Replication of virulent bacteriophages in the gastrointestinal tract: what are we missing?

Marta Mansos Lourenco*[1,2], Luisa De Sordi[1], and Laurent Debarbieux[1]

[1]Group Interactions Bacteriophages Bacteria in Animals, BMGE Unit, Microbiology Department, Institut Pasteur – Institut Pasteur de Paris – France

[2]Université Pierre et Marie Curie, ED-Complexité du Vivant – Université Pierre et Marie Curie - Paris 6 – France

Résumé

The rapid proliferation of multi-drug-resistant bacteria has grown into a critical problem in the last few years. To tackle this problem, our lab investigates the potential of bacteriophages (phages) to treat bacterial infections. Although much is known about phage biology *in vitro*, the physiological, ecological and evolutionary interactions between phages and bacteria in natural environments are still poorly understood.
Up to now, the use of virulent bacteriophages to significantly reduce the levels of targeted bacteria in the gastrointestinal tract (GIT) has often been disappointing, showing at best a moderate effect in contrast to the high efficiency observed *in vitro*. These observations suggests the existence of some factors that can modulate the activity of phages in the GIT.

In order to uncover these factors, phage replication was first assessed in different specific conditions: *in vitro* during both exponential and stationary phase cultures, and *ex-vivo,* using homogenized different gut sections of mice colonized with the targeted bacteria. We observed that while some phages replicate efficiently regardless of the section of the GIT or the state of the *in vitro* cultures, others display a markedly different efficiency that depends on the environment. We hypothesized that the local gut environment may influence the physiological state of the bacterial host, which in turn can impact the efficiency of the phage infection/replication.To further test this hypothesis, we performed comparative genome-wide RNA-sequencing analysis of the *Escherichia coli strain 55989* growing in the different sections of the GIT as well as *in vitro* cultures, during exponential and stationary growth phases. We have identified more than 50 candidate genes that are significantly differentially expressed and might be involved in phage efficiency, supporting a possible connection between the physiological state of the bacteria and the outcome of the phage infection.
The characterization of interactions between phages and bacteria in their natural environment is key to increase knowledge in phage biology and could be useful to design better strategies that can improve the overall efficiency of Phage Therapy.

*Intervenant