On-cell NMR screening of bacterial multivalent ligands

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Abstract: Antimicrobial resistance (AMR) is one of the major threats of the 21st century. Available antibiotics target essential pathways imposing selective pressure that favors resistance development, even across distant bacterial species. This leads to the spread of resistance even to last-resort antibiotics. Further, the broad-spectrum nature of most antibiotics has long lasting detrimental effects on the healthy human microbiota. In addition to the development of novel antibacterial molecules exploiting new mechanisms of action, this alarming scenario requires: 1) diagnostic tools for a fast identification of the class of the pathogen (Gram+, Gram-, mycobacteria), thus allowing for a timely selection of the most appropriate antibiotic class to treat the patient; 2) novel drugs disarming pathogenic bacteria by interfering with their virulence mechanisms. Virulence factors are molecules produced by bacteria enabling them to: a) colonize a niche in the host, b) evade the host's immune response, c) inhibit the host's immune response, or d) scavenge nutrients from the host. Compounds targeting virulence processes will impose less evolutionary pressure than standard antibiotics for the development of resistance, will supplement conventional antibiotics to increase efficacy and will have little or no impact on the host commensal flora. To this aim, we are developing new multivalent bacteria ligands, based on calixarene or dendrimer scaffolds, targeting specific molecular patterns of the different bacteria classes, such as the terminal part of peptidoglycan (D-Ala-D-Ala) and teichoic acids for Gram+ bacteria, LPS for Gram- bacteria, mycolic acid, glycolipids and trehalose transporter for mycobacteria. Moreover, for a specific pathogen targeting, the adhesin FimH located at the pili end of an uropathogenic strain of Escherichia coli can be targeted through the glycoside cluster effect of carbohydrate-lectin interactions. An advanced approach for the screening of these bacteria ligands, based on on-cell STD NMR experiments, has been set up and allowed for the identification of the first promising hit compounds as selective bacteria ligands and anti-virulence factors.

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