Resistance to antibiotics: When 1+1 is not 2

July 24 2009

The evolution of multiple antibiotic resistances is a global and difficult problem to eradicate. Isabel Gordo, a group leader at the Instituto Gulbenkian de Ciência (IGC), Portugal, reports in the paper published in the latest issue of *PLoS Genetics*, that the deleterious effect associated with the acquisition of resistance by a bacteria can be suppressed by the acquisition of a new resistance to another antibiotic. These findings have direct implications for the approaches taken to tackle the problem of multi-resistance to antibiotics and in the choice of antibiotics to be administrated to patients.

Acquisition of mutations is one of the ways by which bacteria become resistant to antibiotics. But this comes with a cost: although crucial for bacteria survival in a medium with antibiotics, in its absence bacteria growth rate is reduced. Although it is not possible to impaired bacteria to evolve and adapt to the environment, it is possible to choose the type of selective pressure (antibiotics) to administrate and, in this way, alter the course of evolution to our favour. This study shows the importance of knowing the costs of multi-resistance to find the best antibiotic combinations (the ones that carry more costs to the bacteria).

In collaboration with two other research groups at the IGC, Isabel's team selected populations of the bacteria, *Escherichia coli*, showing spontaneous mutations that confer resistance to common used antibiotics (the same used in the treatment of tuberculosis). This approach allowed the team to measure the effect of genetic interactions - a phenomenon scientists call epistasis- between the alleles of the genes involved in resistance. Epistasis is considered to be one of the key issues in Biology

research.

Isabel describes their findings, 'To our surprise, when in a medium without antibiotics, bacteria that are carry resistance to two drugs have a higher survival rate than expected, showing a smaller cost to multiple resistance". Even more surprisingly, in some combinations (12%) the double mutants to two given antibiotics survive even better than if they were resistant to only one of the drugs. This is the worst scenario case for the host (including our species) and the best for the bacteria.

This study provides the first insight into the importance of genetic interaction between random alleles in determining antibiotic resistance in bacteria. From a public health point of view, it can also explains multi-drug resistance seen in bacteria associated with many diseases, such as tuberculosis (*Mycobacterium* tuberculosis), for which current treatments involve combinations of the same drugs used in this study.

According to Isabel: "This works shows how important it is to know the clinical history of the patient's antibiotic use as well as the specific bacteria's genotype associated with a given resistance in order to choose the appropriate treatment and obtain the best clinical outcomes". She adds: "From a more general point of view, this work uncovers the complexity associated with genomes ".

More information: Trindade S, Sousa A, Xavier KB, Dionisio F, Ferreira MG, Gordo I(2009) Positive Epistasis Drives the Acquisition of Multidrug Resistance. *PLoS Genet* 5(7): e1000578. doi:10.1371/journal.pgen.1000578

Source: Instituto Gulbenkian de Ciencia (news : web)