.

> "[Studying *Listeria*] allows us to address key issues in cell biology."

Where did you eventually do your PhD?

At the Pasteur Institute. I was interviewed by Jacques Monod, a Nobel laureate, and he told me that if I wanted to work at the Pasteur, I had to learn microbiology. So there again I had to study something new [laughs]. I completed my PhD thesis on protein sequencing, but for my postdoc I decided I had already been in several places, so I just crossed the street and changed labs within the Pasteur Institute. There, I sequenced an *E. coli* gene—the first gene sequenced in the Pasteur Institute—and I have stayed ever since.

IMAGE COURTESY OF FRANÇOIS GARDY, INSTITUT PASTEUR

Pascale Cossart

NEW CHAPTER

What turned your interests to* Listeria*?

I wasn't initially interested in studying *Listeria*, but the Pasteur Institute is devoted to studying infectious diseases, and after working on DNA–protein interactions for a few years I was told that I should try to focus my lab on something that fit that theme. I decided to work on *Listeria* because it's a good model for intracellular pathogens and invasive bacteria. It also allows us to address key issues in cell biology, which is what I really like. Of course, this meant that I had to learn to work in yet another field, but this time I could hire postdocs who knew cell biology to help me.

How do you use* Listeria *to learn about mammalian cells?

One of the things we've studied closely is the *Listeria* protein internalin. It was identified in a genetic screen as something that was important for host cell invasion. Internalin binds to the host transmembrane receptor E-cadherin, which was discovered at the Pasteur Institute as a protein important for compaction of the embryo.

We discovered two fundamental things about *Listeria* entry. One is that there is a

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very strong specificity of this bacterium for human E-cadherin. *Listeria* does not interact with murine E-cadherin because of a single amino acid difference between the human and murine versions of E-cadherin. Another important thing we have recently shown is that when the bacteria enter cells, they not only trigger actin and membrane rearrangements but they also use clathrin, which was thought to only be important for the internalization of molecules or small objects. So, the clathrin-mediated endocytosis machinery is also used for the internalization of big objects like *Listeria* and acts before actin rearrangements during the entry process.

Once inside the cells, what does* Listeria *do?

Many things that are endocytosed are trafficked to the lysosome. Some invasive bacteria can live in vacuoles; they try to modulate this niche so that they can replicate properly. But *Listeria* replicates in the cytosol. Once in the cytoplasm, it co-opts cellular proteins to assemble actin-based structures that look like comet tails. *Listeria* use a protein called ActA, which recruits the host cell's Arp2/3 complex to initiate actin polymerization and propel the bacteria through the host cell. Studying processes like these can tell us a lot about both the bacterium and the biology of its host cell.

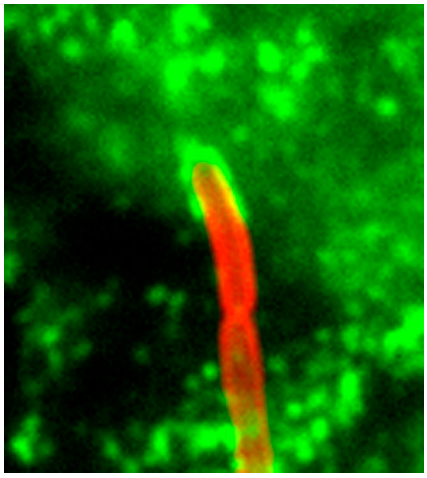

IMAGE COURTESY OF MATTEO BONAZZI, UNITÉ DES INTERACTIONS BACTÉRIES-CELLULES, INSTITUT PASTEUR

Clathrin (green) accumulates at the site of bacterial entry into the cell.

What other host cell processes do* Listeria *modify for their own ends?

Recently I became interested in post-translational modifications. I think this field has been neglected in infection biology, so we decided to look at it. One thing we looked at was SUMO, because SUMOylation modulates a lot of activities that might be critical for infection, like transcription, genome stability, and so on. We showed that SUMOylation is impaired in infected cells and that this is required for efficient infection. So now we are trying to understand how this happens, and we've found that UBC9, the E2 enzyme that carries out SUMOylation, is degraded. We are chasing the aspartate protease that is responsible for this, but we don't have it yet.

> "It's important to create an environment where people will be happy to work."

PAGE TURNER

The bacterium really stages a takeover in cells…

I think it's amazing how it's exploiting everything. At the beginning we were interested in the mechanics of infection, events like the actin cytoskeleton and membrane rearrangements needed to allow entry of the bacterium into cells or actin-based motility. Now I'm more and more interested in the reprogramming of the cells that takes place once the bacterium has entered. For example, we found that once *Listeria* is in the cytosol, it prevents a host cell transcription factor called NF-κB from reaching the nucleus. NF-κB is an important danger signal for the host cell, but *Listeria* has found a way to silence it. We also found that *Listeria* injects a protein into the nucleus which interacts with a previously unknown heterochromatinization factor, BAHD1. The resulting chromatin remodeling allows expression of a subset of genes involved in innate immunity.

There are many projects like this that we are working on. We've been working on this bacterium for more than 25 years, so we know it very well. But it still has new things to teach us. We're working on many aspects of its biology—from RNA regulation in the bacterium to epigenetics in the host cell.

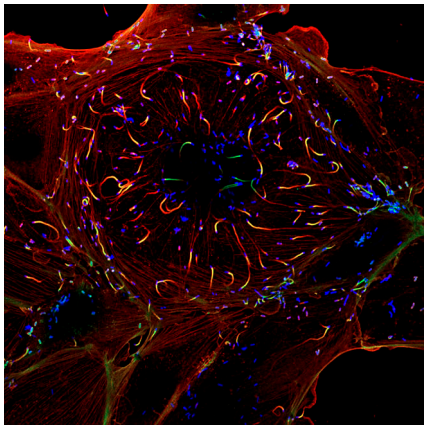

IMAGE COURTESY OF MATTEO BONAZZI AND EDITH GOUIN, UNITÉ DES INTERACTIONS BACTÉRIES-CELLULES, INSTITUT PASTEUR

***Listeria* (green) use actin (red) to move around cells.**

How do you juggle so many projects?

None of the things I have done would have been possible without some really wonderful people in my lab. I am very careful whom I choose to join the lab, because I think it is very important to cultivate a team spirit where everyone feels like they are part of the group. Then they can enjoy each other and work together. Useful collaborations just spontaneously happen.

I like the people around me to be happy to come to work. Science today is very hard; it keeps getting more complicated and progresses very rapidly. Competition is tighter. I know it can be difficult to keep smiling when your project is not working out as well as your neighbor's, but it's important to create an environment where people will be happy to work, even through the hard parts.

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