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

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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* to the Académie des sciences in Paris. Her project will further investigate recent results obtained in epigenetics and bacterial infections, a new research area in infection biology. 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 has recently shown that the bacterial pathogen *Listeria monocytogenes* infection induces the nuclear translocation of 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 has 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 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). A new post-doc is investigating the import of SIRT2 in the nucleus which is independent of the infection. Mélanie Hamon is now extending these studies to another pathogen, *Streptococcus pneumoniae*.

The work realized by the Balzan Prize has thus led to an important set of data and a 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 already 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 entitled "Chromatin and infection" at the Pasteur Institute.