Epigenetics and Bacterial Infections: The Role of a Novel Histone Deacetylase SIRT2

Pascale Cossart

2013 Balzan Prize for Infectious Diseases: Basic and Clinical Aspects

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Period: 2014-2020
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Pascale Cossart is Director of the Unité des Interactions Bactéries-Cellules and Professeur de Classe Exceptionnelle at the Institut Pasteur, Paris. She is also *secrétaire perpetuel* at the Académie des sciences in Paris. Her project has focused on a new research area in infection biology, i.e., epigenetics and bacterial infections, a research area that she launched a few years ago with two senior scientists of her lab, Hélène Bierne and Mélanie Hamon. As a model system, she is using the invasive and intracellular bacterium *Listeria monocytogenes*, a human pathogen.

There is now robust evidence that in order to establish a successful infection, bacteria manipulate the host chromatin structure, dynamics, and function to their own profit. Bacterial pathogens can manipulate chromatin directly by addressing factors that interact with histones or other chromatin components to the nucleus, or indirectly by interacting with signalling pathways which then affect the chromatin structure or dynamics. The Cossart team's research had shown that, in order to deacetylate the histone H3 in the nucleus, the bacterial pathogen *Listeria monocytogenes* induces the nuclear translocation of the deacetylase SIRT2, an event dependent on the interaction between the bacterial protein InlB and its receptor Met on the cell surface, and critical for a successful infection *in vivo* as shown by the resistance to infection of SIRT2-/- mice.

A graduate student and a postdoctoral fellow carried out the project, which had four aims: to elucidate the mechanism underlying SIRT2 nuclear translocation induced by

L. monocytogenes infection; to investigate the genome-wide impact of SIRT2-induced H3K18 deacetylation during infection with *L. monocytogenes*; to determine whether H3K18 deacetylation by SIRT2 is a common strategy used by other pathogens for host subversion; to determine whether *L. monocytogenes* infection induces an epigenetic memory in the host.

Cossart's team has now investigated the nuclear translocation of SIRT2 and discovered a novel post-translational modification of SIRT2, i.e., dephosphorylation of SIRT2 at position 25, which is critical for association of SIRT2 to the chromatin. This dephosphorylation occurs in the nucleus via a complex made of the phosphatases PPM1A and PPM1B. Therefore, their studies have uncovered a novel strategy used by a pathogenic bacterium to reprogram host transcription during infection, thereby providing a new insight into a previously unknown cellular process, and revealing a new role and function for several cellular proteins (i.e., SIRT2, PPM1A and PPM1B).

The postdoc has then investigated the import of SIRT2 in the nucleus which is independent of the infection. He has shown that nuclear import of Sirtuin 2 is controlled by its C-terminus and by the cellular proteins, importins.

Mélanie Hamon is now extending these studies to another pathogen, *Streptococcus pneumoniae*. She has shown that *S. pneumoniae* infection promotes histone H3 dephosphorylation by modulating PP1 phosphatase.

A related but different line of investigation has been launched by Sabrina Jabs. It concerns the mRNA modifications induced by bacteria, whether commensals or pathogens, in the gut and in the liver. The first step in this investigation was to interrogate whether the gut microbiota had an effect on mRNA, and they have highlighted a totally unexpected observation, which is that the gut microbiota induces significant modifications of mRNAs in both the cecum and the liver. Such an observation had never been reported, thus paving the way to important new lines of investigation. This work was recently published in *Nature Communications*.

Altogether, the work realized by the Balzan Prize has thus led to an important set of data with a first major discovery which was published in *Cell Reports* in 2018. This work allowed Jorge Pereira to present and defend a PhD thesis in November 2017. Pereira has been accepted as a postdoctoral fellow in the laboratory of Mélanie Blokesch at EPFL in Lausanne, Switzerland, where he has already given a seminar.

The work was also presented by Melanie Hamon at an EMBO workshop on epigenetic mimicry in Paris in June 2017 and at a Keystone meeting in 2018. Melanie Hamon is now heading a junior group, Chromatin and Infection, at the Pasteur Institute. Her work on *S. pneumoniae* is starting to be internationally recognized, as shown by the several invitations that she has received. The post-doctoral fellow Matthew Elridge is pursuing his activity on SIRT2 in her lab. Finally, a new line of research could be launched concerning the post transcriptional modifications of mRNA in the host. This in-depth study carried out by post-doctoral fellow Sabrina Jabs and completely performed in vivo has established the basis for ongoing molecular and cellular studies trying to understand the role of commensals in the gut and the differences between commensals and pathogens. This work will be pursued by Sabrian Kabs in Kiehl.

Publications

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