Vancomycin resistance regulation in the antibiotic-producers streptomycetes

Reporting

Project Information

Vanrestrep

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Project website

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Project closed

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Periodic Reporting for period 1 - Vanrestrep (Vancomycin resistance regulation in the antibiotic-producers streptomycetes)

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Summary of the context and overall objectives of the project

An active area of research aimed at combatting the growing problem of antimicrobial resistance is to develop compounds that interfere with resistance mechanisms and therefore greatly prolong the use of existing drugs. An example of a condition that attenuates resistance to an antibiotic is found in

Streptomyces coelicolor when high levels of phosphate (in the presence of vancomycin) are added in the growth medium. The general objective of this work was to understand the effect of the availability of phosphate (Pi) on the vancomycin resistance (VR) mechanism of the model Gram-positive bacterium S. coelicolor. In particular, this project had two key Research Objectives: a) the study of the nutritional regulation of VR and its link with the cell wall composition, b) the study of the Post-transcriptional regulation of the VR genes with special focus on the role of small RNAs.

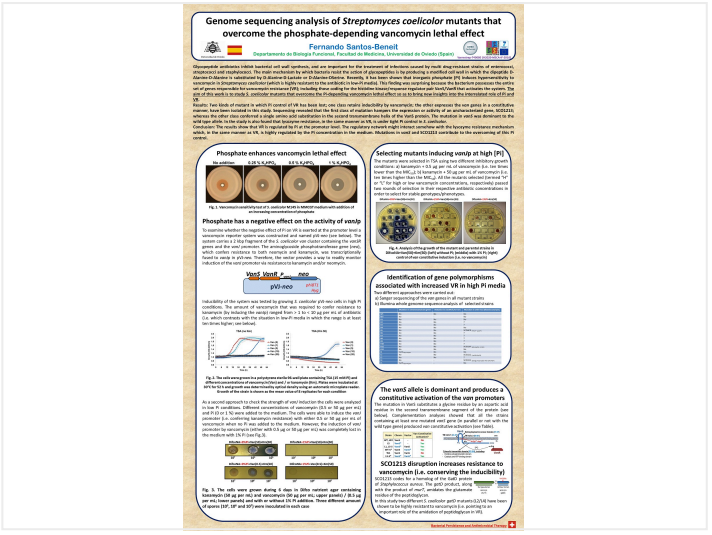
Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

In summary, I have been able to show that S. coelicolor strains with mutations in SCO2594, SCO1213 or vanS can rescue VR in media containing high Pi; although the mechanism of this interference is not yet understood. VanS is the sensor that, combined with VanR, induces the promoters in the VR cluster, whilst both SCO2594 and SCO1213 are thought to encode enzymes that modulate the nature (and the charge) of cell envelope by incorporating large amounts of negatively charged Pi groups to the cell-wall in the form of teichoic acids or other type of Pi polymers and by the amidation of the glutamic acid residues of the peptide chains of the peptidoglycan (which implies a reduction of the number of cell wall negatively charged carboxylate groups), respectively. The same observation (in terms of Pi control) has been also achieved for the lysozyme resistance mechanism of S. coelicolor and with the action of some specific cell-wall lytic enzymes. Therefore, it seems that the effect of Pi in the regulation of these processes is indirect and might be produced by changes in the positive or negative charges of the cell envelope, which might enhance or diminish the non-specific binding of charged antibiotics to the cell wall. For this reason, in future experiments I would redirect my efforts in understanding the role of certain components of the cell wall in antimicrobial resistance rather than to look for specific transcriptional regulators or sRNAs accounting for this phenomenon.
Part of this work has been published in the gold open access journal BMC Genomics. The work is entitled as follows: “Genome sequencing analysis of Streptomyces coelicolor mutants that overcome the phosphate-depending vancomycin lethal effect”. The work has been also disseminated as a communication to the International conference on “Bacterial Persistence and Antimicrobial Therapy” organized by EMBO in 2018 in Ascona (Switzerland). Other part of this work is in preparation for publication and the results have been already presented at the 14th International Symposium on the Genetics of Industrial Microorganisms held in Pisa (Italy) in September 2019.
The results of this project has brought to light evidences with regards to the nutritional regulation of the antibiotic resistance mechanism of certain bacteria and consequently of the protocols for testing antimicrobial resistance. Antimicrobial susceptibility testing (AST) is clinically used to guide antimicrobial therapy. Disk-diffusion and broth or agar dilution assays are the standard methods to evaluate the in vitro antimicrobial activity of a compound. However, as shown in this project, inorganic phosphate has a strong impact in the final results of these AST methods when testing the activity of certain extracts or pure compounds such as vancomycin. Therefore, new media compositions that are not sensitive to the changes in inorganic phosphate should be developed and patented. In this sense, the work carried out in this project is in the process of a patent filling on new process of AST methods and it has been already selected by the Innovation Radar initiative, supported by the European

Commission, as an innovative work under the title: “New media additive for antimicrobial susceptibility testing”.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

Overall, this project has provided scope for further fundamental studies of antibiotic resistance control aimed at understanding the influence of environmental conditions in antimicrobial treatments. The results have brought to light evidences with regards to the importance of the nutritional composition of the culture medium when performing antimicrobial susceptibility tests and analysing the results (for example in hospitals and other healthcare institutions). The importance of this challenge for the EU is evidenced by the existence of the Innovative Medicines Initiative (IMI), which is the largest public-private initiative in Europe aimed to speed up the development of better and safer medicines for patients. Since this work represents a change in the understanding of the antimicrobial resistance testing its impact is key and relevant for clinic and industry.



Poster summarizing the work published and disseminated at EMBO conference

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