PTM's: role of post-translational modifications in antimicrobial resistance

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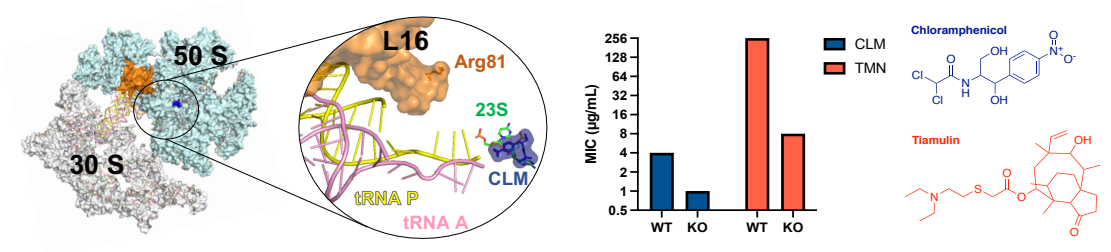
Homeostasis largely depends on cellular dynamics which is in close relationship with proteome diversity. The addition of functional chemical groups to protein residues, post-translational modifications (PTM) seem to be of particular importance for multicellular organisms (1) and now known for unicellular organisms due to the constant exposure to changing environments (2, 3) Antibiotics constitute a selective pressure condition that requires speedy changes to allow cell survival. Therefore, PTMs may have an essential but unravelled role in antimicrobial resistance (AMR). Most of the ribosomal targeting antimicrobial aim for the peptidyl transferase centre (PTC) where the peptidyl transferase reaction occurs between the aminoacyl tRNA in the A site and the peptidyl tRNA in the P site resulting in the transfer of the nascent peptide from the P to the A site (4). Although the inventory for prokaryotic PTMs sites expands over the years, only some of the effort is oriented to understand their function in antibiotic resistance. Here, we have focused on the L16, RlpP protein, and found that ablation of Arg-81 hydroxylation by genetic inactivation of the relevant hydroxylase YcfD, confers sensitivity to antibiotics such as chloramphenicol and tiamulin. Proteomics, transcriptomics and metabolomics data showed a downregulation of the glycolytic pathway when YcfD is absent. These preliminary data would suggest YcfD as a good target for inhibition and hence antibiotic susceptibility restoration. Virtual screening combined with preliminary MS-based assays have given insights into the identification of the responsible enzymatic domain which is key for the future design of inhibitors to improve antibiotic therapy and insights in other medical applications of its human homologs.



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