Fighting for survival in the gut: Unravelling the hidden variation of bacteria

March 6 2014

This shows bacteria carrying different mutations compete for fixation in the gut of the laboratory mouse. Credit: Roberto Keller (IGC).

Our intestines harbour an astronomical number of bacteria, around 100 times the number of cells in our body, known as the gut microbiota. These bacteria belong to thousands of species that co-exist, interact with each other and are key to our health. While it is clear that species imbalances may result in disease, it is unclear at what pace does each

species in the gut evolves, a process that contributes to the chance of a particular innocuous species becoming harmful to the host.

In the latest issue of the scientific journal *PLOS Genetics*, three research groups from Instituto Gulbenkian de Ciência (IGC; Portugal), led by Isabel Gordo, joint efforts to unveil, for the first time, how the bacteria *Escherichia coli* (*E. coli*), one of the first species to colonize the human gut at birth, adapts and evolves in the mouse intestine. The researchers have shown that *E. coli* with different advantageous mutations rapidly emerge and, consequently, a large genetic variation in this species is generated over time. Their results unravelled a layer of complexity of the gut microbiota, which has been unknown so far. This study demonstrates how rich the evolutionary dynamics of each bacteria is in a healthy animal and will be instrumental for the development of new strategies to fight disease by manipulating gut microbes.

It was unknown to Charles Darwin that the process of natural selection that he deduced from observing the diversity in the world surrounding him, could be taking place inside his own body. For several years evolution of bacteria has been studied in Petri dishes, which are highly artificial environments. The laboratories of Isabel Gordo, Karina Xavier and Jocelyne Demengeot, at IGC, joint their expertise in evolution, microbiology and immunology, respectively, and set out to study evolution of *E. coli* in its natural environment: the gut. They fed mice with *E. coli* and analysed mice's faeces for mutations that emerged during bacterial evolution inside the intestine. Their results indicate that many advantageous mutations occur and bacteria carrying different mutations compete for fixation in the gut. The evolution process is the outcome of this continuous competition where a large diversity of *E. coli* strains is observed.

In order to identify the genes important for the adaptation to the gut, the researchers analysed genetically the *E. coli* strains that emerged. Their

results pointed out specific genes inactivation allowing bacteria to grow better in the presence of products generated by the host metabolism. They also reported changes of genes that regulate anaerobic respiration (a process required in environments low in oxygen like the gut). The researchers found that despite the high complexity of the natural environment studied – the intestine – the evolutionary process was highly reproducible as the same mutations occurred in populations of *E. coli* evolving in different mice.

"It is remarkable that we can study evolution with this level of quantitative precision in one of the most complex environments ever tackled", says Isabel Gordo. "The competitive war that appears to take place between emerging new strains of a given species will have to be further integrated with the variation observed between the different species inhabiting the gut along time. No doubt this opens room for many interesting future research studies of ecology and evolution in both healthy and non-healthy hosts."

Karina Xavier adds: "What most surprised me with these experiments was first, how fast these bacteria are evolving inside the mouse and therefore inside our bodies, and secondly, how reproducible the evolutionary path was. The fact that we observed the same mutations appearing over and over again every time we repeated this experiment will enable us to pin point the major factors controlling the microbiota in our gut, being the food we eat, our immune system or the microbes we encounter in the environment."

Jocelyne Demengeot says: "Most state of the art studies in Evolution and Ecology of bacteria are still conducted in vitro, in Petri dishes. Our long-term challenge, here proven feasible, is to move those fields to physiological situation, i.e to in vivo experimentation, in vertebrates. As for other fields of biomedical science, this approach is necessary to walk the scientific paths eventually leading to application for health and

diseases."

More information: Barroso-Batista, J, Sousa, A, Lourenço, M, Bergman, ML, Sobral, D, Demengeot, J, Xavier, KB, and Gordo, I. (2014) The first steps of adaptation of Escherichia coli to the gut are dominated by soft sweeps. *PLOS Genetics* 10 (3): e1004182. www.plosgenetics.org/doi/pgen.1004182

Provided by Instituto Gulbenkian de Ciencia